# Ergebnisbericht

(gemäß Nr. 14.1 ANBest-IF)

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| **Konsortialführung:** | Universitätsklinikum Hamburg-Eppendorf |
| **Förderkennzeichen:** | 01VSF16008 |
| **Akronym:** | IDOMENEO Studie |
| **Projekttitel:** | IST DIE VERSORGUNGSREALITÄT IN DER GEFÄßMEDIZIN LEITLINIEN- UND VERSORGUNGSGERECHT? |
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# I. Abkürzungsverzeichnis

| | |
|---|---|
| *AFS:* | *Amputation-free survival (amputationsfreies Überleben)* |
| *AGENS:* | *Arbeitsgruppe Erhebung und Nutzung von Sekundärdaten* |
| *ASA:* | *American Society of Anesthesiologists* |
| *ATC:* | *Anatomisch-Therapeutisch-Chemisches Klassifikationssystem* |
| *CI:* | *Confidence interval (Konfidenzinterval)* |
| *CLTI:* | *Chronic Limb-Threatening Ischaemia (chronische extremitätengefährdende Ischämie)* |
| *CRO:* | *Clinical Research Organisation* |
| *DeGIR:* | *Deutsche Gesellschaft für Interventionelle Radiologie* |
| *DGA:* | *Deutsche Gesellschaft für Angiologie* |
| *DGG:* | *Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin* |
| *DGEpi:* | *Deutsche Gesellschaft für Epidemiologie* |
| *DGSMP:* | *Deutsche Gesellschaft für Sozialmedizin und Prävention* |
| *DSGVO:* | *Datenschutzgrundverordnung* |
| *EBM:* | *Einheitlicher Bewertungsmaßstab* |
| *ESVS:* | *European Society for Vascular Surgery* |
| *EU:* | *Europäische Union* |
| *IC:* | *Intermittent Claudication (Claudicatio intermittens)* |
| *ICD:* | *International Classification of Diseases* |
| *IDOMENEO:* | ***I**st **D**ie Vers**O**rgungsrealität in der Gefäß**M**edizin L**E**itli**N**i**E**n- und Vers**O**rgungsgerecht?* |
| *IQR:* | *Interquartilsabstand* |
| *InEK:* | *Institut für das Entgeltsystem im Krankenhaus* |
| *MACE:* | *Major Adverse Cardiovascular Event* |
| *MALE:* | *Major Adverse Limb Event* |
| *OPG:* | *Objective Performance Goal* |
| *OPS:* | *Operationen- und Prozedurenschlüssel* |
| *PAVK:* | *Periphere arterielle Verschlusskrankheit* |
| *SF12:* | *Short Form 12 Health Survey* |
| *UKE:* | *Universitätsklinikum Hamburg-Eppendorf* |
| *VQI:* | *Vascular Quality Initiative* |
| *W-DWH:* | *Wissenschafts-Data Ware House* |
| *WIQ:* | *Walking Impairment Questionnaire* |

# II. Abbildungsverzeichnis

*Abbildung 1: Schematische Darstellung des multimethodalen und mehrstufigen IDOMENEO-Projekts.*

*Abbildung 2: Fallzahlkalkulation im Rahmen der prospektiven GermanVasc-Kohortenstudie.*

*Abbildung 3: Darstellung der patientenberichteten Endpunkte in der Basiserhebung der GermanVasc-Kohortenstudie.*

*Abbildung 4: Exemplarische Darstellung der Qualitätsindikatoren im Vergleich mit anderen teilnehmenden Zentren (oben) und beispielhafte Ausgabe von Entlassungsmedikationen in Berichten (unten).*

# III. Tabellenverzeichnis

*Tabelle 1: Ergebnisse der retrospektiven BARMER-Routinedatenauswertungen im IDOMENEO-Projekt; Konfidenzintervall (CI), Interquartilsabstand (IQR), Major Adverse Cardiovascular Event (MACE), Major Adverse Limb Event (MALE), Intermittent Claudication (IC), Chronic Limb-Threatening Ischaemia (CLTI). Die Ergebnisse nach 1 Jahr wurden mit Kaplan-Meier-Schätzern ermittelt.*

*Tabelle 2: Ergebnisse der prospektiven Routinedatenauswertung im IDOMENEO-Projekt; Konfidenzintervall (CI), Interquartilsabstand (IQR), Major Adverse Cardiovascular Event (MACE), Intermittent Claudication (IC), Chronic Limb-Threatening Ischaemia (CLTI). Die Ergebnisse nach 1 Jahr wurden mit Kaplan-Meier-Schätzern ermittelt.*

*Tabelle 3: Ergebnisse der prospektiven GermanVasc-Kohortenstudie im IDOMENEO-Projekt; Konfidenzintervall (CI), Interquartilsabstand (IQR), Major Adverse Cardiovascular Event (MACE), Major Adverse Limb Event (MALE), Intermittent Claudication (IC), Chronic Limb-Threatening Ischaemia (CLTI).*



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## 1. Zusammenfassung

*Hintergrund: Die stationäre Behandlung der symptomatischen peripheren arteriellen Verschlusskrankheit (PAVK) erfolgt in Deutschland durch mehrere Fachdisziplinen und etwa 650 Krankenhäuser, wobei derzeit ungefähr 1 Mio. betroffene gesetzlich Versicherte im stationären Sektor kumulativ mehr als 7 Mrd. Euro an stationären Behandlungskosten pro Jahr generieren. Die verfügbaren Praxisleitlinien enthalten dabei zu mehr als 50% Empfehlungen auf der Basis von Expert:innenmeinungen, weil kaum hochwertige empirische Evidenz aus randomisierten Studien verfügbar ist. Außerdem fehlen konsentierte Qualitätsindikatoren in der PAVK-Behandlung. Das IDOMENEO-Projekt verfolgte das Ziel, geeignete Qualitätsindikatoren zu entwickeln und diese in verschiedenen Datenquellen zur deutschen Versorgungsrealität zu messen.*

*Methodik: Es handelte sich um ein multimethodales mehrstufiges Projekt der Versorgungsforschung. Auf dem Boden einer systematischen Literaturübersicht zu Qualitätsindikatoren der PAVK-Behandlung wurde ein modifiziertes Delphi-Verfahren mit Expert:innen durchgeführt, um klinisch relevante und praktikable Ergebnisqualitätsindikatoren zu konsentieren. Anhand der faktisch anonymisierten Routinedaten der bundesweiten Krankenversicherung BARMER wurden umfassende Analysen der Versorgungsrealität im stationären Behandlungssektor durchgeführt. Insbesondere erfolgte ein Abgleich mit aktuellen Leitlinienempfehlungen. Durch das Konsortium wurde ein datenschutzkonformes Register (GermanVasc-Register) entwickelt, das für die Durchführung einer prospektiven Kohortenstudie verwendet wurde. In die GermanVasc-Kohortenstudie wurden konsekutiv alle invasiven offen-chirurgischen und endovaskulären Revaskularisationen der symptomatischen PAVK eingeschlossen und für bis zu 12 Monate nach der Behandlung verlaufskontrolliert.*

*Ergebnisse: Durch ein interdisziplinäres Expert:innenpanel wurden 12 Ergebnisqualitätsindikatoren konsentiert. In den Routinedatenanalysen zeigte sich ein Zeittrend zu häufigeren stationären Behandlungen, einer zunehmenden Krankenhausprävalenz und Behandlungskosten der PAVK, wobei etwa die Hälfte aller Behandlungsfälle elektiv im Stadium der Claudicatio intermittens durchgeführt wurden. Die Krankenhausinzidenz der Erkrankung ging dabei im Zeitverlauf leicht zurück. Insbesondere bei der optimalen Arzneimittelversorgung zeigten sich unerklärte Abweichungen von den Leitlinienempfehlungen und ein Nachteil bei Frauen. In einer prospektiven Kohortenstudie an 31 Gefäßzentren bestätigte sich das komplexe Komorbiditätsprofil der Zielpopulation. In dieser selektiveren Registerkohorte war der Frauenanteil gegenüber der bundesweiten Versichertenkohorte geringer und Frauen wurden häufiger endovaskulär behandelt. In der vergleichenden Beurteilung der Primärdaten aus der Registerstudie und Sekundärdaten der Krankenkasse zeigten sich zahlreiche Unterschiede bei den Basischarakteristika und Behandlungsergebnissen. Nur 21% der Fragebögen zu patientenberichteten Endpunkten lagen nach 12 Monaten vor.*

*Diskussion: Das IDOMENEO-Projekt konnte die Versorgungsrealität in einer prospektiven Kohortenstudie sowie in verfügbaren bundesweiten Routinedaten darstellen, wobei zahlreiche Ergebnisse darauf hindeuten, dass die flächendeckende Versorgung von High-Volume-Zentren abweicht. Hierbei konnten Qualitätsindikatoren entwickelt werden, die für die Nutzung mit beiden Datenquellen geeignet sind.*



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## 2. Beteiligte Projektpartner

***Universitätsklinikum Hamburg-Eppendorf**, Forschungsgruppe GermanVasc,*
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*Verantwortlichkeiten:*
*Konsortialführung und wissenschaftliche Gesamtprojektleitung,*
*Leiter der Forschungsgruppe GermanVasc, fachlich-inhaltlicher Registerbetrieb,*
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*Verantwortlichkeiten: Konzeptionelle Entwicklung der Techniklösungen, Datenschutz*

***BARMER**, Hauptverwaltung, Dr. med. Ursula Marschall (Leitende Medizinerin)*
*Verantwortlichkeiten:*
*Bereitstellung der Routinedaten über das Wissenschafts-Data-Warehouse*

***Hamburger Informatik Technologie-Center e.V. (HITeC)**, Dr. Lothar Hotz,*
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*Verantwortlichkeiten: Begleitung patientenberichteter Endpunkte, Methodenberatung*

## 3. Projektziele

Das IDOMENEO-Studienvorhaben verfolgte mehrere Ziele in einem multimodalen und mehrstufigen Ansatz, wobei das Gesamtprojekt in die Entwicklung von Qualitätsindikatoren (1), die Prüfung der gesundheitsbezogenen Lebensqualität und anderer patientenrelevanter Endpunkte (2), die Analyse der Prozesse und Ergebnisse der Versorgung (3) und eine Benchmarking-Erprobung (4) unterteilt wurde.

1. Entwicklung von Qualitätsindikatoren
   a) Systematische Sammlung potenzieller Qualitätsindikatoren
   b) Prüfung, welche Qualitätsindikatoren mit Routinedaten valide abbildbar sind
   c) Prospektive Erfassung der Qualitätsindikatoren in einem Register
   d) Vergleich der Ergebnisse aus der prospektiven Registerstudie mit der prospektiven Routinedatenanalyse aus dem gleichen Zeitraum
2. Prüfung der gesundheitsbezogenen Lebensqualität und anderer patientenrelevanter Endpunkte zur Evaluation des Behandlungsergebnisses
3. Analyse der Prozesse und Ergebnisse der Versorgung
   a) Retrospektiv anhand von Routinedaten
   b) Prospektiv anhand von Registerdaten


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4. Erprobung von Benchmarking anhand Rückmeldungen zur Versorgungsqualität aus dem Register

1.) Verfügbare Praxisleitlinien der einschlägigen Fachgesellschaften beinhalten bisher keine konkreten bzw. auf dem Boden anerkannter Verfahren entwickelten Qualitätsindikatoren oder korrespondierende Zielvorgaben für deren Messung in Primär- oder Sekundärdatenquellen. Teilweise beschriebene objektivierbare Leistungszielvorgaben (sogenannte Objective Performance Goals, OPG) wurden dagegen auf dem Boden einer abweichenden Methodik mit retrospektiv analysierten Datenquellen zu Subgruppen in der Zielpopulation entwickelt und sind nicht ohne Weiteres als konventionelle Qualitätsindikatoren geeignet. Das Fehlen von allgemein anerkannten Qualitätsindikatoren in der Behandlung der PAVK wurde bereits seit Längerem als mitursächlich für ungewünschte Unterschiede in der Versorgungsrealität diskutiert. Das IDOMENEO-Projekt verfolgte daher das Ziel, Qualitätsindikatoren auf dem Boden einer allgemein akzeptierten und etablierten Methodik zu entwickeln. Hierbei sollte zunächst eine systematische Literaturübersicht zu Leitlinien, systematischen Reviews und Metaanalysen (1a) und ein modifiziertes mehrstufiges Delphi-Verfahren mit Expert:innen durchgeführt werden, um geeignete Indikatoren zu entwickeln. Das Konsensusverfahren schloss Vertreter:innen aller an der invasiven Behandlung beteiligten Fachdisziplinen ein. Die so entwickelten Qualitätsindikatoren sollten anschließend in Routinedatenanalysen (1b) und Registererhebungen (1c) geprüft werden, um die Versorgungsrealität darzustellen und die Daten zu vergleichen.

2.) Die Prüfung der gesundheitsbezogenen Lebensqualität und allgemein patientenrelevanter Endpunkte gilt als komplex und unzureichend umgesetzt in der PAVK-Behandlung sowie Forschungsvorhaben. Die Ursachen hierfür sind multifaktoriell und schließen sowohl methodische Aspekte als auch die Ärzt:innen-Patient:innen-Kommunikation ein. Das IDOMENEO-Projekt verfolgte daher das Ziel, geeignete Endpunkte zu prüfen und Ansatzpunkte für eine bessere Akzeptanz bzw. Nutzung geeigneter Werkzeuge zu identifizieren. Hierzu wurden Endpunkte definiert, die im Rahmen der Ärzt:innen-Patient:innen-Kommunikation abgefragt wurden. Außerdem sollte die Implementierbarkeit eines generischen und eines spezifischen Fragebogens zur Lebensqualität im Rahmen der Registererhebung geprüft werden.

3.) Die komplementäre Behandlung der PAVK zeichnet sich aufgrund des ausgesprochen komplexen Komorbiditätsprofils und zahlreicher Behandlungspfade im Langzeitverlauf als besondere Herausforderung für Projekte der Qualitätsentwicklung und Versorgungsforschung aus. Im internationalen Kontext sind dabei bemerkenswerte Unterschiede bei der Versorgungsrealität zwischen den Ländern aufgefallen, die sich nur durch externe Faktoren des Gesundheitssystems erklären ließen. Der chronisch progressive Charakter der Erkrankung und die oft zahlreichen aufeinanderfolgenden Behandlungen machen zudem longitudinal verknüpfte patientenbezogene Daten erforderlich. Fall- oder prozedurbezogene Datensätze (z.B. Krankenhausfallstatistik) sind für viele Fragestellungen nicht geeignet, da Verzerrungen durch redundante Behandlungen der gleichen Patient:innen nicht ausgeschlossen werden können. Zudem wird bereits seit einigen Jahren eine Dynamik in der Versorgungsrealität vermutet, die sowohl demographische Entwicklungen als auch eine sich ändernde Patient:innenselektion umfasst. Das IDOMENEO-Projekt verfolgte daher das Ziel, die Versorgungsrealität in retrospektiven Routinedatenanalysen mit Patient:innenbezug weitestgehend explorativ darzustellen. Außerdem sollte eine prospektive Erfassung von Registerdaten erfolgen, um den Ergebnissen aus Sekundärdatenanalysen


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geeignete Primärdatenanalysen entgegenzustellen. Für die explorativen retrospektiven Routinedatenanalysen wurden durch das Konsortium verschiedene Fragestellungen identifiziert: a) Welche Komorbiditätsprofile lassen sich in Routinedaten messen; b) Ist das Risiko von Krebserkrankungen im Langzeitverlauf bei Patient:innen mit PAVK erhöht?; c) Wie erfolgt die Versorgung mit leitliniengerechten Arzneimitteln in Deutschland?; d) Gibt es Hinweise auf geschlechterspezifische Unterschiede bei der PAVK-Behandlung?; e) Lassen sich Langzeitergebnisse nach der Anwendung von Hochrisikomedizinprodukten in der PAVK-Behandlung in Routinedaten messen?; f) Gibt es einen Zusammenhang zwischen PAVK und chronischen Entzündungen der Mundhöhle (Parodontitis)? Für die prospektive Kohortenstudie wurden durch das Konsortium verschiedene Fragestellungen identifiziert: a) Welche Komorbiditätsprofile lassen sich in Registerdaten messen; b) Existieren Unterschiede hinsichtlich der Langzeitergebnisse bei den komplementären invasiven Revaskularisationsverfahren?

4.) In zahlreichen Ländern existieren bereits Qualitätsentwicklungsregister, die ein regelmäßiges Benchmarking, also einen Vergleich der Versorgungsrealität des eigenen Zentrums mit anderen Zentren ermöglichen. Etwa 28 solcher Registerinitiativen sind im VASCUNET Konsortium der European Society for Vascular Surgery (ESVS) vernetzt und haben die Projektschritte des IDOMENEO-Konsortiums aktiv verfolgt bzw. unterstützt. Das IDOMENEO-Projekt verfolgte das Ziel, ein Benchmarking-Konzept in der deutschlandweiten Versorgungsfläche zu erproben, bei dem die Behandlungscharakteristika und Ergebnisse an die jeweiligen Zentren zurückgemeldet werden.

## 4. Projektdurchführung

Das IDOMENEO-Konsortium, bestehend aus dem Universitätsklinikum Hamburg-Eppendorf (UKE, Konsortialführung), der Fakultät für Mathematik, Informatik und Naturwissenschaften der Universität Hamburg sowie der gesetzlichen Krankenkasse BARMER nahm am 1. April 2017 die gemeinsame Arbeit an dem hier beschriebenen multimethodalen mehrstufigen Projekt auf.[1]

Ausgehend von den themenrelevanten Vorarbeiten der federführend verantwortlichen Forschungsgruppe GermanVasc (www.germanvasc.de) erfolgten verschiedene Projektschritte simultan und in einem engen Austausch mit allen projektbeteiligten Konsortialpartnern.

Zunächst erfolgte die Abstimmung geeigneter Aufgreifkriterien für die korrekte Identifizierung der Zielpopulation in den faktisch anonymisierten Routinedaten im BARMER-Wissenschafts-Data-Warehouse (W-DWH). Hierdurch konnten diejenigen 100 Zentren mit dem zahlenmäßig größten Anteil an der jährlichen invasiven Revaskularisation der symptomatischen PAVK identifiziert werden. Alle so identifizierten Zentren wurden anschließend durch die wissenschaftliche Projektleitung per Post und per E-Mail angeschrieben und zur interdisziplinären Teilnahme an einer prospektiven registerbasierten Kohortenstudie eingeladen. Für die Teilnahme wurde die verbindliche aktive Einbeziehung aller für die invasive Versorgung relevanten Fachdisziplinen (Gefäßchirurgie, Angiologie, Radiologie) und die konsekutive Übermittlung von geplanten 250 Patient:innen vorausgesetzt. Die Zentren haben dies vorab schriftlich gegenüber der Projektleitung bestätigt. Parallel hierzu wurde die grundsätzliche Methodik der geplanten Registerstudie bei Clinicaltrials.gov (NCT03098290) und beim Deutschen Register


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Klinischer Studien (DRKS00014649) registriert. Zudem erfolgte eine Publikation der Methodik in einem internationalen gefäßmedizinischen Fachjournal.[4]

Ausgehend von fakultätsübergreifenden Diskussionen und Fokusgruppen zwischen der wissenschaftlichen Projektleitung und dem Arbeitsbereich Sicherheit in Verteilten Systemen (SVS) der Fakultät für Mathematik, Informatik und Naturwissenschaften der Universität Hamburg wurde mit der konzeptionellen Entwicklung der datenschutzkonformen Registerplattform GermanVasc begonnen.[2,5,6] Hierbei wurden zahlreiche Erwägungen und Verbesserungsvorschläge der konsultierten Datenschutzbeauftragten der Konsortialführung und von weiteren Datenschutzexpert:innen in die Entwicklungs- und Weiterentwicklungsschritte einbezogen. Besonders herausfordernd waren hierbei die verschiedenen Vorgaben und Gesetzgebungen auf Bundesländer-, Bundes- sowie EU-Ebene und die anstehende Einführung der Datenschutzgrundverordnung (DSGVO) der Europäischen Union (EU).[2] So war sowohl eine technische sowie organisatorische Trennung der Forschungsaufgaben im Projekt von der klinischen Versorgung erforderlich, was sich durch föderale Unterschiede bei der Gesetzgebung ergab. Zur erweiterten Qualitätssicherung und Prüfung der so entwickelten Techniklösung erfolgte zudem die Hinzuziehung eines erfahrenen überregional tätigen Dienstleisters im Bereich Datenschutz und Datensicherheit. Neben der praxisorientierteren Begleitung und Datenschutzbegutachtung der Technikkonzepte und Dokumente erfolgte im laufenden Registerbetrieb auch eine externe gutachterliche rechtswissenschaftliche Beurteilung der Registererhebung durch die Rechtsfakultät der Universität Hamburg. Bei dieser wurden zahlreiche weitere Aspekte und auch hypothetische Erwägungen diskutiert, um die Techniklösungen und Konzepte weiterzuentwickeln bzw. für den europäischen Registerbetrieb vorzubereiten.

Die systematische Literaturrecherche zur Identifizierung von Qualitätsindikatoren in der PAVK-Behandlung erfolgte im Rahmen einer medizinischen Dissertation unter Mitarbeit und Supervision durch die projektverantwortliche Wissenschaftlerin und den wissenschaftlichen Projektleiter.[18] Eine Listung des Vorhabens ist a priori online im PROSPERO-Register erfolgt (CRD42019116317). Parallel hierzu erfolgte eine weitreichende narrative Literaturrecherche zu weiteren Erhebungsparametern in Registern zur Zielpopulation. Hierbei wurden Publikationen zu PAVK-Registern zwischen 1997 und 2017 gesucht. Zusätzlich wurden die 25 Registerexpert:innen aus 14 Ländern, die regelmäßig im VASCUNET Komitee der ESVS partizipierten, um Übermittlung der Variablenmanuale ihrer eigenen Register gebeten und zu einem modifizierten Delphi-Verfahren eingeladen. Die insgesamt 187 identifizierten Erhebungsparameter wurden in fünf aufeinanderfolgenden Runden und moderierten Diskussionen mit einer 5-Punkt-Likert-Skala hinsichtlich ihrer klinischen Relevanz bewertet. Hierbei konnten etwa 100 Variablen zu Risikofaktoren und Behandlungsparametern identifiziert werden, deren systematische Sammlung in PAVK-Registern empfohlen wurden.[15,17] In einer weiteren systematischen Literaturrecherche zu patientenberichteten Endpunkten konnten weitere 145 Variablen in acht verschiedenen Domänen identifiziert und diskutiert werden.

Die Ergebnisse der systematischen Literaturrecherche zu den Qualitätsindikatoren sind anschließend im Rahmen eines weiteren modifizierten Delphi-Verfahrens mit Expert:innen diskutiert worden.[16] Hierbei wurden die interdisziplinären Vertreter:innen derjenigen deutschlandweiten Zentren eingeladen, die eine Teilnahme an der prospektiven Kohortenstudie zugesagt hatten. Im Rahmen des zweistufigen Delphi-Verfahrens wurden insgesamt 12 Ergebnisqualitätsindikatoren hinsichtlich ihrer klinischen Relevanz und Praktikabilität im klinischen Alltag bewertet und allgemein konsentiert. Obwohl patientenberichtete Endpunkte hierbei aufgrund der geringen Praktikabilität keine allgemeine Zustimmung erhielten, wurden diese durch die Projektleitung in die Erhebung integriert. Die Ergebnisse der letztgenannten Projektschritte und weitere Teilschritte wurden regelmäßig an den Patientenvertreter für „Das PatientenForum e.V.“


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kommuniziert, um eine transparente Einbindung bzw. Einbeziehung der Patient:innen zu gewährleisten. Dieser wurde auch in den wissenschaftlichen Beirat der Studie eingeladen.

Die Erkenntnisse der konzeptionellen Entwicklungsschritte, der rechtlichen Erwägungen und Datenschutzaspekte sowie der durchgeführten Delphi-Verfahren wurden anschließend genutzt, um die Registererhebungen im Rahmen der prospektiven Kohortenstudie als Gesamtkonzept zu verschriftlichen. Die so angefertigten Dokumente und Konzepte wurden anschließend dem einberufenen wissenschaftlichen Beirat, dem Konsortium und den beteiligten Studienzentren sowie der federführenden primär verantwortlichen Ethikkommission der Ärztekammer Hamburg (PV5691) zur Beratung vorgelegt. Nach dem Eingang des positiven Primärvotums erfolgte die Vorlage des Vorhabens sukzessive bei allen zuständigen assoziierten Ethikkommissionen in den betroffenen Bundesländern bzw. Institutionen, wobei verschiedene sprachliche Verbesserungsvorschläge jeweils zu mehreren Amendments des Primärvotums geführt haben. Als wesentliche Anforderung wurde außerdem eine Wege- und Unfallversicherung für alle eingeschlossenen Patient:innen abgeschlossen, die sowohl die Basiserhebung als auch alle Follow-up-Erhebungen für bis zu 10.000 Patient:innen abdeckte. Die wissenschaftliche Projektleitung hat den Zentren zudem Schriftstücke zur umfassenden Information der niedergelassenen Ärzt:innen sowie Krankenhäusern über das Projekt zur Verfügung gestellt.

Nachdem die Vorbereitung der Techniklösungen des GermanVasc-Registers durch den beauftragten Projektpartner HITeC e.V. unter konzeptionell-technischer Supervision durch den Fachbereich Informatik der Universität Hamburg abgeschlossen wurde, erfolgte die Implementierung und der technische Registerbetrieb durch den Geschäftsbereich Informationstechnologie des Universitätsklinikums Hamburg-Eppendorf. Hierfür wurde der technische Netzbereich mit allen assoziierten Sicherheitsmaßnahmen und Zertifizierungen der Konsortialführung genutzt, in dem auch die personenbezogenen bzw. Krankenhausdaten des Universitätsklinikums Hamburg-Eppendorf gespeichert wurden. Die Administration und der inhaltliche Betrieb der Registerplattform erfolgte durch den wissenschaftlichen Projektleiter und die Forschungsgruppe GermanVasc am Universitätsklinikum Hamburg-Eppendorf. Sukzessive sind nach Vertragsabschluss mit 31 teilnehmenden Studienzentren entsprechende Administratorkonten eingerichtet worden und es erfolgten webbasierte Schulung aller beteiligten Mitarbeiter:innen gemäß den Studienprotokollen und ergänzenden Dokumenten. Das Rollenkonzept sah hierbei die eigenständige Einrichtung von Assistenz- sowie ärztlichen Benutzerkonten vor, die für die Dokumentationen und Verifizierungen der Daten genutzt werden konnten.

Mit der Clinical Research Organisation (CRO) CTC North GmbH & Co. KG wurde zudem ein Vertrag zur Durchführung des unabhängigen Datenmonitorings mit stichprobenartigen Vor-Ort-Visits und Queries geschlossen. Hierfür wurden sowohl eine Entbindung von der ärztlichen Schweigepflicht für die Patient:innen als auch eine Verschwiegenheitserklärung für Monitore erstellt, um den Anforderungen der geltenden Gesetze zu entsprechen.

Dieser zentrale Projektbestandteil erfolgte ab dem Vorliegen der ersten 3-Monats-Visiten und bis zum Ende der Datenerhebungen. Der Beginn der Patient:innenrekrutierungen erfolgte ab 1. Mai 2018 und endete am 31. Dezember 2020. Nach jedem Vor-Ort-Monitoring wurden die entsprechenden Queries mit den Zentrums-Projektleiter:innen sowie mit der wissenschaftlichen Projektleitung diskutiert, um systematische Probleme bei der Datenerhebung zu identifizieren. In den kumulativen Berichten nach der ersten und zweiten vollständigen Monitoring-Phase konnte eine gute Datenqualität und Adhärenz zu den studienbedingten Vorgaben bestätigt werden, während die überwiegende Anzahl der Queries aufgrund von organisatorischen Auffälligkeiten angelegt wurden (z.B. fehlender Klinikstempel auf dem Einwilligungsbogen).


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Direkt nach der Einrichtung der datenschutzkonformen Zugriffsmöglichkeiten der Wissenschaftler auf das W-DWH der BARMER erfolgte zum Projektbeginn die strukturierte Qualitätssicherung und Aufarbeitung der vorliegenden faktisch anonymisierten Routinedaten. Der Zugriff auf diese Forschungsdaten erfolgte in Übereinstimmung mit interdisziplinären Leitlinien und nach Ansicht der konsultierten Ethikkommissionen ohne ethische Bedenken. Insbesondere wurden geeignete Aufgreifkriterien zur Identifizierung der Zielpopulation inklusive Subgruppen, der Behandlungen und Komorbiditäten sowie relevanter Endpunkte in Katalogen zusammengestellt und qualitätsgesichert. Hierbei erfolgte die Einbeziehung vorhergehender Arbeiten der eigenen Forschungsgruppe und anderer Gruppen im nationalen und internationalen Umfeld.[10]

In einer ersten retrospektiven Analyse der Routinedaten erfolgte die Darstellung der bundesweiten interdisziplinären Versorgungsrealität im Zeitverlauf, wobei ein besonderer Fokus auf zeitliche Trends und Merkmale der Patient:innenselektion bzw. Indikationsstellung und Verfahrenswahl gelegt wurde.[20] Hierbei konnten wichtige Erkenntnisse zur Validität der Aufgreifkriterien identifiziert und überwunden werden, die mit den Kodierpraktiken der Versorgungseinrichtungen assoziiert werden konnten. Es wurde außerdem deutlich, welchen Einfluss jährliche Änderungen der Kodierrichtlinien auf die Datenbasis haben. Die Ergebnisse dieser Analysen konnten zu zahlreichen Fragestellungen und Hypothesen führen, die im Rahmen regelmäßiger Diskussionen und Fokusgruppen zu Protokollen für weitere Analysen führten.

Insgesamt konnten in der Forschungsgruppe GermanVasc verschiedene Routinedatenanalysen im IDOMENEO-Projekt abgeschlossen werden, die klinisch relevante Einzelfragestellungen beantwortet haben und jeweils zu einer Prüfung und Verbesserung der Aufgreifkriterien, Syntax sowie statistischen Methoden geführt haben. Mit wissenschaftlichen Kolleg:innen der Zahnmedizin und Autor:innen des BARMER Zahnreports erfolgte die Planung und Durchführung einer gemeinsamen retrospektiven Routinedatenanalyse zur Assoziation zwischen entzündlichen Zahnerkrankungen und PAVK, um Ansatzpunkte für Präventionsmaßnahmen zu identifizieren.[19] In einer weiteren longitudinalen Analyse der Routinedaten wurde die Inzidenz maligner Erkrankungen in der Zielpopulation als relevanter Langzeit-Endpunkt ermittelt.[24] Auf dem Boden einer systematischen Analyse der verfügbaren internationalen Praxisleitlinien zur PAVK-Behandlung erfolgte ein Abgleich der Leitlinienempfehlungen zur optimalen Arzneimitteltherapie mit der Versorgungsrealität.[23,28] Hierzu konnten bemerkenswerte Abweichungen und ein Verbesserungspotential identifiziert werden, was in mehreren Originalarbeiten und korrespondierenden Reviews bzw. Editorials aufgearbeitet wurde. Auf dem Boden einer im Dezember 2018 beginnenden Kontroverse zur Langzeitsterblichkeit nach Anwendung mit Paclitaxel-beschichteter Hochrisikomedizinprodukte (Referenz-Nr. 00092/19 des Bundesinstitut für Arzneimittel und Medizinprodukte) in der PAVK-Behandlung erfolgte eine umfassende Aufarbeitung dieser Forschungsfragestellung im Rahmen des IDOMENEO-Projekts, wobei komplexe methodische Limitationen identifiziert und teilweise überwunden werden konnten.[21,22,32] Das Forschungsthema war außerdem für das Gesamtprojekt relevant, weil die Identifizierung und valide Messung der betroffenen Medizinprodukte auch für den Abgleich mit den Primärerhebungen aus dem Register erforderlich waren. Insgesamt konnten während des IDOMENEO-Projekts mehrere Originalarbeiten und zahlreiche Editorials, Reviews und Buchkapitel zu diesem Thema publiziert werden. Ein zentrales Thema in der PAVK-Behandlung stellen geschlechterspezifische Unterschiede und die valide Abbildung beider Geschlechter in unterschiedlichen Primär- und Sekundärdatenquellen dar. Im Rahmen verschiedener Arbeiten konnten die Routinedaten für Langzeitanalysen genutzt werden.[23,26,27,29]

Während der Primärdatenerhebung zwischen 1. Mai 2018 und 31. Dezember 2020 zeigten sich zunehmend Verzögerungen bei der Rekrutierung von Patient:innen im GermanVasc-


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Register. Trotz umfassender Aufklärungs- und Gegenmaßnahmen blieb die Rekrutierung und erreichte Fallzahl hinter der erwarteten Anzahl zurück. Die wissenschaftliche Projektleitung hat während der Rekrutierungsphase auf verschiedenen nationalen und internationalen wissenschaftlichen Kongressen der Fachgesellschaften den Dialog mit den Zentrumsverantwortlichen Projektleiter:innen gesucht und im Rahmen zahlreicher Gespräche mit den Studienteams vor Ort Lösungen erörtert. Im Rahmen von strukturierten Nutzerbefragungen und durch das externe Monitoring wurden vor allem personelle Ressourcendefizite als hauptursächlich beschrieben. Die Rekrutierungsverzögerungen wurden mehrfach mit dem Konsortium und mit dem wissenschaftlichen Beirat kommuniziert. Letztlich wurde vor dem Hintergrund der nicht erreichbaren Fallzahlplanung eine aufwandsneutrale Laufzeitverlängerung um 12 Monate bis zum 31. März 2021 beantragt, wobei eine Powerkalkulation mit entsprechend angepassten Fallzahlen zu der Schlussfolgerung führte, dass keine Gefährdung der Projektziele bestand. Durch die im Frühjahr 2020 einsetzende pandemische Situation mit eingeschränkten Krankenhausleistungen, Quarantänemaßnahmen und Kontaktbeschränkungen kam es zu einer weiteren Einschränkung der Rekrutierung sowie Follow-up-Erhebungen. In zahlreichen Gesprächen wurde deutlich, dass viele Zentren während der COVID-19-Pandemie keine forschungsrelevanten Patientenkontakte ohne klinische Indikation durchführen konnten.

Bis zum 31. Dezember 2020 wurden etwa 5.600 Patient:innen im GermanVasc-Register eingeschlossen. Die Baseline-Charakteristika der eingeschlossenen Kohorte wurden kurz vor Ende der Förderdauer publiziert.[31]

## 5. Methodik

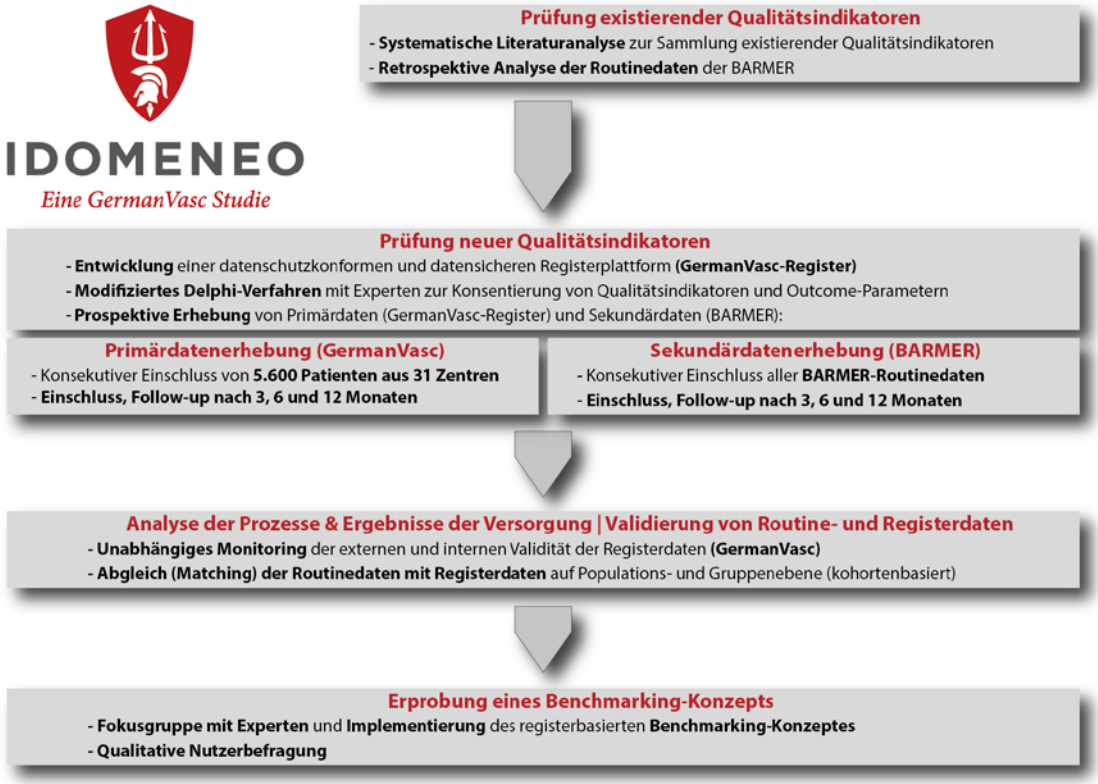


*Abbildung 1: Schematische Darstellung des multimethodalen und mehrstufigen IDOMENEO-Projekts.*

Bei dem hier beschriebenen multimethodalen mehrstufigen Projekt wurden verschiedene Studiendesigns und -typen angewandt (Abbildung 1). Weiterführende Details zu den


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Datenquellen und statistischen Analysen sind den unter Abschnitt 9) aufgeführten projektspezifischen Publikationen zu entnehmen (Anlage 4).[1,4,7,10,18,19-24,26-32]

**Entwicklung von Qualitätsindikatoren**

Die Entwicklung von Qualitätsindikatoren erfolgte in mehreren Schritten. Eine Vordefinition (a priori) von Qualitätsaspekten, -Merkmalen und -Zielen erfolgte im Rahmen der konzeptionellen Vorarbeit nicht.

a) Im ersten Schritt wurde eine systematische Sammlung potenzieller Qualitätsindikatoren durchgeführt. Hierzu wurde eine systematische Literaturübersicht zu Leitlinien, systematischen Reviews und Metaanalysen durchgeführt, deren Methodik im Unterkapitel „**5. Methodik/Systematische Literaturrecherche**“ nachfolgend beschrieben wird. Die Ergebnisse aus der systematischen Literaturrecherche und einer zusätzlichen narrativen Literaturrecherche zu Suchbegriffen „PAVK“ und „Register“ oder „Ergebnisse“ wurden anschließend in einem modifizierten Delphi-Verfahren mit Experten abgestimmt, dessen Methodik im Unterkapitel „**5. Methodik/Modifizierte Delphi-Verfahren mit Experten**“ nachfolgend beschrieben wird.

b) Im zweiten Schritt erfolgte eine Prüfung, welche Qualitätsindikatoren mit Routinedaten abbildbar sind. Hierfür wurden geeignete Aufgreifkriterien für die Qualitätsindikatoren aus Schritt a) in den Routinedaten der BARMER identifiziert. Die Methodik der retrospektiven Routinedatenanalysen werden im Unterkapitel „**5. Methodik/Retrospektive Routinedatenanalysen**“ nachfolgend beschrieben.

c) Im dritten Schritt ist eine Erfassung der Qualitätsindikatoren aus Schritt a) in einem Register erfolgt, dessen Methodik im Unterkapitel „**5. Methodik/ Prospektive Registerdatenanalysen**“ nachfolgend beschrieben wird.

d) Im letzten Schritt ist ein deskriptiver Vergleich der Ergebnisse zu den Qualitätsindikatoren aus Schritt a) anhand der Routinedaten- und Registeranalysen erfolgt.

**Retrospektive Routinedatenanalysen**

Es handelt sich um retrospektive Beobachtungsstudien im Längsschnittdesign mit faktisch anonymisierten verknüpfbaren bundesweit erhobenen Routinedaten über das konzerneigene Wissenschafts-Data-Warehouse (W-DWH) der BARMER. Je nach Berichtsjahr (1. Januar 2005 bis 31. Dezember 2020) enthielt die Datenbasis etwa 9,1 Mio. Versicherte und schloss damit ca. 13% der Zielpopulation ein. Auf der Website des BARMER Instituts für Gesundheitssystemforschung (www.bifg.de) sind bereits zahlreiche Publikationen und Berichte veröffentlicht worden, die im Rahmen von wissenschaftlichen Kooperationen mit dieser Datenbasis entstanden sind.

Von hervorgehobener Bedeutung und zentral für die in diesem Bericht beschriebenen Analysen sind die im W-DWH verfügbaren faktisch anonymisierten Versichertenstammdaten (§ 288 SGB V) sowie Daten zur stationären und ambulanten Versorgung (§ 301, § 115 ff. SGB V), zur vertragsärztlichen Versorgung (§ 295 SGB V), zu Arzneimittelabrechnungen (§ 300 SGB V), zur Vorsorge und Rehabilitation (§ 301 SGB V), zur Arbeitsunfähigkeit (§ 295 SGB V), zur Heilmittelversorgung (§ 302 SGB V), zur Versorgung chronisch Kranker (§ 137f SGB V) und zur Pflege (§§ 36–38, § 41 SGB XI; § 37, § 43 SGB V). Die Daten liegen, je nach Sektor und Datenbasis, zum Beispiel in Form einheitlicher Diagnose- (ICD-10-GM) und Prozedurencodes (OPS) vor oder als Arzneimittel- (ATC) bzw. Gebührenziffer (EBM) vor.[7,10]

Zugegriffen wurde auf Forschungsdaten, die zwischen 1. Januar 2005 und 31. Dezember 2020 erhoben wurden. Der Datenlieferungsverzug (Verfügbarkeit von faktisch anonymisierten Forschungsdaten im W-DWH nach deren primärer Erhebung zu Abrechnungszwecken) betrug ca. drei bis sechs Monate, wobei nach sechs Monaten von


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einer ausreichenden Vollständigkeit der Abrechnungsdaten auszugehen war. Die spezifischen Analysen erfolgten über entsprechend abgesicherte verschlüsselte Tunnel und ferngesteuerte SAS- sowie R-Applikationen. Die Berichterstattung erfolgte in Übereinstimmung mit den gängigen Empfehlungen[39,44] und Leitlinien der Deutschen Gesellschaft für Epidemiologie (DGEpi) und der Deutschen Gesellschaft für Sozialmedizin und Prävention (DGSMP) sowie Empfehlungen der Arbeitsgruppe Erhebung und Nutzung von Sekundärdaten (AGENS).

Ausführliche Informationen zur Datenbasis sowie zu Vorteilen und Limitationen von Routinedaten in der Qualitätsentwicklung und Versorgungsforschung sind dem folgenden Übersichtsartikel (Open Access) zu entnehmen, der während der Projektlaufzeit gemeinsam mit Autor:innen der BARMER und DAK-Gesundheit entstanden ist:[10]

Peters F, Kreutzburg T, Kuchenbecker J, Marschall U, Remmel M, Dankhoff M, Trute HH, Repgen T, Debus ES, Behrendt CA. Quality of care in surgical/interventional vascular medicine: what can routinely collected data from the insurance companies achieve? Gefässchirurgie. 2020;25:19-28. https://doi.org/10.1007/s00772-020-00679-4

Die Zielpopulation im IDOMENEO-Projekt umfasste stationär konservativ-pharmakologisch, endovaskulär und offen-chirurgisch behandelte Patient:innen mit einer symptomatischen PAVK in den Stadien II (Claudicatio intermittens), III (ischämische Ruheschmerzen) und IV (Wundheilungsstörungen und diabetisches Fußsyndrom) nach der Fontaine-Klassifikation. Je nach Selektionsstrategie, Matching- oder Gewichtungsverfahren konnten zwischen 20.000 bis 200.000 individuelle Patient:innen in die Analysen eingehen. Eine Verknüpfung mit anderen Datenquellen bzw. eine Reidentifizierung von Zentren oder Patient:innen erfolgte aufgrund rechtlicher Bestimmungen nicht. Neben multivariaten Regressionsanalysen erfolgte die Adjustierung für Störfaktoren in der Regel durch Propensity Score Matching oder Gewichtungsverfahren. Wenn erforderlich, erfolgte eine Korrektur multiplen Testens durch Bonferroni oder gegebenenfalls Bonferroni-Holm. Fehlende Werte wurden in der Regel durch den Ausschluss der Fälle (Complete Cases) adressiert, wobei dies nur in ca. 0,5% der Fälle auftrat.

Weitere Details zu den Ein- und Ausschlusskriterien sowie zu den genutzten Aufgreifkriterien und statistischen Analyseverfahren sind dem Protokoll[7] und den Einzelpublikationen (Open Access) zu entnehmen:[19-24,26,28,29,32]

Kreutzburg T, Peters F, Rieß HC, Hischke S, Marschall U, Kriston L, L´Hoest H, Sedrakyan A, Debus ES, Behrendt CA. Editor´s Choice - Comorbidity Patterns among Patients with Peripheral Arterial Occlusive Disease in Germany – A Trend Analysis of Health Insurance Claims Data. Eur J Vasc Endovasc Surg. 2020;59:59-66. https://doi.org/10.1016/j.ejvs.2019.08.006

Aarabi G, Raedel M, Kreutzburg T, Hischke S, Debus ES, Marschall U, Seedorf U, Behrendt CA. Periodontal Treatment and Peripheral Arterial Occlusive Disease Severity - A Retrospective Analysis of Health Insurance Claims Data. VASA. 2020;49:128-132. https://doi.org/10.1024/0301-1526/a000846

Kaschwich M, Peters F, Hischke S, Rieß HC, Gansel M, Marschall U, L'Hoest H, Heidemann F, Debus ES, Acar L, Kreutzburg T, Behrendt CA. Long-term incidence of cancer after index treatment for symptomatic peripheral arterial occlusive disease – A health insurance claims data analysis. VASA. 2020;49:493-499. https://doi.org/10.1024/0301-1526/a000901

Behrendt CA, Sedrakyan A, Peters F, Kreutzburg T, Schermerhorn M, Bertges DJ, Larena-Avellaneda A, L'Hoest H, Kölbel T, et al. Editor´s Choice - Long Term Survival After Femoropopliteal Artery Revascularizations With Paclitaxel-Coated Devices – A propensity score matched cohort analysis. Eur J Vasc Endovasc Surg. 2020;59:587-596. https://doi.org/10.1016/j.ejvs.2019.12.034

Heidemann F, Peters F, Kuchenbecker J, Kreutzburg T, Sedrakyan A, Marschall U, L'Hoest H, Debus ES, Behrendt CA. Long-term outcomes after revascularizations below the knee with paclitaxel-coated devices – a propensity score matched cohort analysis. Eur J Vasc Endovasc Surg. 2020;60:549-558. https://doi.org/10.1016/j.ejvs.2020.06.033

Behrendt CA, Sedrakyan A, Katsanos K, Nordanstig J, Kuchenbecker J, Kreutzburg T, Secemsky EA, Debus ES, Marschall U, Peters F. Sex Disparities in Long-Term Mortality after Paclitaxel Exposure in Patients with Peripheral Artery Disease: A Nationwide Claims-Based Cohort Study. J Clin Med. 2021;10:2978. https://doi.org/10.3390/jcm10132978

Heidemann F, Kuchenbecker J, Peters F, Kotov A, Marschall U, L'Hoest H, Acar L, Ramkumar N, Goodney P, Debus ES, Rother U, Behrendt CA. A health insurance claims analysis on the impact of female sex on long-term outcomes after peripheral endovascular interventions for symptomatic peripheral arterial occlusive disease. J Vasc Surg. 2021;74:780-787.E7. https://doi.org/10.1016/j.jvs.2021.01.066

Kotov A, Heidemann F, Kuchenbecker J, Peters F, Marschall U, Acar L, Debus ES, L'Hoest H, Behrendt CA. Sex Disparities in Long-Term Outcomes after Open Surgery for Chronic Limb-Threatening Ischaemia – A Propensity Score Matched Analysis of Health Insurance Claims. Eur J Vasc Endovasc Surg. 2021;61:423-429. https://doi.org/10.1016/j.ejvs.2020.11.006

Peters F, Kreutzburg T, Rieß HC, Heidemann F, Marschall U, L'Hoest H, Debus ES, Sedrakyan A, Behrendt CA. Editor´s Choice - Optimal pharmacological treatment of symptomatic peripheral arterial occlusive disease and evidence of female patient disadvantage: An analysis of health insurance claims data. Eur J Vasc Endovasc Surg. 2020;60:421-429. https://doi.org/10.1016/j.ejvs.2020.05.001


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Peters F, Kuchenbecker J, Kreutzburg T, Marschall U, Debus ES, Behrendt CA. Long-Term Effectiveness and Safety of Initiating Statin Therapy After Index Revascularization In Patients With Peripheral Arterial Occlusive Disease. J Am Heart Assoc. 2020;9:e018338. https://doi.org/10.1161/JAHA.120.018338

**Prospektive Routinedatenanalysen**

Zum Abgleich der im GermanVasc-Register prospektiv eingeschlossenen Kohorte mit der bundesweiten Versichertenkohorte im BARMER W-DWH wurden alle stationär durchgeführten Revaskularisationen der symptomatischen PAVK im gleichen Erhebungszeitraum zwischen 1. Mai 2018 und 31. Dezember 2020 eingeschlossen. Die Aufgreifkriterien und Endpunkte entsprechen den retrospektiven Routinedatenanalysen.

Die wesentlichen Basischarakteristika der Kohorten sowie ausgewählte Ergebnisqualitätsindikatoren wurden anschließend miteinander verglichen, um den Einfluss des Selektionsbias bzw. die Übertragbarkeit der Kohorten zu prüfen.

**Prospektive Registerdatenanalysen**

Es handelt sich um eine prospektive klinische Kohortenstudie im Längsschnittdesign. Das Protokoll zur Studie wurde bei Clinicaltrials.gov (NCT03098290) und beim Deutschen Register Klinischer Studien (DRKS00014649) registriert. Eine positive ethische Begutachtung erfolgte durch die federführende Ethikkommission der Ärztekammer Hamburg (PV5691).[4,7] Etwa 18 assoziierte positive Ethikvoten durch alle beratungszuständigen Ethikkommissionen der Bundesländer und Institutionen wurden sukzessive nach dem Eingang des Primärvotums erteilt.

Die Zielpopulation setzte sich aus Patient:innen ≥18 Jahren mit stationären invasiven endovaskulären, offen-chirurgischen oder Hybridrevaskularisationen der chronischen symptomatischen PAVK zusammen, wobei eine Einteilung nach der Fontaine-Klassifikation in Patient:innen mit Claudicatio intermittens (Fontaine-Stadium II), ischämischen Ruheschmerzen (Fontaine-Stadium III) oder ischämischen Wundheilungsstörungen (Fontaine-Stadium IV bzw. angioneuropathisches diabetisches Fußsyndrom) vorgenommen wurde. Eingeschlossen wurde zwischen dem 1. Mai 2018 (First-patient-in) und dem 31. Dezember 2020 (Last-patient-out).

Akute embolische Gefäßverschlüsse ohne Hinweis auf eine ursächliche chronische PAVK wurden ausgeschlossen.

Nach der expliziten informierten Einwilligung der Patient:innen erfolgte die Datenerhebung im Behandlungsaufenthalt sowie nach 3, 6 und 12 Monaten (Follow-up). Alle Erhebungsparameter wurden im Rahmen von modifizierten Delphi-Verfahren mit Expert:innen konsentiert. Die Basiserhebung umfasste folgende Variablen: Alter, Geschlecht, Aufnahmedatum, Aufnahmeart, ambulante Versorgung, funktioneller Status, Mobilität, Entlassungsdatum, Entlassungsziel, Körpergewicht, Körpergröße, American Society of Anesthesiologists (ASA) Risikoklassifikation, Diabetes, Niereninsuffizienz, Serum-Kreatinin, Tabakkonsum, koronare Herzkrankheit, Herzinsuffizienz, Herzrhythmusstörungen, chronische obstruktive Lungenerkrankung, Bluthochdruck, Revaskularisationen oder Amputationen in der Vorgeschichte, optimale Arzneimitteltherapie bei Aufnahme und Entlassung, modifizierte Rutherford-Klassifikation vor der Behandlung, Fußinfektion, Knöchel-Arm-Index (Ankle-Brachial-Index), Gewebeverlust, endovaskuläre Revaskularisation, Bypass-Operation, Endarteriektomie, postoperatives akutes Koronarsyndrom, postoperativer Schlaganfall, postoperative Dialyse, ungeplante Amputation, postoperativer Verschluss der Indexrevaskularisation, postoperative Dissektion, Graft- oder Deviceversagen, postoperative Blutung, postoperatives Kompartmentsyndrom, postoperative Wundinfektion, Fragebogen zum Gesundheitszustand (siehe Anlage 2).

Die Follow-up-Erhebungen umfassten folgende Variablen: Lebensstatus, funktioneller Status, Mobilität, modifizierte Rutherford-Klassifikation, Fußinfektion, Knöchel-Arm-Index (Ankle-Brachial-Index), Gewebeverlust, Amputation, Offenheit der



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Indexrevaskularisation, erneute Revaskularisation, Major Adverse Cardiovascular Events (MACE), erneute stationäre Aufnahme, Major Adverse Limb Events (MALE), Myokardinfarkt, Schlaganfall oder transiente ischämische Attacke, Wundinfektion im Operationsbereich, schwere Blutungskomplikation.

Die prospektive Messung der Lebensqualität und weiterer patientenberichteter Endpunkte erfolgte durch Verwendung eines kombinierten generischen und spezifischen Fragebogens durchgeführt (siehe folgender Abschnitt).

Eine Fallzahlkalkulation erfolgte auf dem Boden hochgerechneter Routinedatenanalysen und Selbstangaben der Zentren. Zusätzlich ist eine Powerkalkulation mit verfügbaren Literaturangaben erfolgt (Abbildung 2).

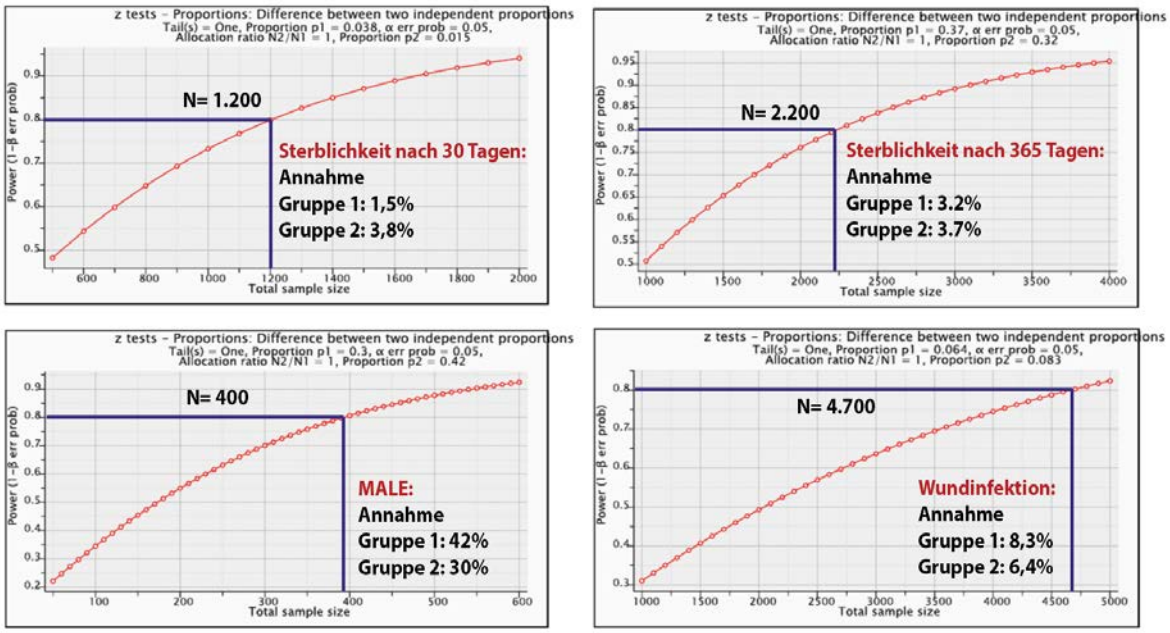


*Abbildung 2: Fallzahlkalkulation im Rahmen der prospektiven GermanVasc-Kohortenstudie.*

Für alle weiteren Endpunkte waren jeweils kleinere Stichprobengrößen erforderlich.

Für die Angabe deskriptiver Analyseergebnisse werden absolute und relative Raten (%) für kategoriale Variablen und Mittelwerte mit Standardabweichungen bzw. Mediane mit Interquartilsabständen für kontinuierliche Variablen verwendet. Für die Vergleiche mit Follow-up-Erhebungen wurden nur vollständige Datensätze verwendet, um den drohenden Selektionsbias (Unterrepräsentation von Patient:innen mit unerwünschten Verläufen in den Follow-up-Erhebungen) zu adressieren.

Ein Signifikanzniveau <0.05 wurde festgelegt. Eine Korrektur für multiples Testen erfolgte nicht.

**Prüfung der gesundheitsbezogenen Lebensqualität und anderer patientenrelevanter Endpunkte zur Evaluation des Behandlungsergebnisses**

Zur Evaluation der Implementierbarkeit der Messung von Lebensqualität und anderer patientenrelevanter Endpunkte für PAVK-Patient:innen wurde die Verwendung eines generischen und eines spezifischen Fragebogens geplant. Zunächst ist eine umfassende narrative Literaturrecherche und eine Fokusgruppendiskussion mit internationalen Registerexperten aus 28 Ländern durchgeführt worden. Ziel war die Identifizierung von patientenberichteten Endpunkten und etablierten Fragebögen in der praktischen Anwendung im Rahmen von Qualitätsregistern. Hierbei wurde durch die Teilnehmer festgestellt, dass die Erhebung von patientenberichteten Endpunkten nur lückenhaft und heterogen erfolgt. In den meisten etablierten Registern wurde der sogenannte VascuQoL-


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6 verwendet. In der Literaturrecherche konnten insgesamt 145 verschiedene Einzelitems identifiziert werden, die formal als patientenberichtete Variable geeignet wären. Die Entwicklung des Fragebogens zum Gesundheitszustand folgte folgenden Auswahlkriterien der Konstrukte und Instrumente: Das Konzeptmodell von Wilson und Cleary[45] und der COMET Initiative[46] sollte ebenso berücksichtigt werden, wie generelle PAVK-spezifische Aspekte der Funktionsfähigkeit, Gesundheitswahrnehmung und Lebensqualität. Es wurde eine psychometrische Validierung auf Grundlage systematischer Reviews gefordert und das Ausfüllen sollte in der Praxis so kurz wie möglich sein,[47,48,49] um den Routinebetrieb nicht zu gefährden. Der GermanVasc-Fragebogen enthielt zwölf Fragen zum Gesundheitszustand (SF-12), vier Fragen zur Gehfähigkeit (WELCH), zwei Fragen zum Schmerzempfinden (PROMIS, VascuQoL), vier Fragen zum seelischen Wohlbefinden (PHQ-4) und zwei Fragen zum Berufsstatus. Außerdem wurde abgefragt, ob eine Unterstützung durch Angehörige oder Gesundheitspersonal beim Ausfüllen erforderlich war. Der Fragebogen wurde in Papierform an die eingeschlossenen Patient:innen ausgehändigt und anschließend durch das Studienzentrum in das elektronische Erhebungsformular überführt. Die Bewertung der Implementierbarkeit folgte keinen a priori festgelegten oder allgemein anerkannten Kriterien. Herangezogen wurde die Rate an Fragebögen, die ohne Unterstützung ausgefüllt werden konnten sowie die allgemeine Responserate (Rückläufer) nach 3, 6 und 12 Monaten. A priori festgelegte Grenzwerte für die Implementierbarkeit, z.B. zur Responserate, existierten ebenfalls nicht, weshalb nur eine deskriptive Beschreibung erfolgte.

**Systematische Literaturrecherche**

Eine Publikation des Protokolls zur systematischen Literaturrecherche ist bei PROSPERO erfolgt (CRD42019116317).

Population: Eingeschlossen wurden Publikationen, die Patient:innen mit chronischer PAVK untersuchten. Es wurden keine Einschränkungen bezüglich Alter, Geschlecht und Ausprägung der Erkrankung getroffen. Ausgeschlossen wurden Patient:innen mit ausschließlich akuten embolischen Gefäßverschlüssen.

Intervention: Eingeschlossen wurden Publikationen, die sich auf die invasive revaskularisierende Therapie der Zielpopulation beziehen. Dazu zählten offen-chirurgische, endovaskuläre und Hybridverfahren. Ausgeschlossen wurden Publikationen, die sich ausschließlich auf die konservative oder medikamentöse Therapie beziehen. Ebenfalls ausgeschlossen wurde die Stammzelltherapie und primäre Amputationstherapie.

Endpunkt: Eingeschlossen wurden Publikationen, die Qualitätsindikatoren beschreiben. Es wurden Prozess-, Struktur- und Ergebnisindikatoren eingeschlossen. Die Qualitätsindikatoren mussten dem allgemeinen und akzeptierten Aufbau eines Qualitätsindikators entsprechen. Ausgeschlossen wurden Beschreibungen, die nicht den Mindestanforderungen eines Qualitätsindikators genügten: (1) numerische Darstellung, (2) Definitionen für Qualitätsziel und (3) Messverfahren.

Publikationstyp: Eingeschlossen wurden Publikationen, die vor dem 1. Dezember 2017 veröffentlicht wurden. Dieses Datum wurde gewählt, da die Literaturrecherche im Dezember 2017 durchgeführt wurde. Eingeschlossen wurden Publikationen in deutscher oder englischer Sprache. Diese Einschränkung wurde getroffen, da für andere Sprachen keine ausreichenden Sprachkenntnisse vorhanden waren. Eingeschlossen wurden folgende Publikationstypen und Grauliteratur: systematische Übersichtsarbeit, Metaanalyse, Leitlinie, Konsensusdokumente, Empfehlung von Fachgesellschaften, Qualitätsindikatordatenbank. Andere Publikationstypen wurden ausgeschlossen (z.B. narrative Übersichtsarbeit, randomisiert kontrollierte Studie (RCT), sonstige klinische Studien, Fallbericht).


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Für die Recherche wurden neben der US Nationalbibliothek für medizinische Literatur (PubMed) auch zahlreiche weitere einschlägige Datenbanken genutzt: TripDatabase, AWMF, Leitlinien.de, Bundesärztekammer, AGREE, BMJ Clinical Evidence, Cochrane, eGuidelines by MGP Ltd, Guidelines Central, Guidelines International Network G-I-N, National clinical guideline center, National Guideline Clearinghouse (NGC), National Institute for Health and Care Excellence (NICE), NICE Evidence, New Zealand Guidelines Group, Scottish Intercollegiate Guidelines Network, Agency of Healthcare Research and Quality, American College of Surgeons NSQIP, American College of Cardiology, American College of Chest Physicians, American Heart Association, Canadian Cardiovascular Society, Clinical Indicator Program, European Society of Cardiology, European Society for Vascular Surgery, National Quality Forum, Society for Cardiovascular Angiography and Interventions, Society for Vascular Surgery, Vascular Cures, Vascular Disease-Foundation, Vascular Quality Initiative, Deutsche Gesellschaft für Angiologie, Deutsche Gesellschaft für Gefäßchirurgie und Gefäßmedizin, Institut für Qualitätssicherung und Transparenz im Gesundheitswesen, BQS Institut für Qualität & Patientensicherheit, Externe Qualitätssicherung Hamburg, GKV-Spitzenverband Qualitätsindikatorenthesaurus, Indicator and Measurement Registry of the WHO, Institut für angewandte Qualitätsförderung und Forschung im Gesundheitswesen, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, National Quality Measures Clearinghouse, Agency for Healthcare Research and Quality, National Health Service England, Health and Social Care Information Centre of the National Health Service England, Physiciancs Consortium for Performance Improvement of the American Medical Association, National Commission for Quality Assurance. Es erfolgte zudem in Übereinstimmung mit dem ursprünglichen Protokoll eine Recherche grauer Literatur.

Weitere Details zur systematischen Literaturrecherche sind der Publikation (Open Access) zu entnehmen:[18]

Hischke S, Rieß HC, Bublitz MK, Kriston L, Schwaneberg T, Härter M, Bertges D, Debus ES, Behrendt CA. Quality Indicators in Peripheral Arterial Occlusive Disease Treatment: A Systematic Review. Eur J Vasc Endovasc Surg. 2019;58:15-22. https://doi.org/10.1016/j.ejvs.2019.06.029

**Modifizierte Delphi-Verfahren mit Experten**

Zur Abstimmung der Indikatoren der Ergebnisqualität sowie der weiteren Variablen, die in der prospektiven GermanVasc-Kohortenstudie erhoben werden sollen, wurden drei modifizierte Delphi-Verfahren mit Experten durchgeführt. Hierbei bestand das Expertenpanel aus Vertretern eines internationalen Qualitätsregisterkonsortiums (VASCUNET) sowie aus interdisziplinären Gefäßmediziner:innen. Die Repräsentativität der Expertengruppen war auf die angebundenen Forschungsnetzwerke mit insgesamt 28 regionalen und nationalen Gefäßregistern in Europa, Asien, Südamerika und den USA limitiert.

Delphi-Verfahren 1) Auf der Basis der Ergebnisse der systematischen Sammlung potenzieller Qualitätsindikatoren, einer zusätzlichen narrativen Literaturrecherche zu Suchbegriffen „PAVK“ und „Register“ oder „Ergebnisse“, einer Extraktion von Erhebungsvariablen in bestehenden internationalen PAVK-Registern und einer ergänzenden Umfrage unter 31 Experten aus 14 Registern wurden insgesamt 187 mögliche Variablen in die erste Umfragerunde eingefügt. Die zentrale Fragestellung war, welche Variablen in Registern zur Behandlung der PAVK erhoben werden sollten. In insgesamt fünf moderierten online-basierten Umfragerunden mit dazwischenliegenden Gruppendiskussionen wurden die Variablen hinsichtlich ihrer Relevanz mittels einer 5-Punkt-Likert-Skala bewertet. Für die Umfragerunden wurde die Open Source Software Limesurvey genutzt. Die Gruppendiskussionen fanden jeweils über eine Online-Videokonferenzsoftware (Cisco Webex Meeting) und zusätzlich drei Mal im Rahmen lokaler Konferenzen statt. Die schriftlichen Aufarbeitungen der Abstimmungsergebnisse und Kommentare wurden jeweils vor der nächsten Abstimmung in Form von PDF-Reports zusammengestellt und unter den Experten zirkuliert. Eine Zustimmung (agree, strongly


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agree) in zwei aufeinanderfolgenden Runden wurde als Kriterium für deren Empfehlung verwendet. Die Endergebnisse wurden in Form des Manuskripts zur Publikation für eine Kommentierung und Freigabe unter den Experten zirkuliert.[15]

Behrendt CA, Bertges D, Eldrup N, Beck AW, Mani K, Venermo M, Szeberin Z, Menyhei G, Thomson I, Heller G, Wigger P, Danielsson G, Galzerano G, Lopez C, Altreuther M, Sigvant B, Rieß HC, Sedrakyan A, Beiles B, Björck M, Boyle JR, Debus ES, Cronenwett J. International Consortium of Vascular Registries Consensus Recommendations for Peripheral Revascularization Registry Data Collection. Eur J Vasc Endovasc Surg. 2018;56:217-237. https://doi.org/10.1016/j.ejvs.2018.04.006

Delphi-Verfahren 2) Auf der Basis des ersten Delphi-Verfahrens wurde ein weiteres modifiziertes Delphi-Verfahren durchgeführt, zu dem 40 internationale Expert:innen eingeladen wurden. In insgesamt zwei moderierten online-basierten Umfragerunden mit dazwischenliegenden Gruppendiskussionen wurden 117 mögliche Variablen hinsichtlich ihrer klinischen Relevanz und Praktikabilität bewertet. Die Bewertung erfolgte dabei subjektiv durch die Experten und ohne a priori festgelegte Gütekriterien. Als Mindestkriterium für die Empfehlung wurde eine Zustimmung für beide Kategorien (agree, strongly agree) in zwei aufeinanderfolgenden Runden mit 5-Punkt-Likert-Skala genutzt. Die Gruppendiskussionen fanden über eine Online-Videokonferenzsoftware (Zoom Meeting) und zusätzlich zwei Mal im Rahmen lokaler Konferenzen statt. Die schriftlichen Aufarbeitungen der Abstimmungsergebnisse und Kommentare wurden jeweils vor der nächsten Abstimmung in Form von PDF-Reports zusammengestellt und unter den Experten zirkuliert. Die Endergebnisse wurden in Form des Manuskripts zur Publikation für eine Kommentierung und Freigabe unter den Experten zirkuliert.[17]

Behrendt CA, Björck M, Schwaneberg T, Debus ES, Cronenwett J, Sigvant B. Editor's Choice – Recommendations for Registry Data Collection for Revascularisations of Acute Limb Ischaemia: A Delphi Consensus from the International Consortium of Vascular Registries. Eur J Vasc Endovasc Surg. 2019;57:816-821. https://doi.org/10.1016/j.ejvs.2019.02.023

Delphi-Verfahren 3) Die Zusammenstellung der Follow-up-Erhebung und die klinisch relevanten sowie praktikabel erhebbaren Ergebnisqualitätsindikatoren (Outcomes) wurden im Rahmen eines dritten Delphi-Verfahrens mit interdisziplinären Gefäßmediziner:innen aus Deutschland konsentiert. Das Expertenpanel unterschied sich damit von den vorhergehenden Delphi-Verfahren, da eine international einheitliche Festlegung von Qualitätsindikatoren auf dem Boden der immanenten Unterschiede zwischen den Gesundheitssystemen nicht als umsetzbar erschien. Hierbei wurden die gleichen Kriterien zur Bewertung der klinischen Relevanz und Praktikabilität, wie in den beiden vorgenannten Verfahren angewandt. Die Bewertung erfolgte dabei durch die Experten und subjektiv ohne a priori festgelegte Gütekriterien. Insgesamt wurden 43 mögliche Ergebnisqualitätsindikatoren in zwei aufeinanderfolgenden Abstimmungsrunden bewertet. Die Ergebnisse der Zwischenrunden wurden in Form von strukturierten Berichten mit Diagrammen und Kommentaren unter den Teilnehmern zirkuliert und in einer Online-Konferenz diskutiert (Zoom). Die Endergebnisse wurden allen Experten in Form des Manuskripts zur Publikation übermittelt.[16]

Rieß HC, Debus ES, Schwaneberg T, Hischke S, Maier J, Bublitz M, Kriston L, Härter M, Marschall U, Zeller T, Schellong SM, Behrendt CA. Indicators of Outcome Quality in Peripheral Arterial Disease Revascularisations - A Delphi Expert Consensus. VASA. 2018;47:491-497. https://doi.org/10.1024/0301-1526/a000720

**Fokusgruppendiskussionen**

Im IDOMENEO-Projekt wurden insgesamt fünf Fokusgruppendiskussionen durchgeführt, um Impulse und Gruppenmeinungen zu den folgenden Themen zu generieren: a) Ausgestaltung einer innovativen datenschutzkonformen Registerplattform für die Durchführung der prospektiven Kohortenstudie unter klinischen Alltagsbedingungen, b) Abbildbarkeit von Qualitätsindikatoren in Routinedaten, c) Patientenberichtete Endpunkte in Qualitätsregistern, d) Benchmarking-Aspekte in der klinischen Routine und Registerforschung. Die homogene Auswahl der Teilnehmer erfolgte unter der Zielvorgabe, möglichst gleichermaßen betroffene Personen einzubinden (z.B. klinische Anwender:innen eines Qualitätsregisters bei der Diskussion von Benchmarking-Aspekten, Versorgungsforscher:innen mit Erfahrung in der Routinedatenanalyse). Es erfolgte jeweils eine Einleitung zum Thema mit Präsentation der zentralen Fragestellung. Anschließend


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erfolgte die moderierte Diskussion über 45 Minuten, wobei sowohl Verständnis- und Vertiefungsfragen als auch vorbereitete Diskussionsaspekte eingeworfen wurden. Aufwandsentschädigungen wurden nicht erstattet.

**Erprobung von Benchmarking anhand Rückmeldungen zur Versorgungsqualität aus dem Register**

Die in der prospektiven Registererhebung verarbeiteten medizinischen Daten zur Behandlung der PAVK sollten zur Erprobung eines Benchmarkings zwischen den teilnehmenden Zentren genutzt werden. Eingangs erfolgte die Durchführung einer Fokusgruppendiskussion mit klinischen Anwender:innen zu „Benchmarking-Aspekten in der klinischen Routine und Registerforschung“, bei der die etablierten Lösungen internationaler Register (z.B. Vascular Quality Initiative, Swedvasc) in Form einer Präsentation vorgestellt und anschließend diskutiert wurden. Die Vorschläge der Teilnehmer bzw. Ergebnisse der Fokusgruppendiskussion wurden anschließend von den Softwareentwicklern technisch umgesetzt. Die Erprobung sah die technische Einführung einer Feedbackfunktion zu medizinischen Daten und Qualitätsindikatoren der Behandlung in der Registerplattform vor, die von einem Newsletter für alle Zentrumsadministratoren und Aufruf zur Testung und kritischen Rückmeldungen begleitet wurden. Die Erprobung war nicht an a priori festgelegte Gütekriterien gebunden, sondern sollte nur die technische Machbarkeit feststellen.

## 6. Projektergebnisse

1. Entwicklung von Qualitätsindikatoren

Im Projekt wurden insgesamt 12 Indikatoren der Ergebnisqualität entwickelt: Major Adverse Cardiovascular Event (MACE), Major Adverse Limb Event (MALE), Myokardinfarkt, Schlaganfall oder transiente ischämische Attacke, Gesamtsterblichkeit, Majoramputation (oberhalb Knöchelebene), Major-Reintervention, jede Reintervention, Wundinfektion, zugangsbedingte Majorkomplikation, Zunahme der maximalen schmerzfreien Gehstrecke, Zunahme der Rutherford-Klassifikation.

a) Systematische Sammlung potenzieller Qualitätsindikatoren

Im Rahmen der systematischen Literaturrecherche wurden 611 Publikationen über die Literaturdatenbank PubMed identifiziert. Weitere 73 Publikationen und 65 Qualitätsindikatoren wurden als Grauliteratur über 41 Webseiten identifiziert.[18]

Nach der Entfernung von 45 Duplikaten wurden 639 Publikationen auf Titel- und Abstractebene evaluiert. Für 81 eingeschlossene Publikationen wurden die Volltexte evaluiert. Insgesamt wurden zwei Studien und drei Qualitätsindikatoren eingeschlossen: Eine systematische Übersichtsarbeit von Bellmunt et al.[38] und ein Konsensuspapier von Olin et al.[37]:

- Anteil der Patient:innen mit Bypass-Transplantation in der Vorgeschichte, denen Thrombozytenaggregationshemmer verschrieben werden
- Anteil der derzeitigen Raucher:innen, nach Bypass-Transplantation, denen eine Maßnahme zur Rauchentwöhnung verschrieben wird
- Monitoring von Venen-Bypass-Transplantaten der unteren Extremitäten

In der Grauliteratur zusätzlich identifizierte Qualitätsindikatoren:

Bestimmung des Fontaine-Stadiums, Indikation nach dem Fontaine-Stadium, Indikationsabstimmung, Überprüfung mit dem Laufband, Präinterventioneller Dopplerverschlussdruck, Indikation von Stents in der Beckenetage, Statintherapie bei Entlassung nach einem Bypass der unteren Extremitäten, Verfahren, bei denen bei der


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Entlassung Statine und Thrombozytenaggregationshemmer verschrieben werden, Gerinnungshemmende Medikation bei perkutaner transluminaler Angioplastie, Ausbleiben schwerwiegender technischer Komplikationen während peripherer arterieller Eingriffe, Rate der chirurgischen Konversion von endovaskulären Revaskularisierungsverfahren der unteren Extremitäten, Postinterventionelles Angiogramm, Postinterventioneller Dopplerverschlussdruck, Verbesserung des Knöchel-Arm-Index (Ankle-Brachial-Index), Postinterventionelle Rest-Stenose, Postinterventionelle Komplikation, Bestimmung der Durchgängigkeit des infrainguinalen Bypasses aufgrund von Claudicatio intermittens mindestens 9 Monate nach chirurgischem Eingriff, Bestimmung der Durchgängigkeit der peripheren vaskulären Intervention mindestens 9 Monate nach einer infrainguinalen peripheren vaskulären Intervention aufgrund von Claudicatio intermittens, Amputationsfreies Überleben mindestens 9 Monate nach einer infrainguinalen Bypassoperation aufgrund von Claudicatio intermittens, Amputationsfreies Überleben mindestens 9 Monate nach einer suprainguinalen Bypassoperation aufgrund von Claudicatio intermittens, Amputationsfreies Überleben mindestens 9 Monate nach einer peripheren vaskulären Intervention aufgrund von Claudicatio intermittens, Wundinfektionsrate (gesamt) nach arterieller Rekonstruktion der unteren Extremität, Wundinfektionsrate (inhouse) nach arterieller Rekonstruktion der unteren Extremität, Krankenhausspezifisches risikoadjustiertes Maß der Sterblichkeit oder schwerer Komplikationen innerhalb von 30 Tagen nach einer Bypassoperation der unteren Extremitäten, Re-Intervention innerhalb von 12 Monaten, Fachliche Befähigung zur interventionellen Radiologie, Apparative Voraussetzung zur interventionellen Radiologie, Räumliche und organisatorische Voraussetzungen zur interventionellen Radiologie, Räumliche und organisatorische Voraussetzungen für die Nachbetreuung bei interventioneller Radiologie, Aufrechterhaltung der fachlichen Befähigung zur interventionellen Radiologie, Dokumentation von diagnostischen Katheterangiographien oder therapeutischen Eingriffen.

Im Rahmen eines zweistufigen modifizierten Delphi-Verfahrens mit interdisziplinären Expert:innen wurden alle Ergebnisqualitätsindikatoren diskutiert und um eigene Vorschläge erweitert.[16] 40 Expert:innen aus allen beteiligten Fachdisziplinen und Berufsgruppen wurden eingeladen. 30 Expert:innen partizipierten in der ersten Delphi-Runde und 24 Expert:innen beendeten die zweite Delphi-Runde. Insgesamt wurden 12 Ergebnisqualitätsindikatoren mit konsensueller Übereinstimmung durch das Gremium empfohlen:

- Major Adverse Cardiovascular Event (MACE)
- Major Adverse Limb Event (MALE)
- Myokardinfarkt
- Schlaganfall oder transiente ischämische Attacke
- Gesamtsterblichkeit
- Majoramputation (oberhalb Knöchelebene)
- Major-Reintervention
- Jede Reintervention
- Wundinfektion
- Zugangsbedingte Majorkomplikation
- Zunahme der maximalen schmerzfreien Gehstrecke
- Zunahme der Rutherford-Klassifikation

Diese vorgenannten 12 Ergebnisqualitätsindikatoren wurden für die Register- und Routinedatenerhebungen im Projekt verwendet.[16]

Für die Ergänzung der Erhebungsformulare wurden die geeigneten Variablen zur Beschreibung der Risikofaktoren und Behandlungsparameter durch zwei weitere Delphi-


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Verfahren konsentiert. Hierbei konnten 79 Variablen (aus 187 bewerteten Variablen) für die chronische[15] und 35 Variablen (aus 117 bewerteten Variablen) für die akute[17] Behandlung der Patient:innen konsentiert werden, die in die elektronischen Erhebungsformulare integriert wurden.

b) Prüfung, welche Qualitätsindikatoren mit Routinedaten valide abbildbar sind

Im Rahmen der verschiedenen Routinedatenanalysen im IDOMENEO-Projekt wurde die Nutzung bzw. Eignung der Ergebnisqualitätsindikatoren in Versorgungsforschungs- und Qualitätsentwicklungsprojekten mit Routinedaten geprüft (Tabelle 1 und 2).

Ein Vorteil von Routinedaten ist deren longitudinale Verknüpfbarkeit. Hierdurch war ein patientenbezogener Ansatz möglich, während verschiedene Qualitätssicherungsregister oder die Daten des Instituts für das Entgeltsystem im Krankenhaus GmbH (InEK) bzw. die Krankenhausdiagnosestatistik des Bundes (Destatis) aufgrund des fall- bzw. prozedurbezogenen Ansatzes nur einen verzerrten Einblick in die Versorgungsrealität ermöglichen.

Zu den in der verfügbaren Literatur am meisten genutzten Composite-Endpunkten gehören das sogenannten Major Adverse Cardiovascular Event (MACE), Major Adverse Limb Event (MALE) sowie das amputationsfreie Überleben (AFS).

Gängige Definitionen schließen dabei Myokardinfarkt, Koronarrevaskularisation, kardiale stationäre Behandlungen, Schlaganfall oder transiente ischämische Attacke, Tod kardialer Ursache und Tod jeder Ursache in den Composite-Endpunkt MACE ein. Aufgrund der Kodierpraxis und Limitationen bei der Todesursachenstatistik in Deutschland ist der Tod kardialer Ursache nicht valide verfügbar, während eine Annäherung an alle anderen Endpunkte mit guter interner Validität möglich erscheint. In der für Routinedatenanalysen angepassten Definition wurde das Überleben ohne kardiovaskuläre Ereignisse genutzt, wobei Myokardinfarkte bzw. Koronarrevaskularisationen, Schlaganfälle und Tod eingeschlossen wurden.

In einer Fokusgruppendiskussion wurde die Frage bearbeitet, welche der entwickelten Ergebnisqualitätsindikatoren valide mit Routinedaten abzubilden sind. Hierbei wurden Versorgungsforscher mit Erfahrungen in der Routinedatenanalyse und Kodierung gefäßmedizinischer Leistungen eingeladen. Im Rahmen des Impulsvortrags wurden die insgesamt zwölf Ergebnisqualitätsindikatoren nacheinander besprochen.

Auf dem Boden der Fokusgruppendiskussion und Aufbereitung der verfügbaren Forschungsdaten kam das Konsortium zu dem Schluss, dass eine relevante Anzahl an Wundinfektionen nicht vollständig in den Routinedaten abgebildet wird. Dies betrifft insbesondere nach der stationären Entlassung ambulant oder primär konservativ durchgeführte Wundbehandlungen. Es ist außerdem davon auszugehen, dass bei endovaskulären Interventionen die zugangsbedingten Majorkomplikationen nicht vollständig erfasst werden, da teilweise endovaskuläre Techniken bzw. Medizinprodukte (z.B. gecoverte Stents) zu deren Behandlung genutzt werden, die nicht als Komplikationsbehandlung markiert werden. Die Behandlung von Blutungskomplikationen mit manueller Kompression bzw. Druckverband sowie gerinnungsfördernden Enzymen ist zusätzlich nicht vollständig in den verfügbaren Daten enthalten.

Die Verbesserung der schmerzfreien Gehstrecke gilt als patientenberichteter Endpunkt und damit nicht mit ausreichender Validität verfügbarer Endpunkt in Routinedaten, wobei eine Annäherung durch die klinischen Stadien mittels Fontaine-Klassifikation teilweise möglich ist. Allerdings ist auch hierbei mit Einschränkungen der Validität und Seitenbeziehbarkeit zu berücksichtigen, weshalb die beiden letztgenannten Ergebnisqualitätsindikatoren nicht valide in Routinedaten verfügbar sind.


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Zusammenfassend sind folgende Ergebnisqualitätsindikatoren in Routinedaten zur Behandlung von Patient:innen mit symptomatischer PAVK abbildbar: Gesamtsterblichkeit, Myokardinfarkt, Schlaganfall, Majoramputation, Re-Intervention, modifiziertes MACE (kardiovaskuläres Event oder Tod), modifiziertes MALE (Amputation oder Tod).


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*Tabelle 1: Ergebnisse der retrospektiven BARMER-Routinedatenauswertungen im IDOMENEO-Projekt; Konfidenzintervall (CI), Interquartilsabstand (IQR), Major Adverse Cardiovascular Event (MACE), Major Adverse Limb Event (MALE), Intermittent Claudication (IC), Chronic Limb-Threatening Ischaemia (CLTI). Die Ergebnisse nach 1 Jahr wurden mit Kaplan-Meier-Schätzern ermittelt.*

| **Endpunkt** | **Krankenhausaufenthalt** | | | **Nach 1 Jahr (Kaplan-Meier-Schätzer)** | | |
|---|---|---|---|---|---|---|
| Index-Behandlung: 2010-2018 | **IC+CLTI** | **IC** | **CLTI** | **IC+CLTI** | **IC** | **CLTI** |
| **Anzahl, N** | **69.701** | **41.378** | **28.323** | **69.701** | **41.378** | **28.323** |
| **Weiblich, n (%)** | 32.289 (46,3) | 18.227 (44,0) | 14.062 (49,6) | 32.289 (46,3) | 18.227 (44,0) | 14.062 (49,6) |
| **Median Alter, Jahre [IQR]** | **72,6** [63,9-79,1] | **69,7** [61,7-76,3] | **77,0** [68,6-84,1] | **72,6** [63,9-79,1] | **69,7** [61,7-76,3] | **77,0** [68,6-84,1] |
| **Gesamtsterblichkeit, n (%) bzw. % (95% CI)** | 1.274 (1,8) | 121 (0,3) | 1.153 (4,1) | **11,3** (11,1-11,6) | **3,5** (3,4-3,7) | **22,7** (22,2-23,2) |
| **Myokardinfarkt, n (%)** | 627 (0,9) | 194 (0,5) | 433 (1,5) | **4,1** (3,9-4,2) | **3,3** (3,2-3,5) | **5,3** (5,0-5,5) |
| **Schlaganfall, n (%)** | 336 (0,5) | 120 (0,3) | 216 (0,8) | **3,4** (3,2-3,5) | **2,3** (2,1-2,4) | **5,2** (4,9-5,5) |
| **Majoramputation, n (%)** | 943 (1,4) | 37 (0,1) | 906 (3,2) | **2,1** (2,0-2,2) | **0,3** (0,3-0,4) | **5,1** (4,8-5,4) |
| **Re-Intervention, % (95% CI)** | - | - | - | **20,0** (19,7-20,3) | **19,3** (18,9-19,7) | **21,6** (21,0-22,1) |
| **Modifiziertes MACE: Kardiovaskuläres Event oder Tod, % (95% CI)** | - | - | - | **16,2** (15,9-16,5) | **8,0** (7,8-8,3) | **28,1** (27,6-28,7) |
| **Modifiziertes MALE: Amputation oder Tod, % (95% CI)** | - | - | - | **12,5** (12,3-12,8) | **3,8** (3,6-3,9) | **25,3** (24,8-25,8) |

*Tabelle 2: Ergebnisse der prospektiven Routinedatenauswertung im IDOMENEO-Projekt; Konfidenzintervall (CI), Interquartilsabstand (IQR), Major Adverse Cardiovascular Event (MACE), Intermittent Claudication (IC), Chronic Limb-Threatening Ischaemia (CLTI). Die Ergebnisse nach 1 Jahr wurden mit Kaplan-Meier-Schätzern ermittelt.*

| **Endpunkte** | **Nach 12 Monaten** | | |
|---|---|---|---|
| BARMER, Indexbehandlung: 2018-2020 | **IC+CLTI** | **IC** | **CLTI** |
| **Anzahl, N** | **30.055** | **16.427** | **13.628** |
| **Weiblich, n (%)** | 13.508 (44,9) | 7.340 (44,7) | 6.168 (45,3) |
| **Median Alter, J [IQR]** | **73,8** [65,3-80,6] | **70,5** [63,3-77,9] | **77,8** [68,9-83,4] |
| **Gesamtsterblichkeit, % (95% CI)** | **12,3** (11,9-12,7) | **3,7** (3,4-4,0) | **23,0** (22,2-23,7) |
| **Myokardinfarkt, % (95% CI)** | **0,4** (0,3-0,5) | **0,2** (0,2-0,3) | **0,6** (0,5-0,8) |
| **Schlaganfall, % (95% CI)** | **0,2** (0,2-0,3) | **0,1** (0,0-0,2) | **0,4** (0,2-0,5) |
| **Majoramputation, % (95% CI)** | **2,1** (2,0-2,3) | **0,3** (0,2-0,4) | **4,7** (4,3-5,1) |
| **Re-Intervention, % (95% CI)** | **25,3** (24,8-25,9) | **24,4** (23,6-25,1) | **26,8** (25,9-27,6) |
| **Modifiziertes MACE: Kardiovaskuläres Event oder Tod, % (95% CI)** | **12,7** (12,3-13,1) | **4,0** (3,6-4,3) | **23,4** (22,7-24,2) |
| **Amputationsfreies Überleben, % (95% CI)** | **12,6** (12,2-13,0) | **3,7** (3,4-4,0) | **23,6** (22,8-24,4) |

c) <u>Prospektive Erfassung der Qualitätsindikatoren in einem Register</u>

In die prospektive GermanVasc-Kohortenstudie wurden insgesamt 5.608 Patient:innen eingeschlossen. Die Basischarakteristika zum Einschlusszeitpunkt (Indexbehandlung) sind der nachfolgenden Publikation (Open Access) zu entnehmen (Anlage 4):

Kotov A, Peters F, Debus ES, Zeller T, Heider P, Stavroulakis K, Remig J, Gussmann A, Hoffmann J, Friedrich O, Nolte T, Behrendt CA. The prospective GermanVasc cohort study. VASA. 2021;In Press. https://doi.org/10.1024/0301-1526/a000966



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Nach 12 Monaten (366 Tage im Median) lagen für insgesamt 2.901 Patient:innen (34,7% Frauen, 69 Jahre im Median) vollständige Follow-up-Erhebungen aus 31 Gefäßzentren vor (Tabelle 3).

Insgesamt 29,9% (95% CI 28,7-31,1) der Kohorte wurde wegen einer kritischen extremitätengefährdenden Ischämie (Fontaine Stadium III oder IV) behandelt, wobei 12,5% (95% CI 11,6-13,4) notfallmäßige Behandlungen waren. Mehr als die Hälfte (54,9%; 95% CI 53,5-56,2) hatten zuvor bereits invasive Revaskularisationen der PAVK und der Anteil der endovaskulären Verfahren betrug 69,3% (95% CI 68,1-70,4). Beim Risikoprofil wiesen 34,5% (95% CI 33,2-35,7) der Patient:innen eine schwere Systemerkrankung und 3,1% (95% CI 2,7-3,6) eine ständige Lebensbedrohung auf. Insgesamt 75,0% (95% CI 73,8-76,1) waren aktive oder frühere Raucher, 35,7% (95% CI 34,5-37,0) hatten eine Diabetesdiagnose und 36,1% (95% CI 34,8-37,4) eine ischämische Herzerkrankung. Zum Zeitpunkt der stationären Entlassung erhielten 93,5% (95% CI 92,8-94,1) eine gerinnungshemmende Therapie mit einem Thrombozytenaggregationshemmer und 76,5% (95% CI 75,4-77,6) ein Statin.

In einer Analyse der Langzeitergebnisse nach 12 Monaten wurden 5.042 Patient:innen mit vollständigen Daten zu femoro-poplitealen Revaskularisationen eingeschlossen. Hiervon wurden 3.428 (68,0%) perkutan endovaskulär, 562 (11,1%) mittels Bypass, 643 (12,8%) mittels offen-chirurgischer Endarteriektomie und 409 (8,1%) mittels Hybridverfahren behandelt. Nach Ausschluss aortaler Interventionen und Patient:innen mit fehlenden Daten konnten 4.354 vollständige Datensätze in die vergleichenden Analysen eingehen. Das Follow-up lag dabei nach 12 Monaten in 75% der Fälle vollständig vor. Nach Adjustierung für relevante Störfaktoren (höheres Alter, Fontaine-Stadium III/IV vs. II, Geschlecht, Rauchen, Versorgungsstatus, Übergewicht, patientenberichteter Gesundheitsstatus, Arbeitslosigkeit, ASA-Klasse, vorhergehende Koronarrevaskularisation, vorhergehende PAVK-Behandlung, Diabetes, Herzinsuffizienz, Statinverordnung, Thrombozytenaggregationshemmung) zeigten sich keine statistisch signifikanten Unterschiede bei den Komposit-Endpunkten Majoramputation oder Tod (Hazard Ratio 1,35, 95% CI 0,95-1,90 für Bypasschirurgie vs. endovaskuläre Intervention), Major Adverse Limb Events (MALE, Hazard Ratio 1,14, 95% CI 0,68-1,93) und jedwede Amputation (Hazard Ratio 0,93, 95% CI 0,69-1,26).

Eine Auswertung der projektrelevanten Ergebnisqualitätsindikatoren ergab die in Tabelle 3 aufgeführten Inzidenzen. Insgesamt waren 3,1% (95% CI 2,5-3,8) der Patient:innen nach 12 Monaten verstorben, die Rate an MACE und MALE betrug 8,5% (95% CI 7,5-9,6) bzw. 7,0% (95% CI 6,1-8,0). Ein Myokardinfarkt trat bei 2,2% (95% CI 1,7-2,8) und ein Schlaganfall/TIA bei 1,7% (95% CI 1,3-2,3) auf. Insgesamt 2,7% (95% CI 2,1-3,3) der Patient:innen wurden oberhalb der Knöchelebene amputiert. Hinsichtlich der Wundheilungsstörungen bzw. Wundinfektionen des chirurgischen und interventionellen Zugangs innerhalb von 12 Monaten zeigte sich eine Rate von 7,6% (95% CI 6,7-8,6).

d) Vergleich der Ergebnisse aus der prospektiven Registerstudie mit der prospektiven Routinedatenanalyse aus dem gleichen Zeitraum

Für einen Vergleich der Ergebnisse der prospektiven Primärdatenerhebung im GermanVasc-Register mit der bundesweiten BARMER-Versichertenkohorte im selben Zeitraum wurden die zentralen Ergebnisqualitätsindikatoren und Charakteristika miteinander verglichen. Sowohl bei der Alters- und Geschlechterverteilung als auch bei den Ergebnisindikatoren zeigten sich substanzielle Unterschiede, was einen Direktvergleich ausschließt. So war die Kohorte des GermanVasc-Registers seltener weiblich (34% vs. 45%) und im Median fast fünf Jahre jünger (69 vs. 74 Jahre) als die Routinedatenkohorte (Tabelle 3). Entsprechend unterscheiden sich auch die Indikatoren der Ergebnisqualität, wobei in der prospektiven Registererhebung eine relevante und statistisch signifikante Unterschätzung der Gesamtsterblichkeit (3,1% vs. 12,3%, $p<0.001$)


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zu beobachten war. Somit ist die Versorgungsrealität in Primärerhebungen (inkl. randomisierten kontrollierten Studien) mit ausgewählten Zentren nicht ohne Weiteres vergleichbar mit der flächendeckenden Versorgungsrealität in Sekundäranalysen.

*Tabelle 3: Ergebnisse der prospektiven GermanVasc-Kohortenstudie im IDOMENEO-Projekt; Konfidenzintervall (CI), Interquartilsabstand (IQR), Major Adverse Cardiovascular Event (MACE), Major Adverse Limb Event (MALE), Intermittent Claudication (IC), Chronic Limb-Threatening Ischaemia (CLTI), N/A: Nicht zutreffend.*

| **Endpunkte** | **Nach 12 Monaten** | | |
|---|---|---|---|
| GermanVasc Kohorte | **IC+CLTI** | **IC** | **CLTI** |
| **Baseline: Anzahl, N** | **5.608** | **3.932** | **1.676** |
| **Baseline: Weiblich, % (95% CI)** | 34.0 (32,7-35,3) | 33,8 (32,3-35,4) | 34,3 (32,0-36,7) |
| **Baseline: Median Alter, J [IQR]** | **69** (62-77) | **68** (61-76) | **72** (64-80) |
| **Gesamtsterblichkeit, % (95% CI)** | **3,1** (2,5-3,8) | **1,1** (0,7-1,7) | **7,7** (6,0-9,7) |
| **MACE, % (95% CI)** | **8,5** (7,5-9,6) | **6,0** (5,0-7,1) | **14,5** (12,3-17,1) |
| **MALE, % (95% CI)** | **7,0** (6,1-8,0) | **4,6** (3,7-5,6) | **12,6** (10,4-15,0) |
| **Myokardinfarkt, % (95% CI)** | **2,2** (1,7-2,8) | **2,0** (1,4-2,7) | **2,8** (1,8-4,1) |
| **Schlaganfall oder TIA, % (95% CI)** | **1,7** (1,3-2,3) | **1,2** (0,8-1,8) | **2,9** (1,9-4,2) |
| **Majoramputation, % (95% CI)** | **2,7** (2,1-3,3) | **0,3** (0,1-0,6) | **8,2** (6,5-10,2) |
| **Postoperative Wundinfektion im stationären Aufenthalt, % (95% CI)** | **3,6** (3,2-4,1) | **2,1** (1,7-2,6) | **6,9** (5,7-8,0) |
| **Jede Wundinfektion nach dem Eingriff (12 Monate), % (95% CI)** | **4,2** (3,4-4,9) | **2,7** (2,0-3,4) | **7,6** (5,9-9,4) |
| **Postoperative Zugangsgefäßkomplikation (inklusive Blutung und Aneurysma spurium), % (95% CI)** | **4,1** (3,6-4,7) | **3,6** (3,0-4,1) | **5,4** (4,3-6,4) |
| **Zunahme der schmerzfreien Gehstrecke, % (95% CI)** | **N/A** | **82,8** (81,0-84,6) | **N/A** |
| **Verbesserung der Rutherford-Klassifikation, % (95% CI)** | **75,5** (74,0-77,1) | **78,7** (77,0-80,5) | **67,7** (64,6-70,8) |

2. <u>Prüfung der gesundheitsbezogenen Lebensqualität und anderer patientenrelevanter Endpunkte zur Evaluation des Behandlungsergebnisses</u>

Im Rahmen der narrativen Literaturrecherche und anschließenden Fokusgruppendiskussion mit internationalen Registerexperten wurden 145 Items bzw. Erhebungsvariablen zum Gesundheitszustand bzw. zur gesundheitsbezogenen Lebensqualität in acht unterschiedlichen Domänen identifiziert. Die überwiegende Zahl der internationalen Qualitätsentwicklungsregister erhebt gegenwärtig entweder keine patientenberichteten Endpunkte (n=11), nutzt den VascuQoL-6 Fragebogen (n=4) oder alternative Fragebögen, wie EQ-5D-5L (n=2) oder Walking Impairment Questionnaire (n=1).

Der im Rahmen der GermanVasc-Registerstudie entwickelte Fragebogen zum Gesundheitszustand wurde bei der Basiserhebung nur von ca. 74% der Patient:innen mit Claudicatio intermittens und von 73% der Patient:innen mit chronischer extremitätengefährdender Ischämie ausgefüllt (Abbildung 3). Hierbei waren etwa 21% der Patient:innen mit Claudicatio intermittens und 36% der Patient:innen mit chronischer extremitätengefährdender Ischämie auf eine aktive Unterstützung beim Ausfüllen


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angewiesen. Bei den Follow-up-Erhebungen nach 3, 6 und 12 Monaten lagen nur ca. 42%, 32% und 21% der Bögen von Patient:innen mit Claudicatio intermittens bzw. 30%, 22% und 21% von Patient:innen mit chronischer extremitätengefährdender Ischämie vor. Bei den Freitextkommentaren zur Begründung für die fehlenden Erhebungsbögen wurde am häufigsten registriert, dass die Patient:innen die Befragung zum Gesundheitszustand ablehnten.

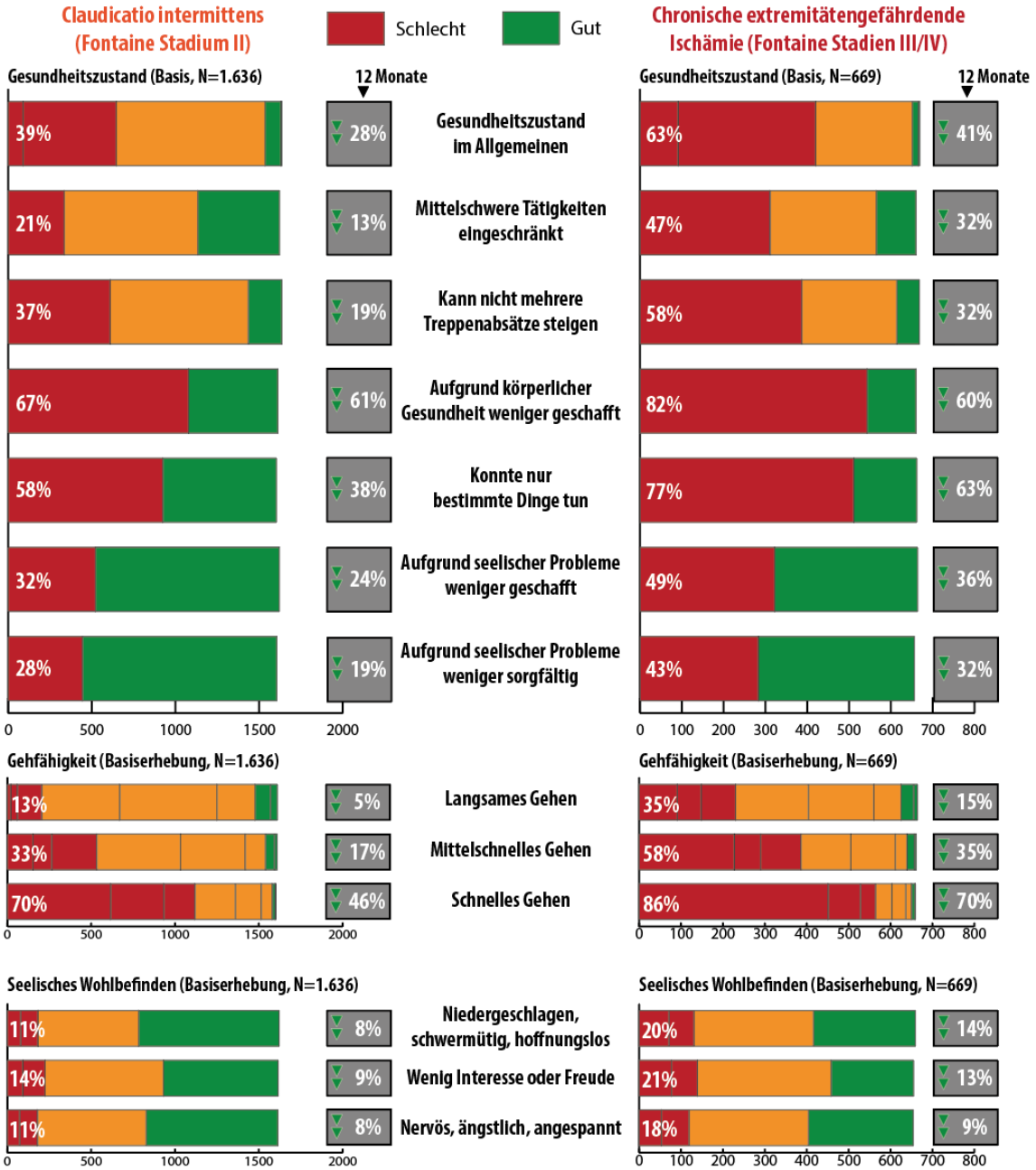


*Abbildung 3: Darstellung der patientenberichteten Endpunkte in der Basiserhebung und Veränderungen (Rate an schlechten patientenberichteten Outcomes) nach 12 Monaten in der GermanVasc-Kohortenstudie. Eingegangen sind Patient:innen, bei denen der Fragebogen zum Gesundheitszustand sowohl in der Basiserhebung als auch im 12-Monats-Follow-up vorlag. Stratifiziert nach Patient:innen mit Claudicatio intermittens vs. chronischer extremitätengefährdender Ischämie.*

Die Rate an Rückmeldungen, die auf einen schlechten Gesundheitszustand, Gehfähigkeit oder seelisches Wohlbefinden hindeuten war höher bei Patient:innen mit chronischer extremitätengefährdender Ischämie als bei Claudicatio intermittens (Abbildung 3). Bei einem stratifizierten Vergleich der vollständigen Erhebungen nach 12-Monaten mit der Basiserhebung war in allen Einzelfragen eine Verbesserung der patientenberichteten Endpunkte zu sehen. So haben 39% der Patient:innen mit Claudicatio intermittens und


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63% der Patient:innen mit chronischer extremitätengefährdender Ischämie bei der Basiserhebung angegeben, dass sie ihren Gesundheitszustand im Allgemeinen mit weniger gut oder schlecht beschreiben würden. Nach 12 Monaten waren es 28% bzw. 41%. In einer Sensitivitätsanalyse mit bzw. ohne Einschränkung auf vollständige Basis- und Follow-up-Erhebungen zeigten sich bei den Domänen Gesundheitszustand und Gehfähigkeit nur geringe Abweichungen von <1%, während beim seelischen Wohlbefinden ein relevanter Unterschied von bis zu 5% beobachtet werden konnte.

3. Analyse der Prozesse und Ergebnisse der Versorgung

a) Retrospektiv anhand von Routinedaten

Insgesamt sind 10 retrospektive Beobachtungsstudien mit Routinedaten im IDOMENEO-Projekt veröffentlicht worden (siehe Abschnitt 9, Anlage 4), die explorativ auf dem Boden der eingangs festgelegten Fragestellungen geplant wurden. Es wurden die einschlägigen Leitlinien zur Berichterstattung und Sekundärdatenanalyse verwendet. Die Analysestrategien und Angaben zur Operationalisierung der Einzelanalysen sind den jeweils genannten Einzelpublikationen sowie den elektronischen Supplements zu entnehmen, die Open Access veröffentlicht wurden.

Kreutzburg T, Peters F, Rieß HC, Hischke S, Marschall U, Kriston L, L´Hoest H, Sedrakyan A, Debus ES, Behrendt CA. Editor´s Choice - Comorbidity Patterns among Patients with Peripheral Arterial Occlusive Disease in Germany – A Trend Analysis of Health Insurance Claims Data. Eur J Vasc Endovasc Surg. 2020;59:59-66. https://doi.org/10.1016/j.ejvs.2019.08.006

In einer Analyse von insgesamt 156.217 Patient:innen und 202.961 stationären Behandlungen der PAVK (49,4% im Stadium der CLTI, 47,3% Frauen) zwischen 1. Januar 2008 und 31. Dezember 2016 wurden die Komorbiditätsprofile und Behandlungscharakteristika untersucht (**Fragestellung a**). Eine Untersuchung auf alters- und geschlechtsstandardisierte Trends erfolgte mit dem Jonckheere-Terpstra Test. Eine Korrektur für multiples Testen erfolgte nicht. Die Operationalisierung der Komorbiditätsgruppen erfolgte mit der Elixhauser-Klassifikation. Hierbei gingen 97.537 erstmalige (Index)Behandlungen in die alters- und geschlechtsstandardisierten Analysen ein. Während eine Zunahme der jährlichen Behandlungsfallzahl und Prävalenz um +25,1% bzw. +23,1% sowie eine Zunahme der endovaskulären Revaskularisationsverfahren um +61,1% beobachtet wurden, ging die jährliche Krankenhausinzidenz um -4,4% zurück. Im gleichen Zeitraum zeigte sich eine Zunahme der stationären Behandlungskosten in der Zielpopulation um etwa +31% (mediane jährliche Behandlungskosten: 6.076 €, IQR: 3.215-10.146 €) und eine Abnahme der Majoramputationen um -15,1%. Beim Komorbiditätsprofil der Zielpopulation zeigten sich seltenere Diagnosen von Diabetes, Herzinsuffizienz und Adipositas trotz einer Zunahme des medianen Patient:innenalters, während eine zunehmende Häufigkeit von Bluthochdruck, Elektrolytstörungen, Niereninsuffizienz, Hypothyroidismus, Koagulopathie, Depression, neurodegenerativen Erkrankungen und kardialen Arrhythmien verzeichnet wurde.

Kaschwich M, Peters F, Hischke S, Rieß HC, Gansel M, Marschall U, L'Hoest H, Heidemann F, Debus ES, Acar L, Kreutzburg T, Behrendt CA. Long-term incidence of cancer after index treatment for symptomatic peripheral arterial occlusive disease – A health insurance claims data analysis. VASA. 2020;49:493-499. https://doi.org/10.1024/0301-1526/a000901

In einer Analyse von 96.528 Patient:innen mit stationären Indexbehandlungen der symptomatischen PAVK (47% Frauen, 44% IC, mittleres Alter 72 Jahre) zwischen 1. Januar 2008 und 31. Dezember 2017 wurde die Langzeit-Inzidenz von malignen Erkrankungen in der Zielpopulation gegenüber der deutschen Gesamtbevölkerung untersucht (**Fragestellung b**). Geschlechterstratifizierte standardisierte Inzidenzraten wurden auf dem Boden der Standardbevölkerung für Deutschland (2012) berechnet und für Alter adjustiert. Eine Korrektur für multiples Testen erfolgte nicht. Zur Operationalisierung der malignen Erkrankungen wurden die entsprechenden C-Diagnosen der Krebsentitäten in der ICD-Diagnose-Nomenklatur verwendet. Die alters- und geschlechtsstandardisierte Inzidenzratio von Lungenkrebs (Frauen: 2,6x vs. Männer: 3,5x), Blasenkrebs (Frauen: 3,2x


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vs. Männer: 4,0x), und Pankreaskrebs (Frauen: 1,4x vs. Männer: 1,6x) war in der PAVK-Kohorte signifikant höher. Während des 10-jährigen Follow-ups wurde bei 7% der Männer und 4% der Frauen eine Lungenkrebsdiagnose festgestellt.

Peters F, Kreutzburg T, Rieß HC, Heidemann F, Marschall U, L'Hoest H, Debus ES, Sedrakyan A, Behrendt CA. Editor´s Choice - Optimal pharmacological treatment of symptomatic peripheral arterial occlusive disease and evidence of female patient disadvantage: An analysis of health insurance claims data. Eur J Vasc Endovasc Surg. 2020;60:421-429. https://doi.org/10.1016/j.ejvs.2020.05.001

Peters F, Kuchenbecker J, Kreutzburg T, Marschall U, Debus ES, Behrendt CA. Long-Term Effectiveness and Safety of Initiating Statin Therapy After Index Revascularization In Patients With Peripheral Arterial Occlusive Disease. J Am Heart Assoc. 2020;9:e018338. https://doi.org/10.1161/JAHA.120.018338

In einer Analyse von Routinedaten zu 83.867 Patient:innen mit stationären Indexbehandlungen der symptomatischen PAVK (45,8% Frauen, mittleres Alter 71,9 Jahre) wurden die Leitlinienadhärenz der optimalen Arzneimitteltherapie und geschlechterspezifische Unterschiede untersucht (**Fragestellung c und d**). Als optimale Arzneimitteltherapie wurde dabei die Verschreibung einer antihypertensiven, antithrombotischen und lipidsenkenden Medikation operationalisiert. Generalisierte lineare Modelle (logit link) zur binäre Analysen und logistische Regressionen wurden genutzt, um für relevante Störfaktoren zu adjustieren. Eine Korrektur für multiples Testen erfolgte nicht. Frauen wiesen eine seltenere Rate an vorhergehenden ambulanten PAVK-Diagnosen (39,8% vs. 47,0%) auf, wurden häufiger im Stadium der CLTI mit ischämischen Ruheschmerzen behandelt (13,9% vs. 10,4%) und waren älter (74 vs. 70 Jahre). Die Rate an optimalen Arzneimittelverschreibungen nach der Krankenhausentlassung war bei Frauen niedriger (37,0% vs. 42,7%), was sich insbesondere auf Unterschiede bei der Statinverordnung zurückführen ließ (52,4% vs. 59,9%). In einer Analyse der zugrundeliegenden Faktoren erklärten insbesondere patientenspezifische und systembezogene Faktoren (z.B. Komorbiditäten, Demographie, Vorbehandlungen) bis zu 56% dieser Geschlechterlücke. Über den Zeitverlauf der Studie zeigte sich eine Zunahme der Verschreibungsraten, wobei die geschlechterspezifischen Unterschiede stabil blieben.

In einer weiterführenden Analyse wurde die Verschreibungsrealität der Statine und deren möglicher Zusatznutzen in der Zielpopulation untersucht (**Fragestellung c**). In einer Propensity-Score gematchten Analyse von 22.208 Patient:innen (10.922 gematcht) konnte gezeigt werden, dass eine Statinverordnung bei zuvor unterversorgten Patient:innen sowohl im Stadium der Claudicatio intermittens (Hazard Ratio 0,80, 95% CI 0,70-0,92) als auch im Stadium der chronischen extremitätengefährdenden Ischämie (Hazard Ratio 0,75, 95% CI 0,68-0,84) mit einer niedrigeren Gesamtsterblichkeit assoziiert war. Für das Matching (nearest neighbor) wurden diejenigen Parameter und Elixhauser-Gruppen verwendet, die in den bivariaten Analysen entsprechend relevante Unterschiede aufwiesen. Ein Cochrane Armitage Trendtest wurde zur Analyse von Statinverordnungsraten verwendet. Eine Korrektur für multiples Testen erfolgte nicht. Auch die Rate an Majoramputationen bei CLTI (Hazard Ratio 0,73, 95% CI 0,58-0,93) und kardiovaskuläre Eventraten bei IC (Hazard Ratio 0,80, 95% CI 0,70-0,92) waren während des 5-Jahres-Follow-up signifikant niedriger. Die Sicherheitsendpunkte inzidenter Diabetes und Myopathien waren dagegen nicht unterschiedlich.

Behrendt CA, Sedrakyan A, Peters F, Kreutzburg T, Schermerhorn M, Bertges DJ, Larena-Avellaneda A, L'Hoest H, Kölbel T, et al. Editor´s Choice - Long Term Survival After Femoropopliteal Artery Revascularizations With Paclitaxel-Coated Devices – A propensity score matched cohort analysis. Eur J Vasc Endovasc Surg. 2020;59:587-596. https://doi.org/10.1016/j.ejvs.2019.12.034

Heidemann F, Peters F, Kuchenbecker J, Kreutzburg T, Sedrakyan A, Marschall U, L'Hoest H, Debus ES, Behrendt CA. Long-term outcomes after revascularizations below the knee with paclitaxel-coated devices – a propensity score matched cohort analysis. Eur J Vasc Endovasc Surg. 2020;60:549-558. https://doi.org/10.1016/j.ejvs.2020.06.033

Behrendt CA, Sedrakyan A, Katsanos K, Nordanstig J, Kuchenbecker J, Kreutzburg T, Secemsky EA, Debus ES, Marschall U, Peters F. Sex Disparities in Long-Term Mortality after Paclitaxel Exposure in Patients with Peripheral Artery Disease: A Nationwide Claims-Based Cohort Study. J Clin Med. 2021;10:2978. https://doi.org/10.3390/jcm10132978

Zur endovaskulären Revaskularisation und insbesondere zur Anwendungssicherheit von Hochrisikomedizinprodukten mit Paclitaxel-Beschichtungen sind insgesamt drei retrospektive Propensity-Score gematchte und stratifizierte Beobachtungsstudien durchgeführt worden (**Fragestellung e**). Die geeigneten Operationen- und



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Prozedurencodes mit Angabe von Paclitaxel-Beschichtung wurden für die Operationalisierung der Intervention verwendet. Eine Adjustierung für Störfaktoren erfolgte durch Propensity-Score Matching und Cox Regressionsanalysen. Eine Korrektur für multiples Testen erfolgte nicht. In die erste Routinedatenanalyse wurden 37.914 Patient:innen (48,8% Frauen, mittleres Alter 73,3 Jahre) eingeschlossen, die zwischen 1. Januar 2010 und 31. Dezember 2018 stationär mit einer symptomatischen PAVK mittels endovaskulärer Techniken in der femoropoplitealen (Oberschenkel)Strombahn revaskularisiert wurden. Während der Studiendauer hat sich die Versorgungsrealität dahingehend geändert, dass die Nutzung von Hochrisikomedizinprodukten mit Paclitaxel-Beschichtung bei der IC von 4% auf 48% und bei CLTI von 3% auf 39% gestiegen ist. Im Langzeitverlauf von fünf Jahren nach der stationären Entlassung im Rahmen einer CLTI-Behandlung war die Anwendung von paclitaxelbeschichteten Ballons und Stents mit einem besseren Gesamtüberleben (Hazard Ratio 0,83, 95% CI 0,77-0,90), amputationsfreiem Überleben (Hazard Ratio 0,85, 95% 0,78-0,91) und Überleben ohne kardiovaskuläre Ereignisse (Hazard Ratio 0,82, 95% CI 0,77-0,89) assoziiert. In der Patient:innengruppe mit IC war die Anwendung beschichteter Ballons (Hazard Ratio 0,87, 95% CI 0,76-0,99) mit einem besseren Gesamtüberleben assoziiert.

Zur Anwendung endovaskulärer Revaskularisationsverfahren in der Unterschenkelstrombahn bei CLTI wurde eine weitere Propensity-Score gematchte Analyse durchgeführt (**Fragestellung e**). Insgesamt sind Daten von 14.738 Patient:innen eingeschlossen worden (43,6% Frauen, mittleres Alter 77,6 Jahre). Die Rate an paclitaxelbeschichteten Ballons und Stents stieg von 6% in 2010 auf 31% in 2018 an. Während des fünfjährigen Nachbeobachtungszeitraums zeigten sich in der Paclitaxel-Gruppe niedrigere Raten an Todesfällen (Hazard Ratio 0,84, 95% CI 0,78-0,91), Amputation und Tod (Hazard Ratio 0,87, 95% CI 0,81-0,94) sowie kardiovaskulären Ereignissen und Tod (Hazard Ratio 0,86, 95% CI 0,80-0,92).

In einer dritten Routinedatenanalyse zu endovaskulären Indexbehandlungen der symptomatischen PAVK zwischen Januar 2013 und Dezember 2017 wurden zugrundeliegende Faktoren für die Ergebnisse der ersten beiden Analysen gesucht (**Fragestellung d**). Eine geschlechterstratifizierte Kohorte von 13.204 Patient:innen (54% Frauen, mittleres Alter 74,0 Jahre) mit einem medianen Follow-up von 3,5 Jahren wurde in adjustierten Regressionsanalysen hinsichtlich derjenigen Faktoren untersucht, die mit einer geringeren Gesamtsterblichkeit assoziiert waren. Frauen waren signifikant älter (77 vs. 71 Jahre), hatten seltener eine koronare Herzkrankheit (23% vs. 33%), Dyslipidämie (44% vs. 50%), Diabetes (29% vs. 41%) und nikotinbezogene Suchterkrankung (10% vs. 15%) in der Vorgeschichte. Alle Mortalitätsunterschiede und damit assoziierte Risikofaktoren waren nur in der weiblichen Subgruppe signifikant, während keine Unterschiede in der männlichen Subgruppe nachgewiesen wurden.

Heidemann F, Kuchenbecker J, Peters F, Kotov A, Marschall U, L'Hoest H, Acar L, Ramkumar N, Goodney P, Debus ES, Rother U, Behrendt CA. A health insurance claims analysis on the impact of female sex on long-term outcomes after peripheral endovascular interventions for symptomatic peripheral arterial occlusive disease. J Vasc Surg. 2021;74:780-787.E7. https://doi.org/10.1016/j.jvs.2021.01.066

Kotov A, Heidemann F, Kuchenbecker J, Peters F, Marschall U, Acar L, Debus ES, L'Hoest H, Behrendt CA. Sex Disparities in Long-Term Outcomes after Open Surgery for Chronic Limb-Threatening Ischaemia – A Propensity Score Matched Analysis of Health Insurance Claims. Eur J Vasc Endovasc Surg. 2021;61:423-429. https://doi.org/10.1016/j.ejvs.2020.11.006

In einer Propensity-Score gematchten Analyse von 50.051 Patient:innen (47,2% Frauen) mit stationären endovaskulären Behandlungen der symptomatischen PAVK wurden geschlechterspezifische Unterschiede untersucht (**Fragestellung d**). Die Analysen wurden nach den Stadien der PAVK stratifiziert, um die drei primären Endpunkte „Freiheit von kardiovaskulären Endpunkten“, „amputationsfreies Überleben“ und „Gesamtsterblichkeit“ abzubilden. Es konnte beobachtet werden, dass Frauen nach fünf Jahren eine niedrigere Gesamtsterblichkeit aufwiesen (Hazard Ratio Fontaine II: 0,69, 95% CI 0,64-0,74; Fontaine III: 0,77, 95% CI 0,67-0,88; Fontaine IV: 0,90, 95% CI 0,85-0,96), seltener amputiert wurden oder starben (Hazard Ratio Fontaine II: 0,70, 95% CI 0,65-0,76;


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Fontaine III: 0,79, 95% CI 0,70-0,91; Fontaine IV: 0,89, 95% CI 0,84-0,94) und weniger kardiovaskuläre Ereignisse und Todesfälle erlebten (Hazard Ratio Fontaine II: 0,78, 95% CI 0,74-0,82; Fontaine III: 0,81, 95% CI 0,73-0,91; Fontaine IV: 0,91, 95% CI 0,87-0,97).

In einer erweiterten Analyse von 9.526 Patient:innen (49,5% Frauen) wurden auch stationäre offen-chirurgische Revaskularisationen der chronischen Extremitäten gefährdenden Ischämie im Langzeitverlauf untersucht (**Fragestellung d**). Hierbei bestätigte sich, dass Frauen zum Zeitpunkt der Behandlung etwa 6 Jahre älter waren und mehr Komorbiditäten aufwiesen. Nach einer medianen Verlaufsbeobachtung von 746 bzw. 871 Tagen war weibliches Geschlecht mit signifikant besseren Überlebensraten (Hazard Ratio 0,80, p<0.001), amputationsfreiem Überleben (Hazard Ratio 0,81, p<0.0001) und Überleben ohne kardiovaskuläre Ereignisse assoziiert (Hazard Ratio 0,84, p<0.001).

Aarabi G, Raedel M, Kreutzburg T, Hischke S, Debus ES, Marschall U, Seedorf U, Behrendt CA. Periodontal Treatment and Peripheral Arterial Occlusive Disease Severity - A Retrospective Analysis of Health Insurance Claims Data. VASA. 2020;49:128-132. https://doi.org/10.1024/0301-1526/a000846

In einer Analyse von 70.944 Patient:innen (55% Frauen), die zwischen dem 1. Januar 2012 und dem 31. Dezember 2016 stationär mit einer symptomatischen PAVK behandelt wurden, sollte dem Zusammenhang zwischen chronischen Entzündungen der Mundhöhle (Parodontitis) und PAVK nachgegangen werden (**Fragestellung f**). Unter allen eingeschlossenen Patient:innen haben 3.567 (5%) eine invasive Behandlung der Parodontitis erhalten. In multivariablen Regressionsanalysen, die auch für höheres Alter, Geschlecht und Diabetes adjustiert wurden, konnte die erfolgte invasive Parodontitisbehandlung mit früheren PAVK-Stadien (Fontaine II vs. III/IV) assoziiert werden (Odds Ratio 1,97. 95% CI 1,83-2,13).

b) Prospektiv anhand von Registerdaten

Während der Projektlaufzeit wurde aufgrund der verzögerten Rekrutierung im GermanVasc-Register die erforderliche Fallzahl von 10.000 auf 5.600 verringert, wobei keine Änderung der Projektziele oder statistischen Analysen notwendig war bzw. beantragt wurde.

Zwischen dem 1. Mai 2018 und dem 31. Dezember 2020 sind 5.608 Patient:innen (34% Frauen, medianes Alter: 69 Jahre) mit endovaskulären, offen-chirurgischen und Hybrideingriffen zur Behandlung der symptomatischen PAVK an 31 teilnehmenden Studienzentren in der prospektiven GermanVasc-Kohortenstudie eingeschlossen worden. Die Baseline-Charakteristika sind der folgenden Publikation (Open Access) zu entnehmen:

Kotov A, Peters F, Debus ES, Zeller T, Heider P, Stavroulakis K, Remig J, Gussmann A, Hoffmann J, Friedrich O, Nolte T, Behrendt CA. The prospective GermanVasc cohort study. VASA. 2021;In Press. https://doi.org/10.1024/0301-1526/a000966

Jedes Studienzentrum wurde mindestens ein Mal durch das unabhängige externe Monitoring-Team besucht. Der Anteil an Behandlungen der CLTI betrug 30% und 13% der Eingriffe wurden notfallmäßig durchgeführt. Hierbei wurden in der GermanVasc-Kohortenstudie ca. 43% der endovaskulären Prozeduren durch die Gefäßchirurgie, 34% durch die Radiologie und 34% durch die Angiologie durchgeführt, wobei etwa 18% unter Einbeziehung von mindestens zwei Fachdisziplinen registriert wurden.

55% der Patient:innen wurden in der Vorgeschichte bereits mindestens ein Mal invasiv revaskularisiert. Unter allen registrierten Prozeduren waren 69% endovaskulär (n=6.449). 35% der Patient:innen wurden gemäß der ASA-Klassifikation als schwer systemisch erkrankt klassifiziert und 3% unterlagen einer konstanten Lebensbedrohung durch die Grunderkrankungen. Beim Risikoprofil gaben 75% der Patient:innen einen aktiven oder früheren Nikotinkonsum an, 36% litten an einem Diabetes und 30% hatten eine ischämische Herzerkrankung. Zum Zeitpunkt der Krankenhausentlassung erhielten 93% einen Thrombozytenaggregationshemmer und 77% erhielten ein Statin.

Nach 12 Monaten (366 Tage im Median, IQR: 341-387) lagen für 2.901 Patient:innen vollständige Verlaufskontrollen vor. Die Detailergebnisse sind Tabelle 2 zu entnehmen. Die


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Gesamtsterblichkeit belief sich auf 1,1% (95% CI 0,7-1,7) bei elektiven Behandlung der IC und 7,7% (95% CI 6,0-9,7) bei Behandlung der CLTI.

4. Erprobung von Benchmarking anhand Rückmeldungen zur Versorgungsqualität aus dem Register

Im Rahmen einer Fokusgruppendiskussion mit den teilnehmenden Zentren wurde die Darstellung der Qualitätsindikatoren in datenschutzkonformer Weise mit gestapelten Balkendiagrammen konsentiert (Abbildung 4). Hierbei wurde zunächst ein Impulsvortrag zu den entwickelten Qualitätsindikatoren sowie zu deren Abbildbarkeit mit Sekundärdaten gehalten. Hierbei wurde insbesondere auch auf die Benchmarkingaspekte des Qualitätsregisters in den USA eingegangen. Anschließend wurde durch die Teilnehmer eine Diskussion darüber geführt, welchen Mehrwert das Benchmarking für Zentren und Ärzt:innen bieten könne und welcher Inhalt für eine Translation der Registerergebnisse in die Praxis geeignet sei. Hierbei wurde explizit auch die Frage diskutiert, ob es Vorbehalte gegen diese vergleichende Darstellung der eigenen Behandlungsergebnisse mit anderen Zentren gebe.

Insgesamt kritisch bewertet wurde die Möglichkeit, Zentren und deren Behandlungsergebnisse in einem Benchmarking zu identifizieren, weshalb alle automatisierten Darstellungen ausschließlich Raten ohne Streumaße und keine absoluten Werte enthielten. In den weiteren Diskussionen wurde rückgemeldet, dass die Teilnahme an einem Qualitätsregister gegenüber den kaufmännischen Klinikbereichen als wünschenswerter Motivationsfaktor bewertet werde und integraler Bestandteil zukünftiger Register sein solle. Die Teilnehmer:innen der Fokusgruppe haben ferner eine evidenzbasierte Zielvorgabe (Threshold) für wesentliche Ergebnisqualitätsindikatoren empfohlen.

Beim Öffnen der Benchmarking-Funktion in der GermanVasc-Registerplattform generiert das System eine zeitaktuelle Übersicht über die vom System vorgegebenen Indikatoren. Im Rahmen der Erprobungsphase wurden hierbei die Variablen: Alter, Aufnahmeart, Rauchstatus, Diabetes, Dialysepflichtigkeit, koronare Herzkrankheit und Funktionsstatus standardmäßig angezeigt. Es werden lediglich relative Werte angezeigt, um eine Identifikation der fremden Zentren anhand der Fallzahl zu verhindern. Die Darstellung erfolgt in gestapelten Balkendiagrammen, wobei die Daten des eigenen Zentrums den Daten der anderen am Register teilnehmenden Zentren gegenübergestellt werden (Abbildung 4).

Eine andere Art des Benchmarkings wurde in Form vordefinierter Berichte erprobt. Hierbei konnten für Teilgruppen (z.B. in einzelnen Zentren behandelte Patient:innen oder mit bestimmten Medizinprodukten behandelte Patient:innen) relevante Parameter gegenüber einer geeigneten Vergleichsgruppe tabellarisch dargestellt werden (z.B. Entlassungsmedikation).

Im Rahmen der Erprobung wurden dabei auch sogenannte Zielvorgaben (Thresholds) grafisch in die Diagramme eingefügt, die bei dauerhaftem Betrieb auch für die visuelle Rückmeldung von Grenzwerten für die Ergebnisqualitätsindikatoren im Langzeitverlauf geeignet wären.


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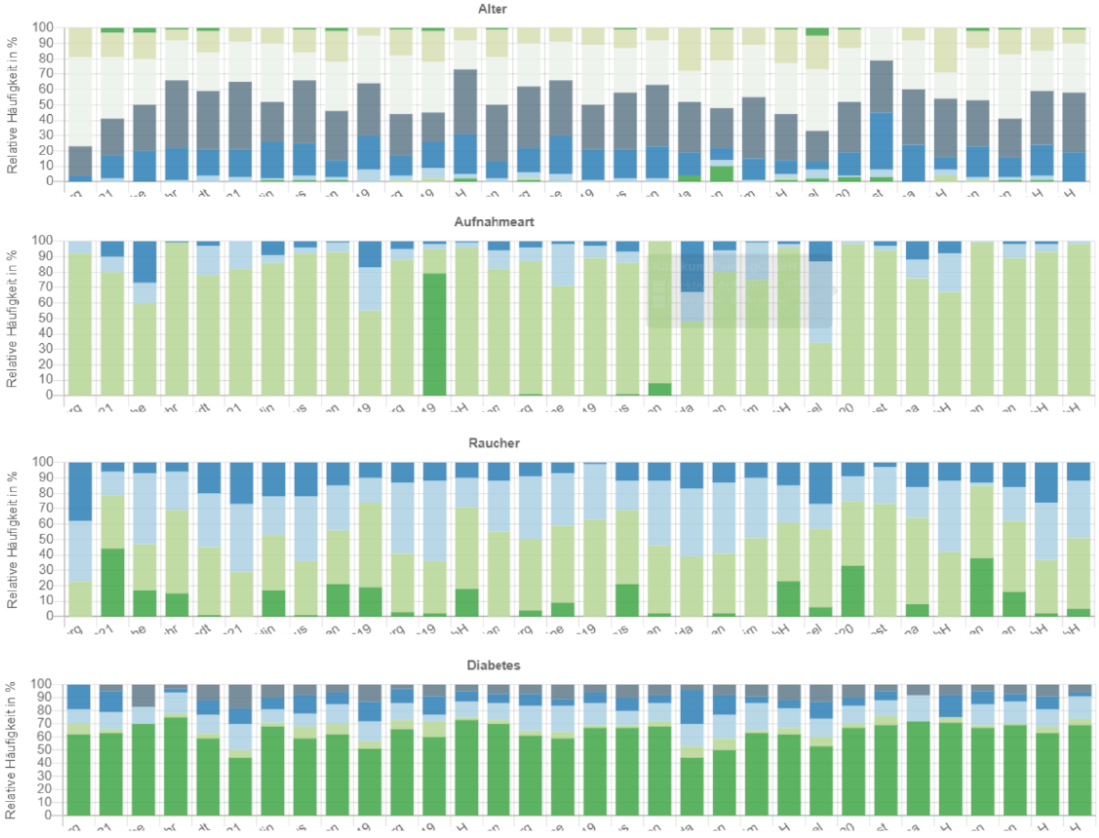
**Basischarakteristika der Zentren**




**Ergebnisse der Qualitätsindikatoren bei Entlassung**

| | | [redacted] | Control |
|---|---|---|---|
| **Number of patients** | **N#** | **78** | **226** |
| **Postoperative acute coronary syndrome** yes | *n\|N (%)* | 0\|78 (0) | 1\|226 (0.4) |
| **Postoperative stroke** yes | *n\|N (%)* | 1\|78 (1.3) | 0\|226 (0) |
| **Postoperative Occlusion of revascularization** yes | *n\|N (%)* | 0\|78 (0) | 8\|226 (3.5) |
| **Postoperative distal embolization** yes | *n\|N (%)* | 1\|78 (1.3) | 8\|226 (3.5) |
| **Postoperative bleeding** yes | *n\|N (%)* | 3\|78 (3.8) | 10\|226 (4.4) |
| **Postoperative compartment syndrome** yes | *n\|N (%)* | 0\|78 (0) | 2\|186 (1.1) |
| **Postoperative wound infection** yes | *n\|N (%)* | 0\|78 (0) | 4\|226 (1.8) |

*Abbildung 4: Exemplarische Darstellung der Basischarakteristika der eingeschlossenen Kohorte im Vergleich mit anderen teilnehmenden Zentren (oben) und beispielhafte Ausgabe von Ergebnisqualitätsindikatoren in Berichten (unten).*



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## 7. Diskussion der Projektergebnisse

In dem hier beschriebenen IDOMENEO-Projekt wurden verschiedene Methoden in mehreren Schritten angewandt, um Fragen aus dem Bereich der Versorgungsforschung und Qualitätsentwicklung zur PAVK-Behandlung in Deutschland zu beantworten. Mit etwa 1 Mio. Betroffenen im morbiditätsorientierten Risikostrukturausgleich zur stationären Versorgung und etwa 14% der 45-74-jährigen in Deutschland zählt die PAVK als Volkskrankheit mit einer außergewöhnlich schlechten Prognose. Je nach individuellem Risikoprofil erleiden bis zu 48% der Patient:innen mit IC und 88% mit CLTI innerhalb von 5 Jahren nach Indexbehandlung eine Majoramputation oder versterben (https://score.germanvasc.de).[40,41] Innerhalb von nur zehn Jahren nach erstmaliger stationärer Behandlung der symptomatischen PAVK wird bei 7% der Männer und 4% der Frauen eine Lungenkrebsdiagnose festgestellt, was ein wichtiger Grund für die Leitlinienempfehlungen zur strikten Nikotinkarenz ist.

Im Rahmen einer systematischen Literaturübersicht mit anschließendem modifiziertem Delphi-Verfahren mit interdisziplinären Experten der Gefäßmedizin sowie registerbasierter Forschung konnten zwölf Ergebnisqualitätsindikatoren entwickelt und in verschiedenen Beobachtungsstudien auf ihre Anwendbarkeit geprüft werden. Bei einer umfassenden retrospektiven Analyse von Routinedaten der gesetzlichen Krankenkasse BARMER wurde die deutschlandweite Versorgungsrealität in der Zielpopulation dargestellt. Hierbei zeigten sich Trends bzw. Entwicklungen bei der Patient:innenselektion, Verfahrenswahl, Ergebnissen und bei den behandlungsassoziierten Gesundheitskosten. Gleichzeitig ließen sich durch die longitudinale Verknüpfung der verfügbaren Forschungsdaten wesentliche Ergebnisqualitätsindikatoren über einen Zeitraum von bis zu fünf Jahren darstellen. In einer prospektiven registerbasierten Kohortenstudie an 31 deutschlandweiten Gefäßzentren wurden ca. 5.600 Patient:innen eingeschlossen, wobei eine Sammlung von fast 100 konsentierten Parametern zur Versorgung und zu den Behandlungsergebnissen erhoben wurden. Die in der IDOMENEO-Studie entwickelten Techniklösungen ermöglichten dabei eine datenschutzkonforme Erhebung und weitere Nutzungsmöglichkeiten der Forschungsdaten im Rahmen eines Benchmarkings der teilnehmenden Studienzentren. Die prospektiv erhobene Datenbasis wurde im Rahmen externer Datenmonitorings und interner Validierungsverfahren mehrfach qualitätsgesichert (NCT NCT03098290),[4,31] was ein Novum gegenüber bestehenden Versorgungs- und Registerdaten darstellt, deren externe und interne Validität zumeist unbekannt ist.

Studienvorhaben zur Darstellung der Versorgungsrealität von Patient:innen mit symptomatischer PAVK unterliegt zahlreichen Störfaktoren und Verzerrungen durch unvollständige Erhebungen, die mit den Analysen interferieren. In den letzten Jahren ist vor diesem Hintergrund auch über den Einfluss des Gesundheitssystems und ökonomischer Aspekte diskutiert worden. So sind im internationalen Vergleich deutliche Unterschiede bei der Patient:innenselektion, Verfahrenswahl sowie Behandlungsergebnissen nachgewiesen worden, welche sich nicht durch unterschiedliche Leitlinienempfehlungen in den betroffenen Ländern erklären ließen. In England wurde vor diesem Hintergrund ein vergleichbares Projekt mit dem Namen „Getting It Right First Time (GIRFT)“ implementiert, welches die Ursachen für unerwünschte Varianzen in der Versorgungsrealität ergründen soll. Im Vergleich mit hochzentralisierten Gesundheitssystemen, wie z.B. in Schweden (<75 Krankenhäuser und nur 30 Gefäßzentren) ist eine vollständige Erhebung der Versorgungssituation in Deutschland bereits durch die große Anzahl an Krankenhäusern (>1.600 allgemeine Krankenhäuser und mehr als 650 Gefäßzentren) erschwert. Zusätzlich beziehen frühere oder bestehende Registerinitiativen nicht immer alle an der Versorgung beteiligten Fachdisziplinen bzw. Behandlungen ein oder deren Erhebungsumfang schließt nur Teilaspekte der Versorgung


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und Ergebnisse ein. Die prozedur- bzw. fallbezogenen Daten des InEK bzw. der Krankenhausdiagnosestatistik des Bundes (Destatis) ermöglichen darüber hinaus insbesondere bei der PAVK-Behandlung lediglich einen stark verzerrten Einblick in die Versorgungsrealität, da die häufigen Reinterventionen in der Zielpopulation bei fehlender longitudinaler Patient:innenbeziehbarkeit ein relevantes Bias einführen. In der aktuellen Studie konnte dargestellt werden, dass mehr als die Hälfte aller invasiv revaskularisierten Patient:innen in der Vorgeschichte bereits mindestens einmal revaskularisiert wurden. Eine weitere wichtige Verzerrung entsteht durch die Nutzung ausschließlich fallbezogener Komorbiditäten und Risikofaktoren, da frühere Vordiagnosen in der longitudinalen Krankengeschichte nicht in die Approximation der Risikofaktoren bzw. Komorbiditäten eingehen können. Insbesondere bei chronischen komplexen Erkrankungen, wie der PAVK, ist allerdings eine ausreichende Rückschauzeit von mindestens zwei Jahren empfohlen worden.[33]

Bestehende Register einzelner Fachgesellschaften, z.B. aus der Deutschen Gesellschaft für Interventionelle Radiologie (DeGIR), schließen ausschließlich Prozedur- bzw. Produktdetails von einer (unter mehreren) Fachdisziplinen ein, sind zudem formal freiwillig und erheben darüber hinaus kein notwendiges Follow-up nach der Krankenhausentlassung. Insbesondere in der invasiven Behandlung der PAVK ist allerdings das Behandlungsergebnis nach der Krankenhausentlassung entscheidend für die patientenzentrierte Therapieentscheidung und gilt als primäres Therapieziel. Fachübergreifende Qualitätsregister, wie z.B. bis 2019 in Hamburg durch die EQS-Landesgeschäftsstelle Qualitätssicherung (bis 2004 bundesweit), schlossen zwar alle perkutanen endovaskulären Behandlungen der drei wesentlich beteiligten Fachdisziplinen ein (38% Radiologie, 37% Gefäßchirurgie, 23% Angiologie), bilden aber die Versorgungsrealität nur einer spezifischen Metropolregion ab, in der eine überdurchschnittlich hohe Versorgungsdichte und ein überdurchschnittlich großer Anteil angiologischer Prozeduren beobachtet werden konnte.[34] Außerdem erfolgte auch im EQS-Register keine Erhebung von Ergebnissen nach der Krankenhausentlassung, was die Nutzung zu Zwecken der Versorgungsforschung und Qualitätsentwicklung einschränkt. Mit dem RECCORD-Register der Deutschen Gesellschaft für Angiologie (DGA) besteht seit 2019 ein weiteres fachgesellschaftlich betriebenes Register, das ausschließlich endovaskuläre Prozeduren einer einzigen Fachdisziplin an etwa 20 deutschen Gefäßzentren einschließt, wodurch sich auch in dieser Erhebung ein relevantes Bias ergibt. Interessanterweise waren die Basischarakteristika der endovaskulär behandelten Patient:innen im GermanVasc- sowie RECCORD-Register vergleichbar, was auf ein ähnlich selektiertes Patient:innengut hinweist.[42]

Zeitlich begrenzte Studienregister, z.B. im Rahmen der CRITISCH-Studie der Deutschen Gesellschaft für Gefäßchirurgie (DGG) oder der PSI-Studie der Forschungsgruppe GermanVasc wiesen ähnliche Limitationen auf und waren darüber hinaus nur für den Zeitraum des Forschungsvorhabens aktiv.[35,43] Zahlreiche Längsschnittanalysen und ein Vergleich aufeinanderfolgender Beobachtungsstudien legen dabei allerdings nahe, dass eine relevante Dynamik im Behandlungsgeschehen dazu führt, dass Daten aus 2016 heute bereits nicht mehr ohne weiteres auf die aktuelle Versorgungsrealität übertragen werden können.

Die GermanVasc-Kohortenstudie schloss zwischen 1. Mai 2018 und 31. Dezember 2020 konsekutiv insgesamt 5.608 Patient:innen an 31 Gefäßzentren ein, wobei eine interdisziplinäre Einbeziehung aller lokal involvierten Fachdisziplinen im Studiendesign verpflichtend festgelegt wurde. Während offen-chirurgische Revaskularisationen lediglich durch die Gefäßchirurgie durchgeführt werden, steht die zunehmende Anzahl endovaskulärer Prozeduren im Zentrum der interdisziplinären Zusammenarbeit. Hierbei wurden in der GermanVasc-Kohortenstudie ca. 43% durch die Gefäßchirurgie, 34% durch die Radiologie und 34% durch die Angiologie durchgeführt, wobei etwa 18% unter


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Einbeziehung von mindestens zwei Fachdisziplinen registriert wurden. Inwiefern diese Aufteilung mit der deutschlandweiten Versorgungsrealität übereinstimmt, kann allerdings nicht mit letzter Sicherheit festgestellt werden, weil auch die GermanVasc-Kohortenstudie designbedingt nur einen Teil der insgesamt an der Versorgung beteiligten Gefäßzentren einschloss. Dieser Aspekt ist kürzlich zur Übertragbarkeit der Ergebnisse aus dem weltweit größten Gefäßregister der Vascular Quality Initiative (VQI) in den Vereinigten Staaten diskutiert worden, da dort in mehreren Studien eine Verzerrung durch die Teilnahme qualitätsorientierter High-Volume-Zentren beobachtet werden konnte.[36]

Passend dazu lässt sich bei einem Direktvergleich der wichtigsten Basischarakteristika der eingeschlossenen Kohorten feststellen, dass in der GermanVasc-Kohorte insgesamt deutlich weniger Frauen (34% vs. 46%) und etwas jüngere Patient:innen (69 vs. 73 Jahre) eingeschlossen wurden als in den bundesweiten Routinedaten der BARMER. Bei einem Vergleich der zentralen Endpunkte wird dieser Unterschied noch deutlicher. Die in Routinedatenquellen in der Altersgruppe über 65 Jahren am validesten enthaltene Gesamtsterblichkeit nach 12 Monaten liegt sowohl bei Patient:innen mit CLTI (23% vs. 8%) als auch bei IC (4% vs. 1%) deutlich über der erfassten Sterblichkeit der Primärdaten aus der GermanVasc-Registerkohorte. Interessanterweise betrug die Gesamtsterblichkeit nach 12 Monaten in der CRITISCH-Registerstudie bei CLTI-Patient:innen mit Bypasschirurgie nur 11% und war damit ebenfalls vergleichbar mit der GermanVasc-Kohorte.

Trotz des möglichen Bias durch den selektiven Einschluss einer High-Volume-Zentrumsgruppe in der GermanVasc-Registerkohorte und der damit eingeschränkten Übertragbarkeit der Ergebnisse auf die deutschlandweite Versorgungssituation stellt diese Kohorte eine wichtige Datenbasis für verschiedene Fragestellungen dar. Zudem muss betont werden, dass die Mehrheit der randomisierten kontrollierten Studien zu Medizinprodukten oder Pharmaka in dieser Zielpopulation einem ähnlichen Selektionsbias und damit assoziiert relevanten methodischen Limitationen unterlagen. So konnte kürzlich mehrfach systematisch nachgewiesen werden, dass weniger als 20% der RCTs zur PAVK-Behandlung einen repräsentativen Frauenanteil rekrutierten, was die valide Ableitung von zentralen Schlussfolgerungen für beide Geschlechter einschränkt. Das zunehmende Problem der Übertragbarkeit bzw. Translation von Ergebnissen randomisierter Studien auf die gesamte Versorgungssituation wird heute im Rahmen sogenannter trainingsbasierter RCTs diskutiert. Zusammenfassend muss also festgehalten werden, dass die in der GermanVasc-Registerstudie prospektiv eingeschlossene Kohorte hinsichtlich der Selektionskriterien, Komorbiditäten und Outcomes nicht mit der in Routinedaten enthaltenen flächendeckenden Versorgungsrealität übereinstimmt. Obwohl die Diskussion der unzureichenden Generalisierbarkeit bisher nur bei randomisierten kontrollierten Studien intensiv diskutiert wurde, erscheint die Einleitung einer weiteren Diskussion angebracht.

Ein primäres Ziel des IDOMENEO-Projekts war auch die systematische Sammlung und Entwicklung von Ergebnisqualitätsindikatoren, die zur Messung der Versorgungsqualität geeignet sind. Die Tatsache, dass in der verfügbaren Literatur nur zwei Studien und drei nach anerkannten methodischen Standards entwickelte Indikatoren identifiziert wurden, illustriert das zugrundeliegende Problem in der interdisziplinären PAVK-Behandlung. Verfügbare Leitlinien enthalten bisher noch keine Qualitätsindikatoren oder sogar Zielvorgaben, wodurch ein Vergleich der Ergebnisse bisher erschwert wurde. Auf dem Boden des VQI-Registers in den Vereinigten Staaten wurden vor kurzem sogenannte objektivierbare Leistungszielvorgaben für die Behandlung der CLTI entwickelt, die aus methodischen Gründen zwar nicht als Qualitätsindikatoren gelten können, sich aber trotzdem in vielen Projekten zur Messung der langfristigen Ergebnisse etabliert haben. Es ist insofern ermutigend, dass unter den im IDOMENEO-Projekt entwickelten Qualitätsindikatoren die meisten dieser Leistungszielvorgaben enthalten sind, was deren


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Akzeptanz erhöht. Zur Behandlung der IC sind im IDOMENEO-Projekt erstmals Indikatoren entwickelt worden, wobei auffallend war, dass vor allem aufgrund der schlechten Praktikabilität im klinischen Alltag keine konventionellen patientenberichteten Endpunkte entwickelt wurden. Als Proxy können hier allenfalls die Verbesserung der maximalen Gehstrecke und die Verbesserung des klinischen Stadiums gewertet werden, während z.B. die Lebensqualität mit einer Praktikabilitätsbewertung von nur 17% ausgeschieden ist. Im IDOMENEO-Projekt wurden insgesamt 28 internationale Qualitätsregister der Gefäßmedizin befragt, welche Erhebungswerkzeuge jeweils implementiert wurden. Zusätzlich wurde eine umfassende Literaturübersicht durchgeführt. Dabei konnten 145 verschiedene Erhebungsparameter in acht Domänen der patientenberichteten Endpunkte identifiziert werden. In vier Ländern erfolgt gegenwärtig eine Erhebung des VascuQoL-6, während zwei Register das Walking Impairment Questionnaire (WIQ) nutzen. Die meisten Register erheben derzeit allerdings keine patientenberichteten Endpunkte. Es erscheint vor diesem Hintergrund bemerkenswert, dass sich verschiedene Leitliniengruppen zur Behandlung der Zielpopulation und das internationale VASCUNET Komitee gegenwärtig auch mit der Frage beschäftigen, wie der subjektive Leidensdruck bei der sogenannten lebensstillimitierenden Claudicatio intermittens objektiviert werden kann.

Mit insgesamt 24 verschiedenen Items fiel der Fragebogen zum Gesundheitszustand in der GermanVasc-Kohortenstudie umfassender aus, als in den meisten etablierten Registern. Damit einhergehend fielen die Rückmeldungen von Patient:innen und Zentrumsmitarbeitern entsprechend negativ aus. Dass nach 12 Monaten nur Fragebögen von weniger als einem Viertel der Patient:innen vorlagen, erhöht das Risiko für einen relevanten Selektionsbias. Obwohl dieses Problem aus vielen rekrutierenden Studien bekannt ist, erscheint die Lost-to-Follow-up-Rate in dieser Zielpopulation besonders hervorzustechen. Die vergleichenden Sensitivitätsanalysen der Gesamtkohorte vs. einer Subkohorte mit vollständigen Basis- und Follow-up-Erhebungen zeigte, dass in den meisten Fragen keine substanziellen (<1%) Änderungen durch Selektionseffekte zu erwarten sind. Allerdings stach der auf Selektionseffekten beruhende Unterschied mit etwa 5% häufigeren Angaben schlechter seelischer Gesundheit hervor. Der allgemein bekannte Zusammenhang zwischen der gesundheitsbezogenen Lebensqualität und modifizierbaren Risikofaktoren (z.B. Nikotinkonsum) unterstreicht die klinischen Implikationen dieser Beobachtung zusätzlich und gibt weiteren Anlass zur Diskussion der besonders hohen Raucherprävalenz in der GermanVasc-Kohorte.

Trotz der beschriebenen Limitationen geben die Ergebnisse einen interessanten Einblick in die Versorgungsrealität an den teilnehmenden Zentren. In beiden Krankheitsstadien wurde durch 41% bzw. 62% der Patient:innen ein insgesamt weniger guter oder schlechter Gesundheitszustand angegeben. Bei 12% bis 23% der Patient:innen konnten Indikatoren eines schlechten seelischen Wohlbefindens identifiziert werden. Obwohl der offensichtliche Healthy-User-Bias und die immer noch hohen Raten eines schlechten Gesundheitszustandes verschiedene Verbesserungspotentiale nahelegen, ist es ermutigend, dass in allen Fragenbereichen nach 12 Monaten eine Verbesserung gegenüber der Basiserhebung gesehen werden konnte.

Nach insgesamt vier Jahren Projektlaufzeit konnten Ergebnisqualitätsindikatoren entwickelt und in Primär- sowie Sekundärdaten geprüft werden. Die Ergebnisse aller Analysen legen dabei nahe, dass immanente Selektionseffekte einen direkten Vergleich zwischen den Registerdaten mit den Routinedaten erschweren oder sogar unmöglich machen. Die offensichtlichen Hürden einer vollständigen, zeitnahen und validen Registererhebung zur PAVK-Behandlung im klinischen Versorgungsbetrieb machen die Erreichung einer hohen externen Validität (Vollständigkeit der Erhebung) nahezu unmöglich, schränken die Nutzung für bestimmte epidemiologische Fragestellungen allerdings nur teilweise ein. So kann die Nutzung für pragmatische Studien,


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Medizinproduktregister oder als freiwillige Qualitätsregisterinitiative durchaus gewährleistet sein.

Folgeprojekte sollten sich vor allem mit der konsensuellen Festlegung von ratenbasierten Kennzahlen (sog. Thresholds) für die im IDOMENEO-Projekt entwickelten Qualitätsindikatoren beschäftigen und dabei auch Methoden zu deren kontinuierlicher Messung und Darstellung erproben. Ein Ansatz ergibt sich hierbei z.B. aus sogenannten risikobasierten kumulativen Summen (sog. CUSUM), die bereits von Qualitätsregistern der Gefäßmedizin in den Niederlanden genutzt werden.

## 8. Verwendung der Ergebnisse nach Ende der Förderung

Das im IDOMENEO-Projekt entwickelte datenschutzkonforme GermanVasc-Register ist bereits im Rahmen einer weiteren Förderung durch den Innovationsfond des Gemeinsamen Bundesausschuss weiterverwendet und weiterentwickelt worden. In der RABATT-Studie (01VSF18035) beschäftigt sich ein Konsortium aus Gefäßmediziner:innen, Rechtswissenschaftler:innen, Informatiker:innen und anderen Beteiligten mit den zahlreichen Schnittmengen zwischen den Anwendungsbereichen.

Insbesondere erarbeitet die wissenschaftliche Projektleitung gegenwärtig Funktionen für die Nutzbarkeit der GermanVasc-Registerplattform zur Langzeitevaluation von Hochrisiko-Medizinprodukten (Surveillance) und für die Durchführung von pragmatischen Registerstudien (Pragmatic Trials), bei denen der immanente Selektionsbias weniger eine Rolle spielt. Die mehrsprachigen Einwilligungskonzepte und die Techniklösungen konnten aufgrund der europaweiten Datenschutzkonformität bereits in Luxemburg und Rumänien getestet werden, was zu einem zukünftigen Wissenstransfer und neuen Anwendungsfeldern führen kann.

Insbesondere die Ergebnisse der Routinedatenauswertungen wurden in der internationalen Community zahlreich diskutiert. Die Unterversorgung der Zielpopulation mit einer optimalen Arzneimitteltherapie trotz der hochwertigen Evidenzbasis für deren Nutzen und die Anwendungssicherheit haben zu Kampagnen und Pressemitteilungen der einschlägigen Fachgesellschaften geführt. Es bleibt abzuwarten, ob die Öffentlichkeitsarbeit auf dem Boden der Projektergebnisse zu einer messbaren Verbesserung der Versorgungsrealität führen kann.

Die komplementären Ergebnisse der Primär- und Sekundärdatenanalysen zur stationären Versorgung der symptomatischen PAVK in Deutschland wurden bereits in zwei internationalen und einer deutschen Leitlinie zur Behandlung der PAVK, an denen die wissenschaftliche Projektleitung mitwirkt, diskutiert. Es ist davon auszugehen, dass verschiedene Ergebnisse, insbesondere zu den Ergebnisqualitätsindikatoren einen Platz in diesen Leitlinien finden werden.

Neben den zahlreichen Hypothesen, die durch die Beobachtungsstudien im Projekt generiert wurden, sind auch weitere Projektideen, Herausforderungen und Forschungslücken identifiziert worden, die in Folgeprojekten bearbeitet werden. Hierzu gehören unter anderem die unzureichende Sammlung von patientenberichteten Endpunkten unter Berücksichtigung einer pragmatischen Datenerhebung, die Untersuchung der Leitlinienadhärenz bei der Arzneimittelversorgung, die Verbesserung der Patientenedukation und Compliance und die Überwindung des immanenten Selektionsbias in einem nicht zentralisierten Versorgungssystem.


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## 9. Erfolgte bzw. geplante Veröffentlichungen

Im Rahmen des IDOMENEO-Projekts sind zahlreiche Publikationen entstanden bzw. veröffentlicht worden. Neben den in diesem Abschnitt genannten Veröffentlichungen sind auch nach Ende der Förderdauer weitere Publikationen zu den hier beschriebenen Ergebnissen geplant.

***Veröffentlichungen im Rahmen des Projektes:***

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***Veranstaltungen und Kongressvorträge:***

*Behrendt CA, Vorstellung der IDOMENEO-Studie und anderer Real-World-Datenerhebungen auf dem Fakultätentag der Fakultät für Rechtswissenschaften der Universität Hamburg (Chancen und Risiken von Big Data) am 23. Februar 2018*

*Behrendt CA, Vorstellung der IDOMENEO-Studie auf der 33. Jahrestagung der Deutschen Gesellschaft für Gefäßchirurgie (DGG) in Frankfurt am 29. September 2017*

*Behrendt CA, Vorstellung der IDOMENEO-Studie auf der 46. Jahrestagung der Deutschen Gesellschaft für Angiologie (DGA) in Berlin am 14. September 2017*

*Behrendt CA, Vorstellung der IDOMENEO-Studie auf der Zi Konferenz für Versorgungsforschung am 13. September 2017 in Berlin*

*Splawinski N, Vorstellung des Projekts und der GermanVasc-Registererhebung durch einen (kostenpflichtigen) Informationsstand auf der Jahrestagung der Deutschen Gesellschaft für Angiologie (DGA) in Münster 2018*

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*Behrendt CA, 2x Präsentationen „Rationale and Methods of the IDOMENEO Health Outcomes of Peripheral Arterial Disease Revascularisations Study in the GermanVasc Registry“ auf der 34. Jahrestagung der Deutschen Gesellschaft für Gefäßchirurgie und Gefäßmedizin (DGG) in Bonn vom 17.-10.10.2018*

*Behrendt CA, Fast Track Präsentation und Preissitzung „Prize Session - The IDOMENEO study - Treatment of Peripheral Arterial Disease in Germany” auf der 32. Jahrestagung der European Society for Vascular and Endovascular Surgery in Valencia, Spanien vom 25.-28.09.2018*

*Behrendt CA, Vorstellung des Projekts auf dem Symposium „Herausforderungen und Möglichkeiten von Big Data – Die IDOMENEO-Studie“ der Fakultät für Rechtswissenschaften der Universität Hamburg am 26.01.2018*

*Hischke S, Posterpräsentation des systematischen Reviews „Qualitätsindikatoren der invasiven stationären Behandlung der peripheren arteriellen Verschlusskrankheit – Erste Ergebnisse einer systematischen Übersichtsarbeit“ im Rahmen der Jahrestagung des Deutschen Netzwerks für Versorgungsforschung in Berlin vom 10.-12.10.2018*

*Posterpräsentation „IDOMENEO-Studie als Beitrag zur Qualitätsentwicklung in der Patientenversorgung (Speaker: C.-A. Behrendt)“ im Rahmen der Jahrestagung des Deutschen Netz-werks für Versorgungsforschung in Berlin vom 10.-12.10.2018*



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*Behrendt CA, Optimal treatment of peripheral arterial occlusive disease (PAOD) - Communication between clinical and outpatient care. Winter Academy 2020 of the University Heart- and Vascular Center Hamburg. January 22, 2020. Hamburg, Germany*

*Behrendt CA, Vorstellung der IDOMENEO-Studie und des GermanVasc-Registers. Kleiner Konvent der leitenden Gefäßchirurgen in der NGM. 10. April 2019. Hamburg, Deutschland*

*Behrendt CA, Long-term survival following Paclitaxel-coated devices in PAD - Analysis of German Health Insurance Claims. 33rd Annual Meeting 24-27 September 2019. Hamburg, Germany*

*Behrendt CA, Recommendations for Registry Data Collection for Revascularisations of Acute Limb Ischaemia: A Delphi Consensus. 33rd Annual Meeting 24-27 September 2019. Hamburg, Germany*

*Behrendt CA, Do "real-world" data confirm differences in mortality after PAD treatment with paclitaxel-coated devices? Munich Vascular Conference 2019. December 6, 2019. Munich, Germany*

*Behrendt CA, Large Population Based Multicenter German Study Indicates Paclitaxel Coated Devices May Be Associated With Lower Late Mortality Than Uncoated Devices In Some Patient Subgroups. VEITHsymposium 2019. November 20, 2019. New York, United States*

*Behrendt CA, The German IDOMENEO study - Quality improvement and Research in vascular medicine. 7th Spring Meeting of the German Society for Vascular Surgery at the 136th Annual Meeting of the German Society of Surgery. March 26 to 29,2019. Munich, Germany*

*Behrendt CA, Big Data and Real-World-Evidence in Cardiovascular Medicine: Why do we need this summit! Summit: Real-World-Evidence in der kardiovaskulären Medizin. 1. November 2019. Hamburg, Deutschland*

*Behrendt CA, Wie unterschiedliche statistische Methoden die Schlussfolgerungen zur Medizinproduktesicherheit beeinflussen können: Die Paclitaxel-Debatte. Summit: Real-World-Evidence in der kardiovaskulären Medizin. 1. November 2019. Hamburg, Deutschland*

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*Bavendiek K, Automatically Proving Purpose Limitation in Software Architectures. ICT Systems Security and Privacy Protection. SEC 2019. IFIP Advances in Information and Communication Technology, Lisbon, Portugal*

*Mueller T, Welche realen Gefahren bestehen bei etablierten Registern in der kardiovaskulären Medizin – Reale Angriffsszenarien. Konferenz „Real-World-Evidence in der kardiovaskulären Medizin", Universitätsklinikum Hamburg-Eppendorf, 1. November 2019*

*Federrath H, Technische Absicherung von sensiblen Registerdaten. Konferenz „Real-World-Evidence in der kardiovaskulären Medizin", Universitätsklinikum Hamburg-Eppendorf, 1. November 2019*

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*Kreutzburg T, Comorbidity Patterns among Patients with Peripheral Arterial Disease in Germany – A Trend Analysis of Health Insurance Claims Data | Komorbiditäten bei Behrendt CA, Patienten mit pAVK / Eine Trendanalyse von Krankenkassendaten. Dreiländertagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Gefäßchirurgie und Gefäßmedizin. 16.10.2019. Mannheim, Deutschland*

*Behrendt CA, Investigatormeeting und Update zur IDOMENEO-Studie. Dreiländertagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Gefäßchirurgie und Gefäßmedizin. 16.-19.10.2019. Mannheim, Deutschland*

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***Promotions- und Masterarbeiten im Rahmen des Projektes:***

*Thea Kreutzburg (geb. Schwaneberg), PhD, M.Sc. – „Versorgungsforschung zum Langzeitverlauf von Patient:innen mit peripherer arterieller Verschlusskrankheit nach invasiver Behandlung anhand von Routinedaten in Deutschland"*

*Nazeh Mahmoud, Dr. med. – „Diabetes Mellitus und Periphere arterielle Verschlußkrankheit - Ein systemisches Review"*



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*Maria Bublitz, Dr. med. dent. – "Qualitätsindikatoren in der invasiven Behandlung der chronischen peripheren arteriellen Verschlusskrankheit - Eine systematische Übersichtsarbeit"*

*Linda Wrobel, M.Sc. – „Gesundheitsökonomische Evaluation von endovaskulären Verfahren im Vergleich zu offenen gefäßchirurgischen Eingriffen bei der Therapie der symptomatischen peripheren arteriellen Verschlusskrankheit"*

*Deven Blasche, Dr. med. – „The impact of renal insufficiency on outcomes after the treatment of symptomatic peripheral arterial disease" (Einreichung ausstehend)*

*Julius Peter Maier, Dr. med. – "Modifiziertes Delphi-Verfahren zu Ergebnisqualitätsindikatoren der PAVK-Behandlung in Deutschland"*

*Max Gansel, Dr. med. – „Untersuchungen zur Assoziation zwischen ausgewählten malignen Tumorerkrankungen und peripherer arterieller Verschlusskrankheit (PAVK) in Deutschland anhand von Routinedaten der gesetzlichen Krankenversicherung BARMER"*

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## 11. Anhang

*Nicht zutreffend!*

## 12. Anlagen

*Anlage 1: Fragebogen zum Gesundheitszustand*

*Anlage 2: Liste mit Variablen zur Beschreibung der Risikofaktoren und Behandlungsparameter in der prospektiven GermanVasc-Kohortenstudie*

*Anlage 3: Liste mit Aufgreifkriterien zur Operationalisierung der Ergebnisqualitätsindikatoren in Routinedaten der Krankenkasse*

*Anlage 4: Volltexte der Publikationen mit Projektergebnissen aus Register- und RoutinedatenanalysenDie im Projekt entstandenen Ergebnis-relevanten Publikationen wurden im Rahmen von Open-Access-Lizenzen veröffentlicht und sind frei abrufbar. Weitere Anfragen zu Publikationen oder Datenauszügen sind über den korrespondierenden Autor (PD Dr. Christian-Alexander Behrendt, behrendt@hamburg.de) zu stellen.*


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# Anlage 1: IDOMENEO-Fragebogen zum Gesundheitszustand

**Wird vom Studienpersonal ausgefüllt**

GermanVasc-Pseudonym: _____

Verantwortlich: _____
Telefonnummer: _____
Klinik: _____
Datum der Ausgabe des Bogens: _____
Datum der Dateneingabe: _____

Anmerkungen: _____

Klinikstempel, Unterschrift Studienpersonal:

Name, Vorname: _____

Geburtsdatum: _____

Befragungszeitpunkt

[1] ☐ Baseline-Visite
[2] ☐ 3 Monate Follow-up
[3] ☐ 6 Monate Follow-up
[4] ☐ 12 Monate Follow-up

Antworten liegen nicht vor, weil:

[1] ☐ Fragebogen nicht ausgehändigt
[2] ☐ Fragebogen nicht zurück erhalten
[3] ☐ Fragebogen nicht auffindbar
[4] ☐ anderer Grund, und zwar _____

# IDOMENEO – Fragebogen zum Gesundheitszustand

**Sehr geehrte Patientin, sehr geehrter Patient,**

in diesem Fragebogen geht es um die Beurteilung Ihres Gesundheitszustandes. Der Bogen ermöglicht uns nachzuvollziehen, wie Sie sich fühlen und wie Sie im Alltag zurechtkommen.

Bitte lesen Sie die Fragen und alle Antwortvorgaben aufmerksam durch und wählen dann die Antwort, die auf Sie am besten zutrifft. Bitte beantworten Sie jede Frage und markieren Sie bei jeder Frage nur eine Antwort, indem Sie das entsprechende Kästchen ankreuzen.

Beispiel:

**Wie häufig treffen Sie sich mit Verwandten oder Freunden?**

[1] ☐ Sehr häufig
[2] ☐ Ziemlich oft
[3] ☒ Manchmal
[4] ☐ Selten
[5] ☐ Nie

Kreuzen Sie die Antwort an, die Ihnen ohne lange überlegen zu müssen am passendsten erscheint. Es gibt weder richtige noch falsche Antworten (die Zahlen neben den Kästchen dienen lediglich der schnelleren Datenverarbeitung). Wenn es Ihnen schwer fällt sich zwischen mehreren Antworten zu entscheiden, kreuzen Sie bitte die Antwort an, die am ehesten zutrifft. Auch wenn wir versucht haben Wiederholungen so weit wie möglich auszuschließen, beziehen sich einige Fragen scheinbar auf ähnliche Inhalte. Dies ist bei einigen Fragen leider unvermeidbar, um wissenschaftlich aussagekräftige Ergebnisse zu erhalten.

Die Beantwortung des Fragebogens dauert in der Regel 5 bis 10 Minuten.

Sollten Sie Fragen haben oder Unterstützung benötigen, rufen Sie uns gerne unter der Telefonnummer an, die oben im schwarzen Kasten angegeben ist.

Vielen Dank für Ihre Unterstützung!

## IHR GESUNDHEITSZUSTAND

**1. Wie würden Sie Ihren Gesundheitszustand im Allgemeinen beschreiben?**

[1] ☐ Ausgezeichnet
[2] ☐ Sehr gut
[3] ☐ Gut
[4] ☐ Weniger gut
[5] ☐ Schlecht

**2. Sind Sie durch Ihren derzeitigen Gesundheitszustand bei mittelschweren Tätigkeiten (z.B. einen Tisch verschieben, staubsaugen, kegeln) eingeschränkt?**

[1] ☐ Ja, stark eingeschränkt
[2] ☐ Ja, etwas eingeschränkt
[3] ☐ Nein, überhaupt nicht eingeschränkt

**3. Sind Sie durch Ihren derzeitigen Gesundheitszustand eingeschränkt mehrere Treppenabsätze zu steigen?**

[1] ☐ Ja, stark eingeschränkt
[2] ☐ Ja, etwas eingeschränkt
[3] ☐ Nein, überhaupt nicht eingeschränkt

**4. Haben Sie in den vergangenen 4 Wochen aufgrund Ihrer körperlichen Gesundheit bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause weniger geschafft als Sie wollten?**

[1] ☐ Ja
[2] ☐ Nein

**5. Konnten Sie in den vergangenen 4 Wochen aufgrund Ihrer körperlichen Gesundheit bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause nur bestimmte Dinge tun?**

[1] ☐ Ja
[2] ☐ Nein

**6. Haben Sie in den vergangenen 4 Wochen aufgrund seelischer Probleme (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten) bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause weniger geschafft als Sie wollten?**

[1] ☐ Ja
[2] ☐ Nein

**7. Konnten Sie in den vergangenen 4 Wochen aufgrund seelischer Probleme (z.B. weil Sie sich niedergeschlagen oder ängstlich fühlten) bei der Arbeit oder anderen alltäglichen Tätigkeiten im Beruf bzw. zu Hause nicht so sorgfältig wie üblich arbeiten?**

[1] ☐ Ja
[2] ☐ Nein

**8. Inwieweit haben die Schmerzen Sie in den vergangenen 4 Wochen bei der Ausübung Ihrer Alltagstätigkeiten zu Hause und im Beruf behindert?**

[1] ☐ Überhaupt nicht
[2] ☐ Ein bisschen
[3] ☐ Mäßig
[4] ☐ Ziemlich
[5] ☐ Sehr

**9. Wie oft waren Sie in den vergangenen 4 Wochen ruhig und gelassen?**

[1] ☐ Immer
[2] ☐ Meistens
[3] ☐ Ziemlich oft
[4] ☐ Manchmal
[5] ☐ Selten
[6] ☐ Nie

**10. Wie oft waren Sie in den vergangenen 4 Wochen voller Energie?**

[1] ☐ Immer
[2] ☐ Meistens
[3] ☐ Ziemlich oft
[4] ☐ Manchmal
[5] ☐ Selten
[6] ☐ Nie

**11. Wie oft waren Sie in den vergangenen 4 Wochen entmutigt und traurig?**

[1] ☐ Immer
[2] ☐ Meistens
[3] ☐ Ziemlich oft
[4] ☐ Manchmal
[5] ☐ Selten
[6] ☐ Nie

**12. Wie häufig haben Ihre körperliche Gesundheit oder seelische Probleme in den vergangenen 4 Wochen Ihre <u>Kontakte zu anderen Menschen (Besuche bei Freunden, Verwandten usw.) beeinträchtigt</u>?**

[1] ☐ Immer
[2] ☐ Meistens
[3] ☐ Manchmal
[4] ☐ Selten
[5] ☐ Nie

## IHRE GEHFÄHIGKEIT

**13. Wie lange können Sie ohne Unterbrechung auf ebener Strecke laufen (oder denken Sie, dass Sie könnten), wenn Sie <u>langsam</u> gehen (langsamer als Ihre Familie, Freunde oder Gleichaltrige)?**

[0] ☐ Gar nicht
[1] ☐ 30 Sekunden
[2] ☐ 1 Minute
[3] ☐ 3 Minuten
[4] ☐ 10 Minuten
[5] ☐ 30 Minuten
[6] ☐ 1 Stunde
[7] ☐ 3 Stunden und mehr

**14. Wie lange können Sie ohne Unterbrechung auf ebener Strecke laufen (oder denken Sie, dass Sie könnten), wenn Sie <u>mit mittlerer Geschwindigkeit</u> gehen (mit derselben Geschwindigkeit wie Ihre Familie, Freunde oder Gleichaltrige)?**

[0] ☐ Gar nicht
[1] ☐ 30 Sekunden
[2] ☐ 1 Minute
[3] ☐ 3 Minuten
[4] ☐ 10 Minuten
[5] ☐ 30 Minuten
[6] ☐ 1 Stunde
[7] ☐ 3 Stunden und mehr

**15. Wie lange können Sie ohne Unterbrechung auf ebener Strecke laufen (oder denken Sie, dass Sie könnten), wenn Sie <u>schnell</u> gehen (schneller als Ihre Familie, Freunde oder Gleichaltrige)?**

[0] ☐ Gar nicht
[1] ☐ 30 Sekunden
(*weitere Antwortmöglichkeiten oben in der nächsten Spalte)*

(*weitere Antwortmöglichkeiten für Frage 15)*
[2] ☐ 1 Minute
[3] ☐ 3 Minuten
[4] ☐ 10 Minuten
[5] ☐ 30 Minuten
[6] ☐ 1 Stunde
[7] ☐ 3 Stunden und mehr

**16. <u>Im Vergleich</u> zur durchschnittlichen Gehgeschwindigkeit von Ihren Verwandten, Freunden und Menschen in Ihrem Alter, <u>gehen</u> Sie in der Regel?**

[1] ☐ Viel langsamer
[2] ☐ Langsamer
[3] ☐ Ein wenig langsamer
[4] ☐ Mit der gleichen Geschwindigkeit
[5] ☐ Schneller

## SCHMERZEN

**17. Wie würden Sie Ihre <u>Schmerzen</u> auf einer Skala von 0 (keine Schmerzen) bis 10 (schlimmsten vorstellbaren Schmerzen) <u>im Allgemeinen</u> einschätzen?**

[0] ☐ 0 Keine Schmerzen
[1] ☐ 1
[2] ☐ 2
[3] ☐ 3
[4] ☐ 4
[5] ☐ 5
[6] ☐ 6
[7] ☐ 7
[8] ☐ 8
[9] ☐ 9
[10] ☐ 10 Schlimmsten vorstellbaren Schmerzen

**18. Wie oft hatten Sie in den letzten zwei Wochen im Ruhezustand <u>Schmerzen in den Füßen (oder Beinen)</u>?**

[1] ☐ Immer
[2] ☐ Meistens
[3] ☐ Oft
[4] ☐ Manchmal
[5] ☐ Selten
[6] ☐ Fast nie
[7] ☐ Nie

## IHR SEELISCHES WOHLBEFINDEN

**19. Wie oft fühlten Sie sich im Verlauf der letzten 2 Wochen durch <u>Niedergeschlagenheit, Schwermut oder Hoffnungslosigkeit</u> beeinträchtigt?**

[0] ☐ Überhaupt nicht
[1] ☐ An einzelnen Tagen
[2] ☐ An mehr als der Hälfte der Tage
[3] ☐ Beinahe jeden Tag

**20. Wie oft fühlten Sie sich im Verlauf der letzten 2 Wochen durch <u>wenig Interesse oder Freude an Ihren Tätigkeiten</u> beeinträchtigt?**

[0] ☐ Überhaupt nicht
[1] ☐ An einzelnen Tagen
[2] ☐ An mehr als der Hälfte der Tage
[3] ☐ Beinahe jeden Tag

**21. Wie oft fühlten Sie sich im Verlauf der letzten 2 Wochen durch <u>Nervosität, Ängstlichkeit oder Anspannung</u> beeinträchtigt?**

[0] ☐ Überhaupt nicht
[1] ☐ An einzelnen Tagen
[2] ☐ An mehr als der Hälfte der Tage
[3] ☐ Beinahe jeden Tag

**22. Wie oft fühlten Sie sich im Verlauf der letzten 2 Wochen beeinträchtigt, weil Sie <u>nicht in der Lage waren, Sorgen zu stoppen oder zu kontrollieren</u>?**

[0] ☐ Überhaupt nicht
[1] ☐ An einzelnen Tagen
[2] ☐ An mehr als der Hälfte der Tage
[3] ☐ Beinahe jeden Tag

## IHR BERUFSSTATUS

**23. Welche der folgenden Angaben trifft auf Ihren <u>derzeitigen Berufsstatus</u> zu?**

[0] ☐ Berufstätig, in Vollzeit
[1] ☐ Berufstätig, in Teilzeit
[2] ☐ Berufstätig, geringfügig beschäftigt
[3] ☐ Ausschließlich Hausfrau/Hausmann
In Rente, …
[4] ☐ … altershalber
[5] ☐ … wegen Erwerbsminderung
[6] ☐ … vorzeitig wegen meiner Gefäßerkrankung
[7] ☐ … vorzeitig wegen einer anderen Erkrankung
[8] ☐ Arbeitslos
[9] ☐ Sonstiges, und zwar _____

**24. Falls Sie berufstätig sind: An wie vielen Tagen waren Sie <u>in den vergangenen drei Monaten krankgeschrieben</u>?**

☐☐ Tage (max. 60 Tage)

## AUSFÜLLEN DES FRAGEBOGENS

**25. Haben Sie diesen Fragebogen alleine oder mit Unterstützung (z.B. durch Angehörige oder Hausarzt) ausgefüllt?**

[1] ☐ Alleine
[2] ☐ Mit Unterstützung

**26. Tragen Sie bitte das Datum ein, an dem Sie den Fragebogen ausgefüllt haben:**

☐☐ Tag ☐☐ Monat ☐☐☐☐ Jahr

Bitte prüfen Sie noch einmal, ob Sie alle Fragen beantwortet haben.

# Vielen Dank für das Ausfüllen des Fragebogens!

# Anlage 2: Liste mit Variablen (GermanVasc-Kohortenstudie)

| | |
|---|---|
| Aufnahmedatum | DD.MM.JJJJ |
| Aufnahmeart | Elektiv, dringlich, notfallmäßig, unbekannt |
| Aufgenommen von | Zuhause, anderes Krankenhaus, andere Fachabteilung des selben Krankenhauses, Rehabilitationseinrichtung, Pflegeeinrichtung, wohnungslos, unbekannt |
| Funktioneller Status | Uneingeschränkt, leichte Arbeit, Selbstpflege, pflegebedürftig, bettlägerig, unbekannt |
| Mobilität | Uneingeschränkt, Prothesenversorgung, Gehhilfe, Rollstuhl, bettlägerig, unbekannt |
| Entlassungsdatum | DD.MM.JJJJ |
| Entlassen nach | Nach Hause, anderes Krankenhaus, andere Fachabteilung des selben Krankenhauses, Rehabilitationseinrichtung, Pflegeeinrichtung, wohnungslos, verstorben, unbekannt |
| Patientenalter | Jahre |
| Patientengeschlecht | Männlich, weiblich, Transgender weiblich, Transgender männlich |
| Körpergewicht | In Kilogramm |
| Körpergröße | In Zentimeter |
| ASA-Klassifikation | I, II, III, IV, V, VI, unbekannt |
| Diabetes | Kein Diabetes, diätetische Behandlung, orale Antidiabetika, alleinige Insulinbehandlung, orale Antidiabetika und Insulinbehandlung |
| HbA1c | In % |
| Niereninsuffizienz | Ja, nein |
| Serum-Kreatinin | In mg/dl oder ymol/L |
| Dialysepflichtig | Ja, nein |
| Tabakkonsum | Aktiver Raucher, früherer Raucher, niemals aktiv geraucht, unbekannt |
| Jahre seit Nikotinkarenz | Jahre |
| Koronare Herzkrankheit | Keine KHK, asymptomatische KHK, Angina pectoris unter plötzlicher und längerer physischer Belastung, Angina pectoris unter Alltagsbelastungen, Ruhebeschwerden oder Beschwerden bei geringster körperlicher Belastung |
| Z.n. Myokardinfarkt in der Vorgeschichte | Kein Myokardinfarkt, vor mehr als 6 Monaten, innerhalb der letzten 6 Monate, unbekannt |
| Herzinsuffizienz | Keine Herzinsuffizienz, NYHA I, NYHA II, NYHA III, NYHA IV, keine gegenwärtige Herzinsuffizienz aber Vorgeschichte |
| Aktuelle Ejektionsfraktion | In % |
| Herzrhythmusstörungen | Nein niemals, Ja gegenwärtig, Ja in der Vorgeschichte |
| COPD | Keine COPD, COPD ohne Behandlung, COPD mit pharmakologischer Behandlung, COPD mit Heimsauerstoffbehandlung |
| Bluthochdruck | Keine Hypertonie bekannt, Hypertonie unter suffizienter Blutdruckmedikation, Hypertonie unter unzureichender Blutdruckmedikation, |

| | |
|---|---|
| | keine gegenwärtige Hypertonie aber Vorgeschichte |
| Z.n. Revaskularisation bei PAVK in der Vorgeschichte | Keine Revaskularisation in der Vorgeschichte, Z.n. endovaskulärer Behandlung, Z.n. offen-chirurgischer Behandlung, Z.n. endovaskulärer und offen-chirurgischer Behandlung, unbekannt |
| Z.n. Amputation in der Vorgeschichte | Keine Amputationen, Minor-Amputationen, Major-Amputationen, unbekannt |
| Thrombozytenaggregationshemmer während der Behandlung | ASS, Clopidogrel, andere |
| Thrombozytenaggregationshemmer bei Entlassung | ASS, Clopidogrel, andere |
| Statine während der Behandlung | Ja, nein |
| Statine bei Entlassung | Ja, nein |
| Modifizierte Rutherford-Klassifikation (Indikation vor Behandlung) linkes Bein | Asymptomatisch, milde Claudicatio intermittens, moderate Claudicatio intermittens (>200m), schwere Claudicatio intermittens (<200m), ischämische Ruheschmerzen, Ulzera oder Nekrosen, nicht-heilende Amputationswunde, beides, akute Extremitätenischämie, unbekannt |
| Modifizierte Rutherford-Klassifikation (Indikation vor Behandlung) rechtes Bein | Asymptomatisch, milde Claudicatio intermittens, moderate Claudicatio intermittens (>200m), schwere Claudicatio intermittens (<200m), ischämische Ruheschmerzen, Ulzera oder Nekrosen, nicht-heilende Amputationswunde, beides, akute Extremitätenischämie, unbekannt |
| Fußinfektion linkes Bein | Keine Infektion, Grad I, Grad II, Grad III, unbekannt |
| Fußinfektion rechtes Bein | Keine Infektion, Grad I, Grad II, Grad III, unbekannt |
| Ankle-Brachial-Index linkes Bein | ABI ab 1.3, 1.3-0.9, 0.9-0.7, 0.7-0.4, unter 0.4, unbekannt |
| Ankle-Brachial-Index rechtes Bein | ABI ab 1.3, 1.3-0.9, 0.9-0.7, 0.7-0.4, unter 0.4, unbekannt |
| Gewebeverlust links | Kein Gewebeverlust, Grad I, Grad II, Grad III, unbekannt |
| Gewebeverlust rechts | Kein Gewebeverlust, Grad I, Grad II, Grad III, unbekannt |
| Durchgeführte Prozedur | Offen-chirurgische Bypassanlage, endovaskuläre Revaskularisation, Hybrideingriff |
| Dringlichkeit der Prozedur | Elektiv, dringlich, notfallmäßig, unbekannt |
| Art der endovaskulären Devices | PTA/Ballon, drug coated balloon, bare metal stent, drug eluting stent, mechanical thrombectomy, covered stent, brachytherapy, atherectomy without optical guidance, atherectomy with optical guidance, aspiration, scoring balloon, cutting balloon, cryoplasty, andere |
| Datum der Prozedur | DD.MM.JJJJ |
| Seite der Behandlung | Links, rechts, beide |
| Behandelte Gefäße | Aorta, A. iliaca communis, A. iliaca externa, A. iliaca interna, A. femoralis communis, A. |

| | |
|---|---|
| | profunda femoris, A. femoralis superficialis, A. poplitea P1, A. poplitea P2, A. poplitea P3, Tractus tibiofibularis, A. fibularis, pedale oder plantare Gefäße, Bypassgefäß, andere |
| Technischer Erfolg bei Ende der Prozedur | Erfolgreich, Verschluss der Zielläsion, Abbruch, unbekannt |
| Postoperatives akutes Koronarsyndrom | Nein, ja mit instabiler Angina pectoris, ja mit NSTEMI, ja mit STEMI |
| Postoperativer Stroke | Nein, ja Minor-Stroke, ja Major-Stroke, andere Symptomatik (z.B. TIA) |
| Postoperative neue Dialysepflichtigkeit | Nein, ja während des Krankenhausaufenthalts, ja chronische Dialysepflichtigkeit |
| Postoperativer Ankle-Brachial-Index links | ABI ab 1.3, 1.3-0.9, 0.9-0.7, 0.7-0.4, unter 0.4, unbekannt |
| Postoperativer Ankle-Brachial-Index rechts | ABI ab 1.3, 1.3-0.9, 0.9-0.7, 0.7-0.4, unter 0.4, unbekannt |
| Postoperative ungeplante Amputation links | Keine, Minoramputation, Majoramputation unterhalb des Kniegelenks, Majoramputation oberhalb des Kniegelenks, andere |
| Postoperative ungeplante Amputation rechts | Keine, Minoramputation, Majoramputation unterhalb des Kniegelenks, Majoramputation oberhalb des Kniegelenks, andere |
| Postoperativer Verschluss der Indexrekonstruktion | Nein, ja ohne Behandlung, ja nur medikamentös behandelt, ja nur endovaskulär behandelt, ja offen-chirurgisch behandelt |
| Postoperative distale Embolisation | Nein, ja ohne Behandlung, ja nur medikamentös behandelt, ja nur endovaskulär behandelt, ja offen-chirurgisch behandelt |
| Postoperative Dissektion | Nein, ja ohne Behandlung, ja nur medikamentös behandelt, ja nur endovaskulär behandelt, ja offen-chirurgisch behandelt |
| Versagen des Grafts oder Devices | Nein, ja ohne Behandlung, ja nur medikamentös behandelt, ja nur endovaskulär behandelt, ja offen-chirurgisch behandelt |
| Postoperative zugangsbedingte Majorkomplikation, Blutung inkl. Aneurysma spurium | Nein, ja ohne Behandlung, ja nur medikamentös behandelt, ja nur endovaskulär behandelt, ja offen-chirurgisch behandelt |
| Postoperatives Kompartmentsyndrom | Nein, ja ohne Behandlung, ja nur medikamentös behandelt, ja nur endovaskulär behandelt, ja offen-chirurgisch behandelt |
| Postoperative Wundinfektion | Nein, ja ohne Behandlung, ja nur medikamentös behandelt, ja offen-chirurgisch behandelt |
| Datum des Follow-up | DD.MM.JJJJ |
| Lebt der Patient | Ja, nein |
| Funktioneller Status | Uneingeschränkt, leichte Arbeit, Selbstpflege, pflegebedürftig, bettlägerig, unbekannt |
| Mobilität | Uneingeschränkt, Prothesenversorgung, Gehhilfe, Rollstuhl, bettlägerig, unbekannt |
| Modifizierte Rutherford-Klassifikation (Indikation vor Behandlung) linkes Bein | Asymptomatisch, milde Claudicatio intermittens, moderate Claudicatio intermittens (>200m), schwere Claudicatio intermittens (<200m), ischämische Ruheschmerzen, Ulzera oder |

| | |
|---|---|
| | Nekrosen, nicht-heilende Amputationswunde, beides, akute Extremitätenischämie, unbekannt |
| Modifizierte Rutherford-Klassifikation (Indikation vor Behandlung) rechtes Bein | Asymptomatisch, milde Claudicatio intermittens, moderate Claudicatio intermittens (>200m), schwere Claudicatio intermittens (<200m), ischämische Ruheschmerzen, Ulzera oder Nekrosen, nicht-heilende Amputationswunde, beides, akute Extremitätenischämie, unbekannt |
| Fußinfektion linkes Bein | Keine Infektion, Grad I, Grad II, Grad III, unbekannt |
| Fußinfektion rechtes Bein | Keine Infektion, Grad I, Grad II, Grad III, unbekannt |
| Ankle-Brachial-Index linkes Bein | ABI ab 1.3, 1.3-0.9, 0.9-0.7, 0.7-0.4, unter 0.4, unbekannt |
| Ankle-Brachial-Index rechtes Bein | ABI ab 1.3, 1.3-0.9, 0.9-0.7, 0.7-0.4, unter 0.4, unbekannt |
| Gewebeverlust links | Kein Gewebeverlust, Grad I, Grad II, Grad III, unbekannt |
| Gewebeverlust rechts | Kein Gewebeverlust, Grad I, Grad II, Grad III, unbekannt |
| Neue Amputation links | Keine, Minoramputation, Majoramputation, unbekannt |
| Neue Amputation rechts | Keine, Minoramputation, Majoramputation, unbekannt |
| Erneute Revaskularisation links | Keine, endovaskulär, offen-chirurgisch, beides |
| Erneute Revaskularisation rechts | Keine, endovaskulär, offen-chirurgisch, beides |
| Major Adverse Cardiovascular Events (MACE) | Ja, nein, unbekannt |
| Major Adverse Limb Events (MALE) | Ja, nein, unbekannt |
| Myokardinfarkt | Ja, nein, unbekannt |
| Schlaganfall oder transiente ischämische Attacke (TIA) | Ja, nein, unbekannt |
| Wundinfektion des OP-Wundbereichs | Ja, nein, unbekannt |
| Patientenberichtete Endpunkte | Siehe Lebensqualität-Fragebogen (Anlage 1) |

# Anlage 3: Liste mit Aufgreifkriterien zur Operationalisierung

| Variable | ICD-10 code, ATC code, OPS code |
|---|---|
| Fontaine Stadien | Before 2015: I70.21, pelvic-leg arteries with exercise induced pain, walking distance <200 m, Fontaine II; I70.22, Pelvic-leg arteries with rest pain, Fontaine III; I70.23-24, pelvic-leg arteries with ulcerations and/or gangrene, Fontaine IV<br>2015 onward: I70.21-22, pelvic-leg arteries with exercise induced pain, Fontaine II; I70.23, pelvic-leg arteries with rest pain, Fontaine III; I70.24-25, pelvic-leg arteries with ulcerations and/or gangrene, Fontaine IV<br>Other: E10.50-51, type 1 diabetes mellitus with peripheral vascular complications; E10.7, type 1 diabetes mellitus with diabetic foot syndrome; E11.50-51, type 2 diabetes mellitus with peripheral vascular complications; E11.7, type 2 diabetes mellitus with diabetic foot syndrome; I73.0, other peripheral vascular diseases, Raynaud syndrome; I73.1, Other peripheral vascular diseases, thrombangiitis obliterans; I73.8, other peripheral vascular diseases; I73.9, other peripheral vascular diseases; I74.0, arterial embolism and thrombosis, aorta abdominalis; I74.1, arterial embolism and thrombosis, aorta; I74.2, arterial embolism and thrombosis, upper extremities; I74.3, arterial embolism and thrombosis, lower extremities; I74.4, arterial embolism and thrombosis, arteries of the extremities; I74.5, arterial embolism and thrombosis, aorta iliac; I74.8, arterial embolism and thrombosis, other arteries; I74.9, arterial embolism and thrombosis, other arteries; L03.01-2, L03.11, cellulitis of finger and toe, including acute lymphangitis; L98.4, chronic ulcer of skin, not elsewhere classified; R02, gangrene, not elsewhere classified |
| Schlaganfall oder Transiente Ischämische Attacke (TIA) | I61, I63, I64, G45 |
| Modifiziertes Major Adverse Cardiovascular Event (MACE) | Kardiovaskuläres Ereignis oder Tod |
| Modifiziertes Major Adverse Limb Event (MALE) | Amputation oder Tod |
| Sterblichkeit | In Routinedaten als Austrittsgrund “Tod“ oder Entlassungsgrund „Tod“ enthalten |
| Kardiovaskuläres Ereignis | I20.0, I21-I24 Myocardial infarction, I61, I63, I64, G45 Schlaganfall/TIA |
| (Inzidenter) Diabetes | E10, E11, E12, E13, E14 or ATC A10 |
| (Inzidente) Myopathie | G72.0, G72.8, G72.9, M60.8, M60.9, M79.1 |
| Dyslipidämie | E78 |
| Koronare Herzkrankheit | I20-25 |
| Rauchen | F17 |
| Myokardinfarkt | I20.0, I21-I24 |
| Krebs | Metastatic cancer: C77-C80<br>Solid tumor without metastasis: C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C97 |
| Polypharmazie | Number of different prescriptions during 1 year before index admission |

| Variable | ICD-10 code, ATC code, OPS code |
|---|---|
| Lipidsenker | C10 |
| Statine | C10AA, C10BA, C10BX |
| Antithrombotika | B01 |
| Antihypertensiva | C02, Antihypertensive drugs; C03, diuretic drugs; C07, β-blocking agents; C08, calcium channel blockers; C09, agents acting on renin-angiotensin system |
| Orale Antikoagulanzien | B01AA, B01AE, B01AF |
| Antidiabetika | A10 |
| Betablocker | C07 |
| Kalziumkanal-Blocker | C08 |
| ATII-Rezeptorantagonisten oder ACE-Hemmer | C09A-D |
| Amputation | 5-864, Major amputation, above the ankle; 5-865, Minor amputation, below the ankle |
| Endovaskuläre Revaskularisation | |
| Aortoiliakal | 8-836.04, 8-836.14, 8-836.24, 8-836.74, 8-836.p4, 8-836.r4, 8-836.34, 8-836.84, 8-83c.b4, 8-840.04, 8-840.14, 8-840.24, 8-840.34, 8-840.44, 8-840.54, 8-841.04, 8-841.14, 8-841.24, 8-841.34, 8-841.44, 8-841.54, 8-843.04, 8-843.14, 8-843.24, 8-843.34, 8-843.44, 8-843.54, 8-845.04, 8-845.14, 8-846.04, 8-846.14, 8-849.04, 8-849.14, 8-84a.04, 8-84a.14, 8-836.0q, 8-836.09, 8-836.1h, 8-836.19, 8-836.2h, 8-836.29, 8-836.7h, 8-836.79, 8-836.ph, 8-836.p9, 8-836.rh, 8-836.r9, 8-836.3h, 8-836.39, 8-836.8h, 8-836.89, 8-83c.b9, 8-840.0q-.5q, 8-840.09, 8-840.19, 8-840.29, 8-840.39, 8-840.49, 8-840.59, 8-841.0q-.5q, 8-841.09, 8-841.19, 8-841.29, 8-841.39, 8-841.49, 8-841.59, 8-842.0q-.5q, 8-842.09, 8-842.19, 8-842.29, 8-842.39, 8-842.49, 8-842.59, 8-843.0q-.5q, 8-843.09, 8-843.19, 8-843.29, 8-843.39, 8-843.49, 8-843.59, 8-845.0q, 8-845.1q, 8-845.09, 8-845.19, 8-846.0q, 8-846.1q, 8-846.09, 8-846.19, 8-848.0q-.5q, 8-848.09, 8-848.19, 8-848.29, 8-848.39, 8-848.49, 8-848.59, 8-849.0q, 8-849.1q, 8-849.09, 8-849.19, 8-84a.0q, 8-84a.1q, 8-84a.09, 8-84a.19, 8-84d.0q-.5q |
| Femoropopliteal | 8-836.0s, 8-836.0b, 8-836.1k, 8-836.1b, 8-836.2k, 8-836.2b, 8-836.7k, 8-836.7b, 8-836.pk, 8-836.pb, 8-836.rk, 8-836.rb, 8-836.3k, 8-836.3b, 8-836.wk, 8-836.wb, 8-836.8k, 8-836.8b, 8-83c.bb, 8-840.0s-.5s, 8-840.0b-.5b, 8-841.0s-.5s, 8-841.0b-.5b, 8-842.0s-.5s, 8-842.0b-.5b, 8-843.0s-.5s, 8-843.0b-.5b, 8-845.0s, 8-845.1s, 8-845.0b, 8-845.1b, 8-846.0s, 8-846.1s, 8-846.0b, 8-846.1b, 8-848.0s-.5s, 8-848.0b-.5b, 8-849.0s, 8-849.1s, 8-849.0b, 8-849.6b, 8-84a.0s, 8-84a.1s, 8-84a.0b, 8-84a.1b, 8-84d.0s-.5s |
| Krural | 8-836.0c, 8-836.1c, 8-836.2c, 8-836.3c, 8-836.7c, 8-836.8c, 8-836.pc, 8-836.rc, 8-836.wc, 8-83c.bc, 8-840.0c-.5c, 8-841.0c-.5c, 8-842.0c-.5c, 8-843.0c-.5c, 8-844.0c-.5c, 8-845.0c, 8-845.1c, 8-846.0c, 8-846.1c, 8-848.0c-.5c, 8-849.0c, 8-849.1c, 8-84a.0c, 8-84a.1c, 8-84d.0c-.5c |
| Offen-chirurgische Revaskularisation | 5-380, 5-381, 5-382, 5-383, 5-384, 5-38c, 5-38d, 5-38e, 5-38f, 5-393, 5-394, 5-395, 5-396, 5-98a |
| „Frailty“ | A04, A09, A41, B95, B96, D64, E05, E16, E53, E55, E83, E87, F00, F01, F03, F05, |

| Variable | ICD-10 code, ATC code, OPS code |
|---|---|
| | F10, F32, G20, G30, G31, G40, G45, G81, H54, H91, I63, I67, I69, I95, J18, J22, J69, K26, K52, K59, K92, L03, L08, L89, L97, M15, M19, M25, M41, M48, M79, M80, M81, N17, N18, N19, N20, N28, N39, R00, R02, R11, R13, R26, R29, R31, R32, R33, R40, R41, R44, R45, R47, R50, R54, R55, R56, R63, R69, R79, R94, S00, S01, S06, S09, S22, S32, S42, S51, S72, S80, T83, U80, X59, Y84, Z22, Z50, Z60, Z73, Z74, Z75, Z87, Z91, Z93, Z99 |
| Drug-coated balloon | 8-83b.b0, 8-83b.b2-b5, 8-83b.ba-bd |
| Uncoated balloon | 8-836.04/09/0b/0c/0e |
| Drug-eluting stent (paclitaxel) | 8-840.04/9/q/b/s/c/e, 8-841.04/9/q/b/s/c/e, 8-842.04/9/q/b/s/c/e, 8-848.04/9/q/b/s/c/e, 8-83b.03-06 |
| Drug-eluting stent (other) | 8-83b.0a-f, 8-83b.0x |
| Bare metal stent | 8-840.04/9/q/b/s/c/e, 8-840.14/9/q/b/s/c/e, 8-840.24/9/q/b/s/c/e, 8-840.34/9/q/b/s/c/e, 8-840.34/9/q/b/s/c/e, 8-840.44/9/q/b/s/c/e, 8-840.54/9/q/b/s/c/e, |

*ATC,* Anatomical Therapeutic Chemical; *ICD-10,* International Classification of Diseases, 10th revision; *OPC,* operational and procedure coding.

Übersichten

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# Quality of care in surgical/interventional vascular medicine: what can routinely collected data from the insurance companies achieve?

## Introduction

Countless laws and directives oblige stakeholders in the German healthcare system to continuously assure and improve the quality of patient care. Further motivators arise from reasons of competition, regulatory influence (e.g. pay for performance, EU Medical Device Regulation) or scientific interest; however, assuring and improving quality requires valid measurement of the quality of medical care.

Although modern funding structures were developed for the healthcare system as early as the nineteenth century, a broad public debate on performance-related remuneration only began in the USA in the 1960s [17]. It was also during this time that work started at Yale University on the development of a uniform classification system for diseases and treatments. This classification was introduced some 20 years later as the diagnosis-related groups (DRG) within the Centers for Medicare & Medicaid Services (CMS) system [5]. Even back then, the treatment and its quality were to already be linked to the remuneration structures, whereby this raised countless questions and led to partial interests. At its core, the discussion has always been about the objective measurement of the quality of medical care. A construct that differentiates between the quality of the structure and process and the quality of the outcome is still generally accepted today [17]. To date, this has required the collection of valid primary data in clinical registries [8]; however, more than half a century after the broad public debate, many questions have still not been conclusively answered.

Surgical and interventional vascular medicine is a subject that is continuously evolving and counts among the great challenges in modern medicine, both in clinical and scientific terms. Here, common diseases such as peripheral arterial occlusive disease (PAOD) occur at the same time as rare diseases, such as the genetic aortic syndrome. Established low-risk procedures are accompanied by extremely complex endovascular procedures involving very high risks. The discipline is also characterised by rapid innovation cycles in medical devices. Besides the procedure-related parameters and direct technical outcomes, numerous predictors play a vital role in the long-term survival of patients. Finally, patients with vascular diseases are nowadays treated by several specialist disciplines using complementary conservative pharmacological and endovascular treatment as well as open surgery procedures. These factors significantly impact the measurement of all levels of quality and their validity and complicate the comprehensive collection of primary data in clinical registries for quality assurance [9].

Legally binding registries of external cross-sectoral quality assurance in Germany (§ 137a of Book V of the German Social Code [SGB V]) harbor advantages due to the potentially high external validity. They comprehensively cover almost all procedures performed, although only the respective inpatient stay. A few registries sometimes provide a longer follow-up and include subsequent hospital stays. As a rule, however, a hospital's participation in the registries of professional societies or research groups is voluntary, and the selection of cases and endpoints is not homogeneous, which reduces the internal and external validity [58]. This aspect may be less significant in highly centralised Scandinavian

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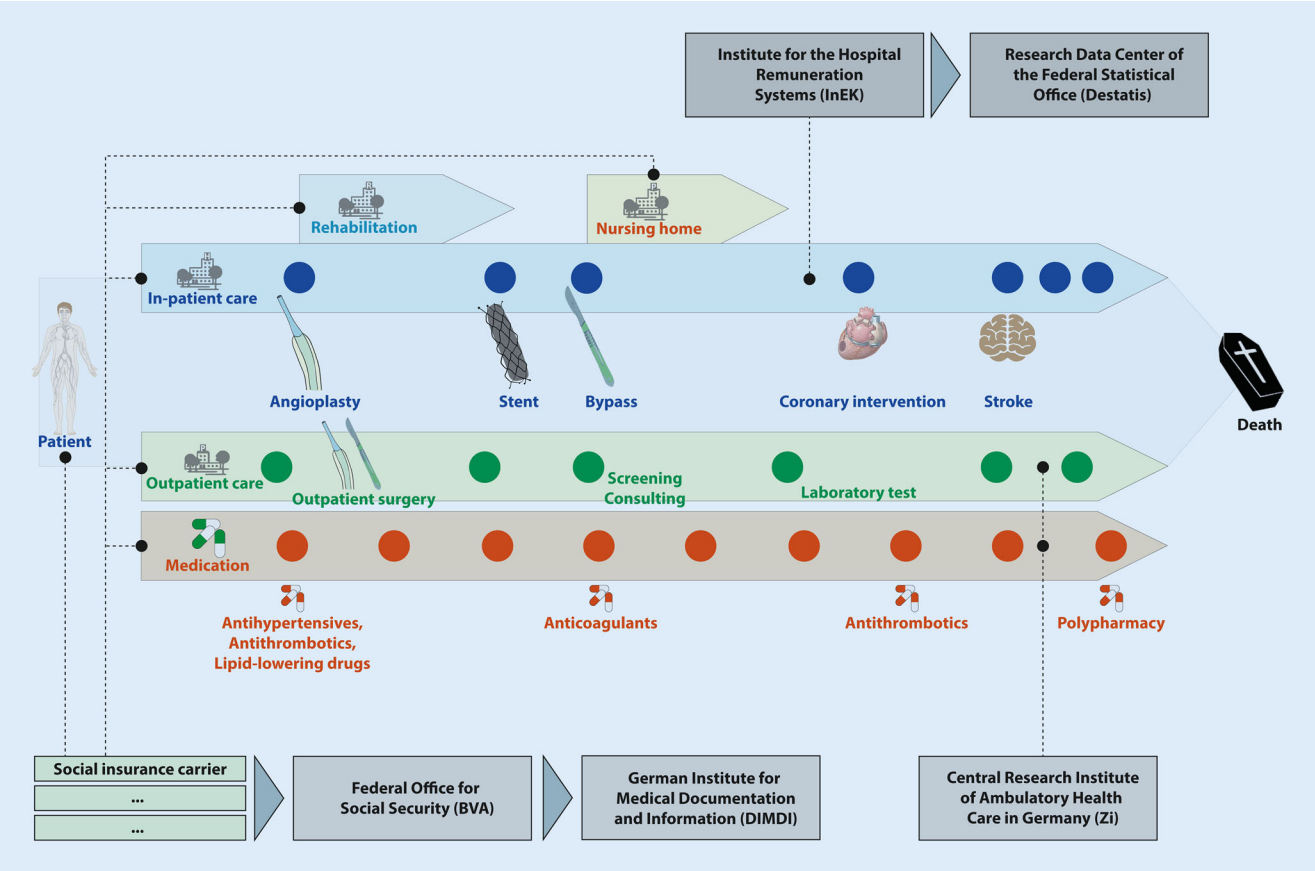


**Fig. 1** ▲ Examples of data generation and data flow in cross-sectoral care for vascular diseases. A sensible link between all sectors and the long-term course is only possible through the social data of the social insurance carrier

countries than in Germany, where of the around 2000 hospitals up to 650 centers with different specialist departments provide vascular treatment. It is also possible to achieve an almost national survey of inpatient care using the data obtained pursuant to § 21 of the German Hospital Reimbursement Act (*Krankenhausentgeltgesetz* [KHEntgG]) from the Institute for the Hospital Remuneration System (Institut für das Entgeltsystem im Krankenhaus [InEK]), which ultimately also forms the basis for the diagnostic hospital statistics of the German Federal Statistical Office (Deutsches Statistisches Bundesamt [Destatis]). Here too, however, the observation period is restricted to the hospital stay. This limits the validity and clinical relevance of the findings and key conclusions. Furthermore, the lack of longitudinal linking between the cases prevents a patient-oriented approach. Depending on the reason for examination or index disease, this may ultimately make quality assurance impossible. Although the interdisciplinary outpatient care of vascular patients also plays an important role in the long-term success of treatment, this aspect has not yet been adequately represented in all available data sources on inpatient care. Hence differences in outpatient secondary prevention are an important influencing factor in the assessment of the quality of revascularization.

Against this backdrop, suitably prepared routinely collected data from social insurance institutions provide a useful complement for quality improvement projects. Motivators inherent to the system (revenue generation) enable the timely and comprehensive generation of these data by the service providers without any limitation to individual specialist disciplines. Through a person-related longitudinal linkage of all available datasets, long-term observation of individual patients over periods of up to 15 years is theoretically possible, provided that the appropriate anonymization using all of the currently established measures has been carried out beforehand (◘ **Fig. 1**; [11, 54]). Care in accordance with the guidelines with respect to inpatient treatment but also outpatient aftercare can therefore be adequately evaluated using routinely collected data from the social insurance institutions [37].

This review article examines the advantages and challenges of using routinely collected data for quality improvement projects in interdisciplinary vascular medicine. After reading this article, readers will be able to assess the different sources of routinely collected data and their potential usefulness for improving the quality of vascular treatment.

## Routinely collected data in Germany

Routinely collected data is commonly associated with other terms, although on closer inspection the distinction is not

always clear cut. Thus, all data generated during routine care and their metadata can be considered routinely collected data [9, 50]. A number of research consortiums are currently working intensively on the harmonization and scientific use of these data [8, 22, 46]. The term secondary data derives from secondary purposes (e.g. quality assurance, research) beyond the primary purpose (mainly administration and accounting) [51]. Today, the debate on the evaluation and management of the healthcare system primarily centers on the data collected by social insurance institutions (**Fig. 1**). Of particular importance and central to this article are the data from insured persons available here (§ 288 SGB V), along with the data on inpatient and outpatient care (§ 301, § 115 f. SGB V), contractual medical care (§ 295 SGB V), pharmaceutical billing (§ 300 SGB V), prevention and rehabilitation (§ 301 SGB V), incapacity to work (§ 295 SGB V), provision of therapeutic products (§ 302 SGB V), care for the chronically ill (§ 137f SGB V) and nursing care (§§ 36–38, § 41 SGB XI; § 37, § 43 SGB V). The data are also available at various institutions in the corresponding anonymized format for scientific use by authorized institutions. It is then no longer considered social data in the legal sense (**Table 1**).

The scientific use of routinely collected data on inpatient care is most common, whereby the International Classification of Diseases (ICD) of the World Health Organization (WHO) valid in the reporting year is used to analyze primary and secondary diagnoses as well as operations and procedures. Deviating from this, the German uniform assessment standard (*Einheitlicher Bewertungsmaßstab* [EBM]) and the drug regulations via the anatomical therapeutic chemical (ATC) classification system are for example available for the outpatient sector in addition to the less comprehensive diagnosis coding. Despite the differences in diagnostic quality between sectors, a lack of better alternatives means that routinely collected data is frequently used.

The relevance of routinely collected data in the observation of population-related morbidity structures is thus demonstrated directly through the use of outpatient and inpatient information in Germany (**Table 2**; [27]).

## Consensus recommendations and guidelines on routinely collected data

In the international context, the validity and (international) comparability of routinely collected data has been the subject of controversial debate since it first began to be used for scientific purposes [6, 20]. One main criticism is the limited comparability of the findings of routinely collected data studies due to the large number of classification systems used, with different versions and revisions as well as the project-specific selection of suitable inclusion criteria. With this in mind, uniform classifications of comorbidities and risk scores have been developed over the past 20 years to predict the severity

## Abstract · Zusammenfassung

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### Quality of care in surgical/interventional vascular medicine: what can routinely collected data from the insurance companies achieve?

**Abstract**

The complexity and diversity of surgical/interventional vascular medicine necessitate innovative and pragmatic solutions for the valid measurement of the quality of care in the long term. The secondary utilization of routinely collected data from social insurance institutions has increasingly become the focus of interdisciplinary medicine over the years. Owing to their longitudinal linkage and pan-sector generation, routinely collected data make it possible to answer important questions and can complement quality development projects with primary registry data. Various guidelines exist for their usage, linkage, and reporting. Studies have shown good validity, especially for endpoints with major clinical relevance. The numerous advantages of routinely collected data face several challenges that require thorough plausibility and validity procedures and distinctive methodological expertise. This review presents a discussion of these advantages and challenges and provides recommendations for starting to use this increasingly important source of data.

**Keywords**

Routinely collected data · Health research · Validity · Quality indicators · Administrative data

### Behandlungsqualität in der operativ-interventionellen Gefäßmedizin – was können Routinedaten der Krankenkassen leisten? Englische Version

**Zusammenfassung**

Die Komplexität und Diversität der operativ-interventionellen Gefäßmedizin macht innovative und pragmatische Lösungsansätze zur validen Messung der langfristigen Behandlungsqualität erforderlich. Die sekundäre Nutzung von Routinedaten der Sozialversicherungsträger gerät dabei seit Jahren zunehmend in den Fokus der interdisziplinären Fachwelt. Routinedaten ermöglichen durch ihre longitudinale Verknüpfung und sektorenübergreifende Generierung die Beantwortung wichtiger Fragestellungen und können Qualitätsentwicklungsprojekte mit Primärdaten komplementär ergänzen. Es stehen verschiedene Leitlinien zu deren Nutzung, Verknüpfung und Berichterstattung zur Verfügung. Insbesondere bei Endpunkten mit großer klinischer Relevanz wurde in Studien eine gute Validität nachgewiesen. Den vielen Vorteilen von Routinedaten stehen spezifische Herausforderungen gegenüber, die umfassende Plausibilitäts- und Validierungsverfahren und eine ausgeprägte Methodenkompetenz erfordern. Diese Übersichtsarbeit beschäftigt sich kritisch mit diesen Vorteilen und Herausforderungen und bietet Empfehlungen für den Einstieg in die Nutzung dieser zunehmend wichtigen Datenquelle.

**Schlüsselwörter**

Routinedaten · Versorgungsforschung · Validität · Qualitätsindikatoren · Administrative Daten

**Table 1** Supraregional availability of frequently used German routine data

| Institution and data owner | Characteristics |
|---|---|
| Scientific institutes of health insurance funds | E.g. BARMER science data warehouse (W-DWH), DAK-Gesundheit, AOK Research Institute (WIdO); cross-sectoral longitudinal and cross-sectional studies; limited to insured population |
| Federal Institute for Drugs and Medical Devices (DIMDI) | Partially limited datasets (e.g. no place of residence, admission date or quarterly pharmaceutical prescriptions) |
| Central Research Institute of Ambulatory Health Care in Germany (ZI) | Outpatient standard care and supply of pharmaceuticals; no data linkage to inpatient care |
| Institute for the Hospital Remuneration System (InEK) | Inpatient care data in accordance with § 21 KHEntgG; no data linkage |
| Federal Statistical Office (Destatis) | Microdata by the Research Date Center; hospital statistics |

*KHEntgG* German Hospital Reimbursement Act

of diseases and in-hospital mortality [18, 41, 59].

Numerous guidelines and recommendations are currently also available from the German Society for Epidemiology (DGEpi) and the German Society for Social Medicine and Prevention (DGMSP) on the subject of routinely collected data. The Working Group for the Survey and Utilization of Secondary Data (AGENS) already published guidelines on secondary data analysis back in 2005; the publication is now in its third edition [50]. Against this backdrop, further guidelines developed since 2016 address the increasingly important subject of ensuring compliance with data protection regulations when linking datasets [34]. Finally, the standardized reporting of secondary data analyses (STROSA) reporting standard is available for Germany and also in the second edition [49].

## Validation studies and transferability of findings

In addition to random sampling and additional needs-based reviews by the medical service of German statutory health insurance providers (Medizinischer Dienst der Krankenversicherung [MDK]), scientifically initiated validation studies with routinely collected data sources are available in Germany, for example, on mortality in the German pharmacoepidemiological research database (GePaRD) with high sensitivity (95.9%) and specificity (99.4%) [33] and on diagnoses (sensitivity to dementia 80%, heart failure 97% and tuberculosis 100%) [45]; however, outpatient diagnoses can have significantly lower sensitivity rates, which is attributed to the (quarterly) coding practices in Germany (sensitivity to tuberculosis 40%) [45].

In principal, validation should always be context-specific and take the external framework conditions of the target population into account [25]. A prerequisite for validation is a review of the plausibility and consistency of the data. This can for example include repeat diagnoses of chronic diseases and a comparison between drug and diagnostic data. It holds that greater severity of the endpoint is associated with higher validity, while less relevant observations have lower validity (inpatient sensitivity to hypertension 65%, cancer 91% and acute myocardial infarction 94% [44], outpatient sensitivity to back pain 74% and hypertension 81% [19]). Good validity can especially be assumed for mortality-related endpoints among the vascular patient cohort over the age of 65 years [15, 16, 25, 32, 38].

Adequate consideration of the diagnosis-free history (lookback) is recommended for incidence predictions. Czwickla et al. were able to show that by taking a lookback period of 7 years, the incidence of cancer is estimated to be about 10% lower (breast cancer 138.7 vs. 129.0 per 100,000 persons, prostate cancer 103.6 vs. 95.1 and colorectal cancer 42.1 vs. 38.3) [16].

For internal data validation, it can also be checked whether the same diagnosis codes predict comparable prevalences during different observational periods. It could for example be shown using routinely collected data from the BARMER health insurance provider that inclusion criteria for PAOD treatment and its clinical comorbidities as well as interventions correlated over a longer period [30]. Registry data can be used for the further validation of routinely collected data. One approach using model-based validation and a second approach using stratification-based validation have been developed within the IDOMENEO study funded by the German Federal Joint Committee (Gemeinsamer Bundesausschuss [G-BA]) [12]. In the model-based approach, the data is hierarchically ordered according to the hospital treating the patient, i.e. patients from one hospital form a cluster, both in the registry and in the routinely collected data from BARMER. Hospital-specific deviations can thus be taken into account and the multilevel models of the two data sources compared on the patient level. In the stratification-based approach, patients are divided into subgroups according to their characteristics, such as age, gender and the individual comorbidity profile. This them enables a comparison by means of subgroup analyses between the two data sources. The more similar the two data sources are, the higher the validity. Both approaches can ensure k-anonymity in compliance with data protection regulations [54].

## Data protection and ethical considerations

The introduction of the General Data Protection Regulation (GDPR) of the European Union and its national implementation a few years ago led to the substantial restriction of healthcare research and quality improvement using real-world data sources. At the same time, however, legal grey areas that existed in the past have been replaced by

**Table 2** Possibilities and limitations of selected quality indicators of different data sources

| Indicator | Claims data of health insurance funds (e.g. BARMER, DAK-Gesundheit) | Inpatient care data in accordance with § 21 KHEntgG (InEK, Destatis) |
|---|---|---|
| *Quality of results* | | |
| Mortality | High validity over entire duration of insurance up to 15 years (infrequent change of provider above the age of 65 years) | Discharge reason death limited to in-hospital deaths |
| Inpatient readmission | Possible with limitation in cause of readmission (e.g. emergency or identical main diagnosis as index case) | No data linkage possible (case-based analysis) |
| Reintervention | Possible for entire duration of insurance via procedure coding (limitations regarding side of body due to incomplete coding) | Limited to current hospital case |
| Amputation | Possible for entire duration of insurance via procedure coding (limitations regarding side of body due to incomplete coding) | Limited to current hospital case |
| Myocardial infarction | Possible via main or admission diagnosis or procedures | Limited to current hospital case |
| Stroke | Possible via main or admission diagnosis or procedures | Limited to current hospital case |
| Wound healing disorder | Possible via main or admission diagnosis or procedures | Limited to current hospital case |
| Acute limb ischemia | Possible via main or admission diagnosis or procedures | Limited to current hospital case |
| Bleeding complication | Possible via main or admission diagnosis or procedures | Limited to current hospital case |
| Decreasing kidney function and dialysis | Possible via main or comorbid diagnosis or procedures | Limited to current hospital case |
| *Other levels of quality (quality of process and structure)* | | |
| Pharmaceutical prescription according to guidelines | All pharmaceutical prescriptions and filled prescriptions via ATC classification available quarterly | No outpatient pharmaceutical prescription data available |
| Diagnostics according to guidelines | Inpatient and outpatient care over entire duration of insurance | Limited to inpatient and reimbursed procedures in current hospital case |
| Case volume | Limited to population insured by provider | Complete data collection |
| Length of stay | Complete data collection | Complete data collection |
| Weekend effect | Complete data collection | Complete data collection |
| *Adjusting factors and others* | | |
| Comorbidities | Previous outpatient and inpatient diagnoses and pharmaceutical prescriptions up to index case (e.g. prescription for insulin as indication of diabetes) | Limited to main and secondary diagnosis as well as current hospital case |
| Medication history prior to admission | Complete data collection (except for over-the-counter pharmaceuticals) | No outpatient pharmaceutical data available |
| Socioeconomic status | Limited. Can be inferred from co-payment exemptions or proxy variables | Not available in valid form |
| Diagnostic or screening prior to admission (outpatient) | If EBM-number is available (e.g. screening and consultation on abdominal aortic aneurysms) | No outpatient data available |

*ATC* anatomical therapeutic chemical, *EBM* German uniform assessment standard, *InEK* Institute for the Hospital Remuneration System, *KHEntgG* German Hospital Reimbursement Act

legally verifiable regulations. The GDPR places high demands on the anonymization of data, as the purely hypothetical linking of datasets or individual characteristics is already explicitly described as a criterion for personal data. To ensure that the social data collected by social insurance institutions in compliance with the law can also be used by researchers for the purposes of quality improvement and healthcare research, the data owners perform comprehensive processing or de facto anonymization. Through appropriate aggregations, censoring and logically meaningful date shifts, these data are altered in such a way that they are no longer considered personal or social data but still allow valid evaluations. One alternative is to obtain the explicit informed consent of all insured persons; however, this would create a disproportionate amount of work for many projects. With respect to ethical considerations, the interdisciplinary good practice in secondary data analysis clearly states in its first guidelines that although secondary data analyses must be carried out in accordance with ethical principles, an ethics committee only needs to be consulted in individual cases [50].

## Methodological considerations

From a methodological, statistical perspective, routinely collected data represent a particularly interesting source of secondary data and an important basis for health services research. Similar to information from vital statistics, these data contain relevant information on the entire target population rather than on just a random sample [35]. Another statistically interesting aspect is the process of data generation, which is standardized and independent of possible scientific questions. Both the recording of the population and the availability of data entail methodological necessities and must be taken into account in the research design accordingly. Since routinely collected data do not represent a random sample, inferential statistical methods and especially hypothesis testing with associated *p*-values play a far lesser role here than they do with primary data [57]. This is further emphasized by the high statis-

**Table 3** Strengths and limitations of selected indicator of quality in various data sources

| Parameter | Randomized control trial | Routine data |
|---|---|---|
| *Coverage of the population* | Low, often only high-volume centers included and small selective samples | High, all service providers included but often only access to a single health insurance fund |
| *Diversity of the population* | Exceptionally low because study population tailored to a specific disease and intervention. Focus on typical cases | Exceedingly high because full real-world representation of provision of health care |
| *Internal validity* | Medium to high, due to randomization blinding and controlled intervention. But large variation of the quality of a specific trial<br>CONSORT statement | Low to medium and dependent on methodology for adjustment for bias and validation of variables used for the analysis<br>STROBE statement |
| *External validity* | Low, due to highly selected population | High, because data collected during routine care |
| *Laboratory parameters* | Partly included. Biobanking enables additional biomarker-based and genetic analyses | Usually not included. Could be approximated partly via ICD codes (hypertension, hypercholesterolemia) |
| *Number of cases* | Low. Usually minimum size for detecting treatment effects. Underpowered for (rare) long-term outcomes | Exceedingly high. Challenges arising from potential false positive findings. Sensitivity analyses necessary |
| *Adverse events* | High. Recorded according to protocol | Available for a long follow-up duration but dependent on quality of documentation (outpatient, inpatient) |
| *Costs* | High, additional effort for screening, recruitment, conduct and documentation | Low, no additional effort for documentation |
| *Availability* | Low. Data mostly analyzed within project partners and not generally publicly available | High. Simpler since innovation funding, consortium projects established |
| *Estimation of prevalence* | Yes | Yes |
| *Estimation of incidence* | Barely | Yes, if patient history is assessed |
| *Follow-up* | Mostly short follow-up duration | Many years of follow-up without additional effort of documentation |
| *Cross-sectoral* | Rarely | Yes, outpatient and inpatient data could be linked |
| *Selection and recall bias?* | Yes. Selection bias due to hospital and specifics of patients | Barely |
| *Assessment of comparative effectiveness?* | No | Yes |
| *Suitable for quality control/ benchmarking?* | Less suitable | Well suited for parameters like mortality, diagnoses and procedures |
| *Assessment of causality?* | Yes | Partly, rather correlations and associations. Quasi-experimental approaches possible |
| *Patient-reported outcomes, lifestyle variables* | Yes, depending on research question | No, only available via proxy variables |
| *Unspecific diagnoses* | Barely | Yes, especially in outpatient sector |

*CONSORT* consolidated standards of reporting trials, *STROBE* strengthening the reporting of observational studies in epidemiology, *ICD* International Classification of Diseases

tical power due to the large number of cases and the possibility of multiple testing, which leaves analyses prone to false positive outcomes. For these reasons, standardized differences combined with considerations of medical relevance are better suited to the assessment of differences than the consideration of *p*-values alone. This applies to the assessment of gender disparities in secondary prevention following inpatient PAOD hospitalization [40]. Likewise, absolute differences should also always be considered in addition to any potentially statistically significant relative differences with respect to indicators of outcome quality.

Since routinely collected data are already available when new studies are designed, a deductive approach is not possible without restrictions and variables are measured based on the existing database in addition to prior theoretical considerations [52]. As a consequence, required target variables (e.g. laboratory parameters or patient-reported endpoints) might not be available or at least not in the desired format. Proxy variables must be used in this case. One example is the measurement of smoking status using the ICD-10 code F17 (mental and behavioral disorders due to use of tobacco) as a proxy for nicotine consumption [43]. This also applies to complex diagnoses and procedures, which must be compiled individually from a multitude of billing codes in order to approximate the target intervention as accurately as possible. This raises the potential statistical problem of omitted variable bias. Further bias arises from the lack of randomization of the data in relation to the primary hypothesis, which can lead to unmeasured confounding.

Critics of routinely collected data analyses, big data and data-driven research often generally doubt the potential of this research area to provide statements on relevant issues [2]; however, this perspective ignores the fact that findings from secondary data analyses do not intend to replace evidence from randomized trials but should rather be seen as complementary to this (**Table 3**). For example, the idea, development, exploration, assessment, and long-term follow-up (IDEAL) framework even explicitly emphasizes the

complementary function of routinely collected data in the review of the surgical efficacy of interventions (especially for rare events and long-term outcomes) [47]. During pragmatic trials, the aim is increasingly to also use intervention studies in everyday care or to link routinely collected data with primary surveys via data linkage [53]. Finally, quasiexperimental study designs are used in billing data to approximate causal statements [62]. There is a growing realization that different types of data and analysis can each supply their own evidence building blocks whose synthesis can generate further knowledge.

The recent global debate on the safety of drug-coated stents and balloons in femoropopliteal arteries is one example of the interplay of different types of data and analysis strategies [10]. In December 2018, safety concerns were published regarding long-term survival following the use of paclitaxel-coated medical devices in the femoral region [28]. These findings led to a global response, with recruitment for studies halted and usage warnings issued by national authorities. Neither clinical studies nor registry data could subsequently be used to validate this initial suspicion as long-term data of a sufficient quantity and quality were not available. Drawing on routinely collected data from BARMER, two comprehensive analyses of routinely collected data were conducted in parallel and independently of each other, taking very different methodological approaches. On the one hand, propensity score matching was implemented to compensate for the lack of randomization at the time of the intervention [13]. On the other hand, information on multiple interventions per patient was used to model a possible dose-response relationship [21]. Despite the different methodologies, both studies came to the conclusion that in the unselected real-world samples, the suspected safety concerns ultimately did not arise. The same discrepancy between secondary evaluations of intervention studies and routinely collected data has recently been observed regarding the use of paclitaxel coating in the arteries of the lower leg [24, 29].

## Risk prediction with routinely collected data

Due to their longitudinal data structure, abundance of variables and large number of cases, routinely collected data also provides numerous opportunities for long-term risk predictions. Within the RABATT project funded by the Federal Joint Committee (G-BA), a learning risk score was recently developed for 5-year amputation-free survival following invasive revascularization of symptomatic PAOD [46]. This score was calculated using routinely collected data from BARMER and validated using GermanVasc registry data. Machine learning and regularization procedures, such as the LASSO selection procedure with cross-validation were used to identify variables with a high association with survival [56]. With good discrimination, predictors could be identified that enable a pragmatic classification of patients into low-risk to high-risk groups. In this application, such data-based machine learning procedures may of course also only be considered complementary to existing evidence and must always be viewed in the respective medical context in order to prevent spurious correlation [31]. It is therefore particularly important to also pursue external validation and continuous development when using prognosis models.

# Discussion

In recent decades, various factors including the digital revolution and the introduction of the DRG in global health systems have led to a significant increase in the scientific use of routinely collected data. The growing amount of clinical documentation that doctors and nursing staff must complete and the commonly known limitations of primary data from registries make this source of data a valuable complement to quality improvement [3, 42]. Suitable selection criteria in the available datasets not only enable the measurement of process and structural quality indicators, but also an analysis of outcome quality indicators in the long term. Here, the particular challenge lies in the selection of suitable criteria and their (inter)national comparability.

Critics of secondary data usage, not just routinely collected data, reiterate the insufficient internal validity as the purpose of data generation (billing, revenue generation) leads to systematic bias. Indeed, such coding effects must be assessed on a project-specific basis and adequately taken into account. The fact is that revenue incentives have a measurable impact on patient selection and the choice of treatment [4, 61]. While routinely collected data is at least subject to regular independent review by the MDK, virtually no external validation has taken place so far for primary data in registries, which limits its usefulness [60].

Given that the statutory and private health insurance provider market remains highly fragmented despite market adjustment, population-specific selection effects arise from their different morbidity structures [26]; however, this mainly relates to the representativeness of the data and less to its contribution to quality improvement. This again underlines the relevance of sound methods, such as adjustment and standardization.

The hypothetical disadvantages of routinely collected data are also outweighed by significant advantages. While strict inclusion and exclusion criteria with corresponding data validation in randomized controlled trials (RCT) result in a higher internal validity, the routinely collected data of social insurance institutions reflects the reality of care far better and thus result in higher external validity. Due to the large number of cases (several million patients), it is also possible to analyze symptoms and patient groups that it is difficult for primary surveys to access. This particularly applies for severely ill multimorbid patients and residents of nursing homes, which underlines the association with vascular medicine. Compared to registries and RCTs, routinely collected data continue to exhibit a particularly high level of completeness, both at the start of the study and during the recording of study endpoints. Moreover, the data are available comparatively quickly and at low costs [36]. Similarly, automated billing data do not experience problems caused by a lack of response or incorrect patient information. This is

particularly advantageous in studies involving pharmacological treatment over a longer period [39]. Even if routinely collected data do not contain certain information, such as patient-reported endpoints and lifestyle characteristics, newer approaches provide the possibility of identifying relevant proxy variables from the tremendous wealth of information in a data-based manner using machine learning algorithms [55]. In the near future an abundance of further applications for new analytical methods will arise in this research area. These must then be monitored critically by experienced clinicians.

Countless publications demonstrate the benefits of routinely collected data for quality improvement in vascular medicine. In current routinely collected data studies conducted by BARMER, indications of potential for improvement could be found in the provision of drugs. Only about 60% of all patients with invasive revascularization of symptomatic PAOD received statins after the inpatient stay despite the fact that current guidelines clearly recommend this [1]. The challenge is now to transform these findings into better care [40]. As part of a quality initiative between the GermanVasc research group and DAK-Gesundheit health insurance provider on the treatment of aortic aneurysms, established outcome quality indicators for the weekend treatment of emergencies [14], severe bleeding complications [7] and spinal cord ischemia [23] could be evaluated. The outcomes of this work support the current debate on the necessary centralization of vascular medicine services and lead to further studies, for example on the introduction of patient blood management and CSF drainage in complex endovascular aortic surgery.

Meanwhile, the international vascular medicine community has already recognized the complementary benefits of routinely collected data. Hence cooperation, such as the VASCUNET committee (www.vascunet.org) and the medical device epidemiology network (MDEpiNet; www.mdepinet.org) are already working intensively on methodological aspects and the enhanced harmonization of routinely collected data research [48]. In the current VASCUNET quality report on the interdisciplinary care of PAOD in 11 countries, for example, routinely collected data have been received for more than 1.1 million hospital cases. The report is expected to lead to extensive debates on quality and programs in the participating countries.

It is clear that the findings from routinely collected data studies are not without repercussions for the doctor-patient relationship. The benchmarks of medical standards cannot ignore the knowledge acquired through such long-term studies without change. In itself this is not unusual; however, this legal aspect gains new weight when routinely collected data are combined with machine learning to develop algorithm-based forecasting tools. As already impressively demonstrated in the data protection considerations, this means that one is always moving within legally relevant areas and this must be kept in mind. Against this backdrop, it would appear crucial for medical and legal practitioners to face these new challenges together and in synergy, and to develop solutions to overcome them.

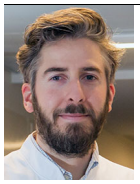
To conclude, it is important and correct to carefully weigh up the advantages and limitations of routinely collected data from health insurance providers and their importance in quality improvement. Challenges should not lead to a general rejection of this data basis but rather prompt a constructive exchange and methodological improvement.

Only through continuous usage and a controversial discussion will it be possible to improve the quality of routinely collected data research and thus also the quality of patient care.

## Conclusion

- **The use of routine data from social security institutions for secondary purposes in health services research and quality development has significantly increased in recent decades and a further increase is foreseeable.**
- **There are interdisciplinary and generally accepted guidelines and consensus recommendations for their use, linkage and reporting.**
- **Working with routine data requires not only medical but also a strong methodological expertise and can certainly provide high-quality complementary evidence for interventional studies.**
- **A representation of healthcare provision in longitudinal and cross-sectional perspectives is only possible via the social insurance institutions or in correspondingly merged data records of other data owners.**
- **The case-related data records of the Institute for the Remuneration System in Hospitals, the German Federal Statistical Office and the Central Institute for Statutory Health Insurance in Germany offer helpful insights into provision of healthcare, but are restricted to the assessment of the quality of the results due to the lack of longitudinal linkage.**
- **Depending on the research question, the restriction of the insured population to a single health insurance fund could potentially be a limitation for epidemiological questions, which requires appropriate methodological measures (e.g. standardization).**
- **Numerous routine data studies have already been published that have proven the benefits for quality development in interdisciplinary vascular medicine.**
- **Further context-specific validation studies for the German healthcare situation and methods for data protection-compliant validation of routine data are necessary.**

## Corresponding address



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## Compliance with ethical guidelines

**Conflict of interest.** F. Peters, T. Kreutzburg, J. Kuchenbecker, U. Marschall, M. Remmel, M. Dankhoff, H.-H. Trute, T. Repgen, E.S. Debus and C.-A. Behrendt declare that they have no competing interests.

**Ethical standards.** For this article no studies with human participants or animals were performed by any of the authors. All studies performed were in accordance with the ethical standards indicated in each case.

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# Editor's Choice – Comorbidity Patterns Among Patients with Peripheral Arterial Occlusive Disease in Germany: A Trend Analysis of Health Insurance Claims Data

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**WHAT THIS PAPER ADDS**

A large scale retrospective cohort study was conducted to highlight trends in treatment patterns and comorbidities in peripheral arterial occlusive disease. To date, the knowledge base remains limited and valid comprehensive patient related data from Germany are lacking. In this study, it was noted that increasing numbers of peripheral vascular interventions were performed on ageing and sicker patients, resulting in increasing costs but correlating with decreasing major amputation rates. These findings generate additional hypotheses for future studies aiming to identify clusters of comorbidities for comparative outcomes and quality improvement projects.

**Objective:** Patients suffering from peripheral arterial occlusive disease (PAOD) are a central target population for multidisciplinary vascular medicine. This study aimed to highlight trends in treatment patterns and comorbidities using up to date longitudinal patient related data from Germany.

**Methods:** This study is a retrospective health insurance claims data analysis of patients insured by the second largest health insurance provider in Germany, BARMER. All PAOD patient hospitalisations between 2008 and 2016 were included. The comorbidities were categorised with Elixhauser groups using WHO ICD-10 codes and summarised as the linear van Walraven score (vWS). A trend analysis of the comorbidities was performed after standardisation by age and sex.

**Results:** A total of 156 217 patients underwent 202 961 hospitalisations (49.4% for chronic limb threatening ischaemia in 2016) with PAOD during the study period. Although the estimated annual incidence of PAOD among the BARMER cohort decreased slightly (− 4.4%), an increase was observed in the prevalence of PAOD (+ 23.1%), number of hospitalisations (+ 25.1%), peripheral vascular interventions (PVI, + 61.1%), and disease related reimbursement costs (+ 31%) from 2008 to 2016. Meanwhile, the number of major amputations decreased (− 15.1%). The proportion of patients aged 71–80 years increased about +10% among PAOD patients and the mean vWS also increased by two points during the study period. Considerable increases were found in the rates of hypertension, renal failure, and hypothyroidism, whereas the rates of diabetes and congestive heart failure decreased over time.

**Conclusion:** Increasing numbers of PVI performed on these ageing and sicker patients lead to rising costs but correlate with decreasing major amputation rates.

**Keywords:** Chronic limb threatening ischaemia, Comorbidity, Elixhauser coding, Health insurance claims data, Peripheral arterial disease, van Walraven score

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## INTRODUCTION

As measured by the crude number of annual hospital admissions, patients with peripheral arterial occlusive disease (PAOD) can be rated as a central target population for multidisciplinary vascular medicine. An increasing number of more than 200 million people have been reported to be

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affected worldwide.[1] This has been associated with rising healthcare expenditure and increased disability adjusted life years (DALYs)[2–4] with increased morbidity and mortality.[5] In recent decades, the widespread adoption of endovascular techniques has led to changing environments.[4,6] PAOD patients identified by a low or high ankle brachial index ($< 0.9$ or $> 1.3$)[7] have a two to four times higher relative risk of cardiovascular events and all cause mortality.[8] In Germany, currently more than 200 000 invasive revascularisations are performed annually in approximately one million insured PAOD patients,[9] leading to disease related health costs of approximately 6250€ per capita per year in this population.[10,11] Although these numbers might create the opposite impression, PAOD is known to be under diagnosed because up to 50% of patients are asymptomatic.[12] In addition, the evidence basis for choosing the optimal treatment remains limited.[13–16]

Comorbidity patterns and trends in this large patient group deserve special consideration because they inevitably help in finding the optimal individual patient centred treatment strategy, such as best medical treatment (BMT), peripheral vascular interventions (PVI), or open-surgical (OSR) revascularisation. Large prospective epidemiological cohort studies highlighting cardiovascular disease comorbidities such as the Gutenberg Health Study[17] are mostly limited in their generalisability by the fact that they are primarily designed for heart diseases involving patients only up to 74 years of age. However, approximately 25% of PAOD patients are $\geq 80$ years of age when they are hospitalised[18] (Table S1).

The research question of this secondary data analysis is based on the IDOMENEO study,[11] which is currently collecting and analysing retrospective and prospective data on the treatment of patients suffering from symptomatic PAOD. The primary aim of this study was to describe the hospitalisation characteristics of a contemporary population of inpatients treated for PAOD in Germany using large scale health insurance claims data.

## METHODS

### *BARMER cohort*

The health insurance claims data of Germany's second largest insurance provider, BARMER, include the medical care provided to approximately 9.4 million German citizens (13.2% of Germany's insured population). The BARMER cohort includes nationally generalisable data with comparable gender and age distribution to the entire German population and has been widely used for research projects.[4,19,20] For this study, the German adaptation of the International Classification of Diseases (ICD-10-GM) was used to identify diagnoses and Operations and Procedures Codes (OPS) coding to identify procedures. The German OPS code is adapted to the International Classification of Procedures in Medicine (ICPM).

### *Study population*

This study is a retrospective analysis of inpatient discharge data of the years 2008–2016. Updated daily diagnoses of inpatient discharge data were used as they have the highest completeness and data quality level as a result of several validation processes in Germany compared with outpatient data, which are collected quarterly and voluntarily.[6,21] The ICD-10-GM codes used for identification of patients with asymptomatic or symptomatic PAOD were I70.0, I70.20–24, and I70.9 up to 2014, and I70.0, I70.20–25, I70.29, and I70.9 from 2015 in common with Reinecke *et al.*[6] For PAOD patients with invasive procedures, the corresponding OPS codes for PVI, OSR, and amputation were used (see Table S3). The ICD primary or secondary diagnosis codes for inpatient records with at least one hospital stay, including hospital ambulance records in the observational period, were used. In the inpatient setting, the primary diagnosis describes the diagnosis that was the most severe and/or resource intensive during the hospital stay. The secondary diagnoses (also known as "other diagnoses") describe any additional conditions that affected the patient's care and required any evaluation, diagnostics, therapy, medication, nurse care, monitoring, or additional hospital stay. The ICD codes are categorised in Fontaine stages for severity of PAOD. Stage I is asymptomatic PAOD, while stages II-IV describe symptomatic PAOD, with stage II for intermittent claudication (IC), stage III for ischaemic rest pain, and stage IV for ischaemic ulcers or gangrene. Stages III and IV can be summarised as chronic limb threatening ischaemia (CLTI).[22]

For inpatients, two patient groups were differentiated in terms of diagnosis: (1) PAOD newly diagnosed as incidence estimation, and (2) PAOD as a continuous (already known) diagnosis, which represents a prevalence estimation on PAOD. For further stratification into the Fontaine stages I-IV, patients with PAOD were used as primary diagnosis (more precise qualified diagnosis when compared with all secondary diagnoses).

The reporting of this study is in accordance with the reporting of studies conducted using observational routinely collected health data (RECORD) statement[23] and good practice of secondary data analysis.[24]

### *Elixhauser comorbidity groups and linear van Walraven score*

In 1970, Feinstein defined comorbidity as "any distinct additional clinical entity that has existed or may occur during the clinical course of a patient who has the index disease under study."[25] Elixhauser and colleagues used this definition and categorised ICD-10 codes separated into 30 comorbidity groups to transform the information for health insurance claims data.[26,27] The present study used all comorbidity diagnoses that occurred during three years before the first PAOD diagnosis (to go back to 2005 for patients initially treated in 2008). The linear van Walraven score (vWS) is a weighted sum score based on the Elixhauser groups regarding the risk of in hospital mortality, and has been validated.[28] Each of the 30 groups is categorised by the ICD code. With a logistic regression approach on Canadian administered mortality data, van Walraven *et al.* derived a score based on weight points for the Elixhauser

**Table 1. Patient characteristics with PAOD as primary diagnosis as incident and prevalent patient and hospitalisations as treatment cases.**

| | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | 2014 | 2015 | 2016 | Absolute change (*n*2016-*n*2008) | Relative change ([*n*2016-*n*2008]/*n*2008) | Percentage change (*p*2016- *p* 2008) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Incident patients with newly diagnosed PAOD, *n* | 11 172 | 10 843 | 10 815 | 10 984 | 10 801 | 10 806 | 10 837 | 10 599 | 10 680 | −492 | −4.4% | – |
| *Female patients, n (%)* | 5141 (46.0) | 4943 (45.6) | 4855 (44.9) | 5095 (46.4) | 4984 (46.1) | 5001 (46.3) | 5107 (47.1) | 5038 (47.5) | 5055 (47.3) | −86 | −1.7% | +1.3% |
| *Age at index procedure* | | | | | | | | | | | | |
| Mean (SD) | 71.4 (11.7) | 71.5 (11.8) | 71.4 (11.7) | 71.6 (11.6) | 71.6 (11.6) | 71.6 (11.8) | 72.0 (11.7) | 71.8 (11.6) | 72.3 (11.5) | +0.9 y | – | – |
| 0–50 y, n (%) | 434 (3.9) | 456 (4.2) | 405 (3.7) | 406 (3.7) | 404 (3.7) | 409 (3.8) | 329 (3.0) | 366 (3.5) | 302 (2.8) | −132 | −30.4% | −1.1% |
| 51–60 y, n (%) | 1588 (14.2) | 1520 (14.0) | 1562 (14.4) | 1550 (14.1) | 1510 (14.0) | 1570 (14.5) | 1514 (14.0) | 1496 (14.1) | 1379 (12.9) | −209 | −13.2% | −1.3% |
| 61–70 y, n (%) | 2987 (26.7) | 2770 (25.6) | 2811 (26.0) | 2625 (23.9) | 2571 (23.8) | 2512 (23.3) | 2555 (23.6) | 2499 (23.6) | 2612 (24.5) | −375 | −12.6% | −2.2% |
| 71–80 y, n (%) | 2962 (26.5) | 2946 (27.2) | 2947 (27.3) | 3288 (29.9) | 3351 (31.0) | 3377 (31.3) | 3387 (31.3) | 3316 (31.3) | 3262 (30.5) | +300 | +10.1% | +4.0% |
| 81–90 y, n (%) | 2793 (25.0) | 2769 (25.5) | 2722 (25.2) | 2708 (24.7) | 2532 (23.4) | 2417 (22.4) | 2502 (23.1) | 2437 (23.0) | 2572 (24.1) | −221 | −7.9% | −0.9% |
| 90 y or older, n (%) | 408 (3.7) | 382 (3.5) | 368 (3.4) | 407 (3.7) | 433 (4.0) | 521 (4.8) | 550 (5.1) | 485 (4.6) | 553 (5.2) | +145 | +35.5% | +1.5% |
| *Fontaine stages, n (%)* | | | | | | | | | | | | |
| Stage I | 382 (3.4) | 354 (3.3) | 377 (3.5) | 401 (3.7) | 347 (3.2) | 360 (3.3) | 379 (3.5) | 171 (1.6) | 160 (1.5) | −222 | −58.1% | −1.9% |
| Stage II | 5110 (45.7) | 4909 (45.3) | 4965 (45.9) | 5062 (46.1) | 4953 (45.9) | 4874 (45.1) | 5033 (46.4) | 5024 (47.4) | 5079 (47.6) | −31 | −0.6% | +1.9% |
| Stage III | 1422 (12.7) | 1388 (12.8) | 1374 (12.7) | 1406 (12.8) | 1354 (12.5) | 1335 (12.4) | 1263 (11.7) | 1249 (11.8) | 1173 (11.0) | −249 | −17.5% | −1.7% |
| Stage IV | 4226 (37.8) | 4156 (38.3) | 4083 (37.8) | 4096 (37.3) | 4125 (38.2) | 4216 (39.0) | 4143 (38.2) | 4025 (38.0) | 4105 (38.4) | −121 | −2.9% | +0.6% |
| Stage III-IV (CLTI) | 5648 (50.6) | 5544 (51.1) | 5457 (50.5) | 5502 (50.1) | 5479 (50.7) | 5551 (51.4) | 5406 (49.9) | 5274 (49.8) | 5278 (49.4) | −370 | −6.6% | −1.2% |
| Unspecified | 32 (0.3) | 36 (0.3) | 16 (0.2) | 19 (0.2) | 22 (0.2) | 21 (0.2) | 19 (0.2) | 130 (1.2) | 163 (1.5) | +131 | +409.4% | +1.2% |
| *Van Walraven score* | | | | | | | | | | | | |
| Median (IQR) | 5 (2–12) | 5 (2–12) | 5 (2–12) | 5 (2–12) | 5 (2–12) | 7 (2–12) | 7 (2–12) | 7 (2–13) | 7 (2–13) | +2 | – | – |
| Prevalent patients with continuous PAOD, *n* | 15 292 | 15 906 | 16 484 | 17 192 | 17 560 | 17 909 | 18 567 | 18 490 | 18 817 | +3525 | +23.1% | – |
| *Amputations, n (%)* | | | | | | | | | | | | |
| Major (OPS 5–864) | 1051 (6.9) | 1102 (6.9) | 1043 (6.3) | 979 (5.7) | 951 (5.4) | 908 (5.1) | 968 (5.2) | 926 (5.0) | 892 (4.7) | −159 | −15.1% | −2.2% |
| Minor (OPS 5–865) | 1787 (11.7) | 1932 (12.2) | 2004 (12.2) | 1997 (11.6) | 2084 (11.9) | 2194 (12.3) | 2295 (12.4) | 2352 (12.7) | 2294 (12.2) | +507 | +28.4% | +0.5% |
| *Revascularisation, n (%)* | | | | | | | | | | | | |
| PVI | 6842 (44.7) | 7457 (46.9) | 7987 (48.5) | 8852 (51.5) | 9136 (52.0) | 9661 (53.9) | 10 312 (55.5) | 10 537 (57.0) | 11 020 (58.6) | +4,178 | +61.1% | +13.9% |
| Open-surgical | 5325 (34.8) | 5489 (34.5) | 5531 (33.6) | 5762 (33.5) | 5402 (30.8) | 5572 (31.1) | 5726 (30.8) | 5603 (30.3) | 5578 (29.6) | +253 | +4.8% | −5.2% |
| *All cause in hospital mortality, n (%)* | 1167 (7.6) | 1209 (7.6) | 1184 (7.2) | 1193 (6.9) | 1225 (7.0) | 1253 (7.0) | 1265 (6.8) | 1307 (7.1) | 1250 (6.6) | +83 | +7.1% | −1.0% |
| 30 day mortality | 787 (5.2) | 800 (5.0) | 781 (4.7) | 791 (4.6) | 866 (4.9) | 885 (4.9) | 897 (4.8) | 935 (5.1) | 940 (5.0) | +153 | +19.4% | −0.2% |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 90 day mortality | 1447 (9.5) | 1525 (9.6) | 1457 (8.8) | 1469 (8.5) | 1602 (9.1) | 1648 (9.2) | 1717 (9.3) | 1726 (9.3) | 1710 (9.1) | +263 | +18.2% | −0.4% |
| *Hospitalisation, days* | | | | | | | | | | | | |
| Median (IQR) | 10 (3 −20) | 10 (3.5 −21) | 10 (3 −21) | 9 (3 −20) | 9 (3 −19) | 9 (3 −18) | 8 (3 −18) | 8 (3 −18) | 8 (3 −17) | −2 | – | – |
| *Costs, €* | | | | | | | | | | | | |
| Median (IQR) | 4630 (2331 −8092) | 5030 (2644 −8620) | 5062 (2681 −8581) | 5108 (2735 −8957) | 4879 (2780 −8766) | 5087 (2947 −9075) | 5406 (3049 −9746) | 5628 (3048 −9853) | 6076 (3215 −10146) | +1,446 | – | – |
| Hospitalisations, treatment cases, *n* | 19 655 | 20 582 | 21 308 | 22 361 | 22 748 | 23 243 | 24 280 | 24 199 | 24 585 | +4930 | +25.1% | – |
| *In hospital mortality per treatment case, n (%)* | 651 (3.3) | 677 (3.3) | 697 (3.3) | 642 (2.9) | 637 (2.8) | 679 (2.9) | 660 (2.7) | 641 (2.7) | 653 (2.7) | +2 | +0.3% | −0.6% |

The numbers represent absolute (*n*) and relative frequencies (%) including the difference from 2008 to 2016. CLTI = chronic limb threatening ischaemia; IQR = interquartile range; OPS = Operations and Procedures Codes; PAOD = peripheral arterial occlusive disease; PVI = peripheral vascular interventions; SD = standard deviation; y = years.

groups ranging from −7 weight points (for drug abuse) to +12 points (for metastatic cancer). The summary score ranged from −19 to +89, with high scores representing higher risk of in hospital death.[28,29]

## Statistical analysis

The characteristics of patients hospitalised at least once with PAOD were compared with PAOD patients without any PAOD related inpatient stay and at least one inpatient stay for reasons other than PAOD in the BARMER cohort. They were described over years with descriptive statistics for age, sex (male/female), Fontaine stages (I-IV, unspecified), amputation (major/minor), revascularisation (endovascular/open surgical), all cause in hospital mortality, 30 day and 90 day mortality, Elixhauser groups, and linear vWS using mean, standard deviation, median, and interquartile range for continuous and proportions for categorical variables. Comorbidity trends were analysed with the Jonckheere–Terpstra test based on age and gender standardised rates, with the calendar year 2008 as the reference year for consistent population structure. As PAOD is included in the comorbidity group of peripheral vascular disorders, this comorbidity group was not regarded in further analyses.

For all data analyses, missing or implausible data were not substituted and all analyses were performed with software SAS version 9.04 (SAS Institute, NC, USA).

## Ethical considerations

The studies comply with the Helsinki Declaration 2013. Several review boards determined that using anonymised data from claims or from national statistics retrospectively is not human subject research because de-identified

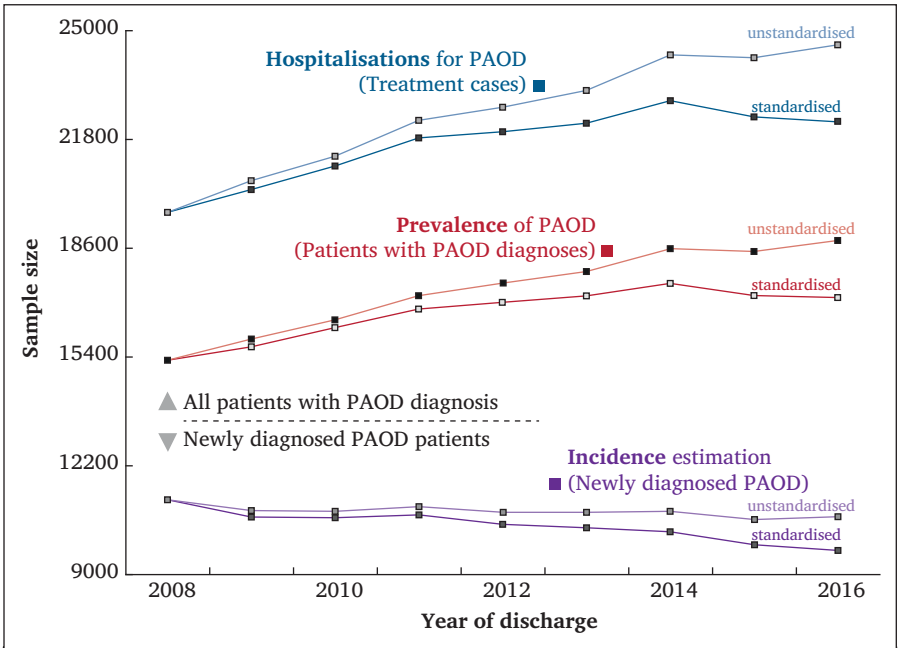


**Figure 1.** Annual sample size of all hospitalisations (treatment cases) for peripheral arterial occlusive disease (PAOD) (blue), prevalence of PAOD for continuous diagnosis (red), and incidence for newly diagnosed PAOD patients (violet).

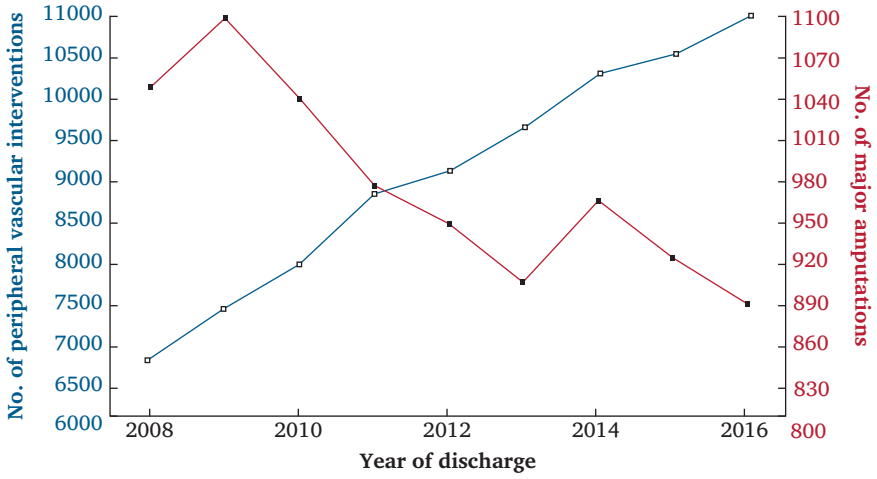


**Figure 2.** Annual number of peripheral vascular interventions (PVI) (blue) and major amputations above the ankle (red).

datasets were used. All analyses were in accordance with the European Union General Data Privacy Regulation (EU-GDPR), taking into account the theoretical concept of k-anonymity first described by Sweeney *et al.*[30,31] Thus, patient informed consent was not obtained for this retrospective secondary data analysis.

## RESULTS

### *Baseline characteristics*

Between January 2008 and December 2016, 202 961 admissions of 156 217 patients with PAOD as the primary diagnosis were identified (a mean of 1.3 admissions per patient). Of these, 97 537 patients (47.3% females) were treated for the first time for PAOD during the study period (incidence estimation). Table 1 shows the annual trends in the treatment of inpatients suffering from PAOD. While the total number of annual inpatient treatment cases (19 655 in 2008 to 24 585 in 2016, + 25.1%) and PVI was increasing (+ 61.1%), the hospital incidence of new PAOD diagnoses decreased slightly at 10 800 annually (− 4.4%) (Fig. 1). There was a slight decrease of in hospital (− 1.0%), 30 day (−0.2%), and 90 day mortality (− 0.4%), although there was an increase in the absolute number of deaths. During the study period, the major amputation rate decreased (− 15.1%) (Fig. 2). The median PAOD related costs per hospital stay increased from 4630€ in 2008−6076€ in 2016 (+ 1446 €).

**Table 2. Elixhauser coding groups with the highest rate in 2016 as age and sex standardised relative frequencies (%) including the trend from 2008 to 2016 and *p* value of the Jonckheere−Terpstra test for trends.**

| | 2008 | 2016 | Change 2008 −2016 | Jonckheere −Terpstra test |
|---|---|---|---|---|
| Incident patients (standardised, *n*) | 11 172 | 9701 | −13.2%* | – |
| Hypertension | 65.6 | 72.2 | +6.6%* | p<.001 |
| Fluid and electrolyte disorders | 24.6 | 29.0 | +4.4%* | 0.01 |
| Renal failure | 21.8 | 28.0 | +6.2%* | 0.002 |
| Diabetes | 29.8 | 25.4 | −4.4%† | 0.002 |
| Cardiac arrhythmias | 20.0 | 22.4 | +2.4%* | 0.001 |
| Congestive heart failure | 19.6 | 17.8 | −1.8%† | 0.09 |
| Obesity | 14.6 | 13.2 | −1.4%† | 0.35 |
| Hypothyroidism | 6.2 | 12.0 | +5.8%* | p<.001 |
| Neurodegenerative disorders | 10.2 | 11.8 | +1.6%* | 0.07 |
| Coagulopathy | 5.6 | 8.2 | +2.6%* | 0.001 |
| Depression | 6.4 | 8.0 | +1.6%* | 0.004 |
| Valvular disease | 6.2 | 7.6 | +1.4%* | 0.004 |

* Difference; increase.
† Difference; decrease.

The changes from 2008 to 2016 in the 12 highest comorbidities coded by Elixhauser groups of patients with a new PAOD diagnosis (incident patients) are shown in Table 2. The total burden of comorbidities calculated by the vWS comorbidity score increased during the observation period (median score value: 5−7, +2). Patients with newly diagnosed PAOD most commonly suffer from hypertension (72.2% in 2016), fluid and electrolyte disorders (29.0%), renal failure (28.0%), and diabetes (25.4%).

### *Trend analysis (standardised values)*

The comparison of the incident and prevalent patients, as well as hospitalisation as treatment cases over time, for unstandardised and standardised values are shown in Fig. 1. Standardisation by age and sex was used to ensure a consistent population structure over time, as in the reference year 2008.

Most of the Elixhauser comorbidity groups showed a slight increase between 2008 and 2016 for age and sex standardised rates (see Table 2). The greatest increases were observed for hypertension (+ 6.6%), renal failure (+ 6.2%), and hypothyroidism (+ 5.8%) (all $p < .01$), whereas rates of diabetes (− 4.4%, p = .002), congestive heart

failure (−1.8%, $p = .09$), and obesity (−1.4%, $p = .35$) were decreasing (for more details about all 30 Elixhauser groups, see Table S2).

## DISCUSSION

In this large scale population based analysis of health insurance claims data from Germany between 2008 and 2016, it was found that even though the age standardised annual incidence of patients with newly diagnosed PAOD decreased slightly over time, the annual number of hospitalisations and PVI and correlating reimbursement costs were increased, leading to a remarkable economic burden. However, these developments were accompanied by decreasing major amputation rates, which might improve the quality of life of affected patients. Furthermore, today, hospitalised patients have a higher degree of morbidity involving major comorbidities such as hypertension and renal failure when compared with 2008. By conducting analyses for patients over time, it was possible to improve the existing limitations of prior studies.

In a population based analysis of nationwide Diagnosis Related Groups (DRG) from Germany, Malyar *et al.* identified an increase of PAOD (+20.7%) and endovascular revascularisations (+46%) and highlighted high amputation rates and in hospital mortality between 2005 and 2009.[4] However, as this analysis was based on hospitalisations or procedures and not on individual patients, repeated procedures might lead to a bias limiting the validity of results in terms of comorbidities and estimation of incidence or prevalence rates in the target population. To date, this remains a major limitation of hospital episode statistics (HES) such as the nationwide DRG statistics. A cross linking of hospitalisations or procedures with patient identifiers would allow longitudinal studies and probably increase the validity, but this is restricted for legal reasons.[31]

Using a patient based approach and more up to date data, it was possible to confirm and to augment the important findings of Malyar *et al.* regarding the increase of PVI, hospitalisations, and PAOD related reimbursement costs. It appears challenging to identify underlying reasons for increasing costs using only health insurance claims data. Besides well known inflation effects, there are probably other factors such as changes in patient selection or the adoption of costly devices that are possible factors driving this development. In another analysis of health insurance claims from the same research group, patient based data were used on hospitalisations reimbursed between 2009 and 2011 and reported poor outcomes, especially in patients suffering from CLTI. Comparable comorbidities rates such as hypertension and obesity were reported. The authors also stated a remarkably high rate of amputations at one year after index hospitalisation.[6]

Against this backdrop, a decrease in major amputations was observed over time, confirming reports by Kröger *et al.* in 2017 for Germany,[32] and other studies considering worldwide development in amputation practice.[33–36] The question arises of whether this trend is correlated with increasing revascularisations or whether it is caused by other factors such as improved treatment of diabetes and declining tobacco use.[36] Undoubtedly, there are various underlying root causes of a multifactorial nature. Interestingly, the rates of diabetes were decreasing in the trend analyses. Unfortunately, the observational design of this study does not allow for any valid conclusions about underlying causes.

The results of this study suggest that even though the hospital incidence of PAOD decreased over time, increasing numbers of revascularisations causing rising costs were performed in increasingly ill and older patients. As a result of continuous improvements in the medical healthcare system, fewer PAOD patients suffer from major amputations and resulting adverse reactions and the overall in hospital mortality has decreased in the last 10 years. Nevertheless, future research is needed to fill the empirical gaps in clinical practical guidelines.[16,37,38] In a following project, the present authors aim to develop a PAOD related comorbidity risk score regarding recommended quality indicators to predict the optimal treatment strategy taking comorbidities into consideration. The results of this study could help in future updates of practice guidelines on PAOD treatment by providing a comprehensive insight into treatment patterns and comorbidities in a large cohort. The increasing proportion of aged patients and certain comorbidities (e.g., renal insufficiency) heighten the need to develop specific recommendations on how to treat these patients, not only invasively but also with best medical treatment.

### *Strengths and limitations*

An important strength of the inpatient data is that the diagnoses in Germany are seen as the gold standard, including the documentation of diagnostics and therapy.[6] Health insurance claims data are valid for performing incidence and prevalence estimations and standardisations by age and sex because of the population based approach to insurance, as reported in several studies.

Besides the various strengths of this study, it also has several limitations. First, health insurance claims data are not collected for scientific evaluation but rather for reimbursement purposes.[39] However, such claims are subject to increasing awareness from the scientific audience.[40] There is corroboration that there might be a progression toward upcoding of comorbidities and complications in claims;[40] however registry data are known to be affected by some degree of underreporting. Nevertheless, the validity of claims seems to be sufficient for major healthcare events such as vascular trauma (sensitivity > 90%, positive predictive value, PPV 95%),[41] and for chronic conditions such as diabetes (sensitivity 86%, PPV 80%)[42] or hypertension (sensitivity 73%, PPV 82%)[43] in larger validation studies. In Germany, by law, all inhabitants must be insured by private or public health insurance, which results in high completeness. Further, health insurance data are cross checked by special software and 20% are reviewed and

corrected by special physicians (Medizinischer Dienst der Krankenversicherung) independently,[6] which results in high data validation in Germany.

Secondly, for incidence estimations there is a limited observational time and a limited number of insured people, so a decrease in incident patients, as in the present analysis, could be a natural consequence because at the end of the time frame there are fewer people at risk. Efforts were made to standardise for this in all analyses.

Thirdly, this study is limited to inpatient data. To date, no valid data are available on the outpatient PAOD treatments in Germany. Although the fee for service reimbursement system in Germany probably motivates interventionalists to perform inpatient procedures rather than outpatient procedures, there might be another target population not included in this study. Lastly, the trend toward an increasing number of PAOD treatments can be explained by multiple factors such as general demographic changes in the entire German population and by possible economic and reimbursement effects. However, this retrospective study is not suitable to uncover causal mechanisms. Thus, the reported findings should be considered exploratory and tested in future research to overcome the limitations of prior studies.[44–53]

## CONCLUSIONS

While the hospital incidence of PAOD slightly decreased over time, increasing numbers of PVI performed on these increasingly ill and older patients caused rising costs but correlated with decreasing major amputation rates. There is an increasing trend in relevant cardiovascular comorbidities such as hypertension, cardiac arrhythmias, and renal failure, emphasising the need for multidisciplinary care. To fill gaps in clinical practice guidelines, future research projects should aim to highlight differences in outcomes between relevant subcohorts defined by their comorbidity profiles.

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST

None.

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## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2019.08.006.

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Thematic focus: Vascular claims – Original communication

# Periodontal treatment and peripheral arterial disease severity – a retrospective analysis of health insurance claims data

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**Summary:** *Background*: Although epidemiological data suggest an association between periodontitis (PD) and peripheral arterial disease (PAD), it is currently unclear whether treatment of PD influences the severity of PAD. *Patients and methods*: Whether periodontal treatment is associated with PAD disease severity was examined by analysing health insurance claims data of patients insured by the German health insurance fund, BARMER, between January 1, 2012 and December 31, 2016. The presence of PAD was determined in individuals using International Classification of Diseases (ICD) 10$^{th}$ revision codes for intermittent claudication (IC) or chronic limb threatening ischaemia (CLTI). Treatment of PD was assessed by adequate ambulatory coding for non-surgical and surgical treatment of PD. Multivariate logistic regression analysis was performed to evaluate the association between PAD stages and periodontal treatment, adjusted for diabetes, age and sex. *Results*: The study cohort included 70,944 hospitalized patients with a diagnosis of symptomatic PAD (54.99 % women, 49.05 % IC). Among these patients, 3,567 (5.03 %) had received prior treatment for PD by supra- or sub-gingival debridement. PAD patients who had received periodontal treatment showed a lower proportion of CLTI (28.76 % among treated vs. 52.12 % among non-treated). Using multivariable regression methods, exhibiting a CLTI (vs. IC) was associated with not being treated for PD (Odds Ratio 1.97, 95 %–CI 1.83–2.13) after adjustment for age, gender, and diabetes. *Conclusions*: In this large-scale retrospective analysis of health insurance claims data comprising hospitalized symptomatic PAD patients, treatment of PD was associated with PAD disease severity independent of age, gender and diabetes. A potential benefit of periodontal treatment in relation to PAD will have to be determined in further prospective studies.

**Keywords:** Peripheral artery disease, PAD, lower extremity artery disease, periodontitis, PD, gum disease

## Introduction

Peripheral arterial disease (PAD) is an important manifestation of atherosclerosis that has become a global problem with significant impact on national healthcare systems [1, 2]. Besides risk factors, such as age and diabetes, also chronic inflammatory conditions, such as periodontitis (PD), may increase the risk of PAD [3–5]. PD is a chronic inflammatory disease. It leads to a degradation of the tooth-supporting structures and it is caused by oral microorganisms. A respective inflammatory response causes a progressive periodontal tissue destruction, a loss of alveolar bone and finally tooth loss [6]. The treatment armamentarium consists of nonsurgical (e.g., scaling, root planning, antibiotics) and surgical treatments (e.g., flap surgery, soft tissue grafts, bone grafting, guided tissue regeneration, tissue-stimulating proteins). Transient bacteremias were shown in patients with PD after tooth brushing and following periodontal treatment [7–9]. Several studies have identified high levels of periodontal pathogens such as *P. gingivalis* and *T. denticola* in atherosclerotic lesions [10–12]. In contrast, biopsies taken from non-atherosclerotic aortic tissue

provided mostly only signals around the detection limit for these bacteria using polymerase chain reaction (PCR) [13]. These findings could provide a plausible mechanism for a potential worsening effect of PD on PAD.

Prior studies showed that PD was significantly associated with PAD and that incident tooth loss was significantly associated with elevated risk of subsequent occurrence of PAD (relative risk (RR) for history of PD: 1.41, RR for any tooth loss during follow-up: 1.39, after controlling for traditional risk factors of cardiovascular disease) [15]. Among men with a history of PD, the relative risk of tooth loss increased to 1.88, whereas no association was found between tooth loss and PAD among those without PD (RR, 0.92) [15]. However, a randomized controlled trial (RCT) on the efficacy of periodontal treatment for patients with PAD is lacking and would probably be subject to ethical considerations. Thus, it is unclear whether PAD patients should be screened for the necessity of periodontal treatment.

This study aims to determine potential associations between PAD and periodontal treatment using a large-scale population-based cohort. The null hypothesis was, that periodontal treatment does not affect PAD.

## Methods

For this study, health insurance claims data of hospitalized adults insured with the German health insurer BARMER between January 1st, 2012 and December 31st, 2016 were used. This BARMER cohort is similar compared to the entire German population [16]. Each year's cohort consisted of all insured patients who were insured at least 1 day in all four quarters.

The presence of PAD was assessed and graded according to the Fontaine classification scheme in intermittent claudication (IC) (ICD-10 codes I70.20 and I70.21 until 2014; I70.21 and I70.22 since 2015), and chronic limb threatening ischaemia (CLTI) (ICD-10 codes I70.22, I70.23 and I70.24 until 2014; I70.23, I70.24 and I70.25 since 2015). Further PAD diagnoses could be identified by assessing a diagnosis of diabetic foot syndrome (ICD-10 codes E1050, E1051, E1150, EE1151, E107, E117, L0301, L0302, Lo311, L984, I730, I731, I738-I745, I748, I749, R02) as main diagnosis with one of the ICD-10 codes for IC or CLTI as secondary diagnosis [17].

Data on all hospitalized patients with previous ambulatory treatment of PD were extracted from the PAD cohort based on the presence of standard rating codes for dental services (BEMA) codes P200, P201, P202, P203, which indicated claims of costs for ambulatory treatment of PD. Codes P200 and P201 referred to non-surgical treatment (supra- and sub-gingival debridement), while codes P202 and P203 referred to surgical treatment procedures, which are usually performed only in cases with very severe PD.

Patients were described with descriptive statistics for age, sex, diabetes (ICD-10 codes E10.x, E11.x, E12.x, E13.x, E14.x), PAD stages (IC vs. CLTI), and periodontal treatment using mean, standard deviation, minimum and maximum for continuous variables and absolute numbers (n) and percentages (%) of the total numbers (for each subgroub) for categorical variables.

Multivariate logistic regression models were constructed to ascertain associations between PAD stages (IC *vs.* CLTI) and periodontal treatment, adjusted for diabetes, age, and gender. Odds Ratios (OR) with corresponding 95% confidence interval (CI) obtained after appropriate adjustments are reported and shown for each covariate.

All analyses were performed with software SAS Enterprise Guide version 7.1 (SAS Institute, North Carolina, USA). A p-value less than 0.05 was considered statistically significant.

### Ethical considerations

This study was performed in accordance with the Helsinki Declaration 2013. Anonymized datasets from health insurance claims registers were used retrospectively without any possibility to identify the individuals. All analyses were conducted in accordance with the European Union General Data Privacy Regulation (EU-GDPR) [18].

## Results

We identified 70,944 hospitalized patients with a diagnosis of symptomatic PAD (54.99 % of them were men) (Table I). 49.05 % of the patients were treated for IC. CLTI patients were older than those with IC (75.5 *vs.* 69.3 yrs., Table I). 3,567 (5.03 %) of these patients (57.19 % men) had received previous treatment for PD by supra- or sub-gingival debridement (Table II). PAD patients who had received previous periodontal treatment were younger than those who had not received periodontal treatment (66.1 vs. 72.8 yrs., Table II).

PAD patients who had received previous periodontal treatment showed a lower proportion of CLTI (28.76 % treated vs. 52.12 % non-treated) (Table III).

Multivariate logistic regression analyses revealed that patients without periodontal treatment had 1.97-times the odds of being a PAD patient in the more progressed CLTI group ($p < 0.0001$; 95 % confidence interval: 1.83–2.13) compared to those who had received periodontal treatment after adjusting for age, diabetes and gender. The respective odds ratios for age, gender and diabetes are shown in Table IV.

## Discussion

The main finding of this study was that PAD patients who had received periodontal treatment, showed a higher proportion of moderate IC and a lower relative proportionof progressed CLTI grades when compared to PAD patients who had not received periodontal treatment.

**Table I.** Peripheral arterial occlusive disease by stages, gender and age.

| | IC | CLTI | Sum (%) |
|---|---|---|---|
| All [N] (%) | 34,799 (49.05) | 36,145 (50.95) | 70,944 (100.0) |
| Men [N] (%) | 20,016 (57.52) | 18,999 (52.56) | 39,015 (54.99) |
| Mean age [yrs.] (SD) | 69.3 (10.2) | 75.5 (11.4) | 72.5 (11.3) |

IC: intermittent claudication, CLTI: chronic limb threatening ischaemia, SD: standard deviation.

**Table II.** Periodontal treatment by gender and age.

| | Treatment* | | |
|---|---|---|---|
| | No | Yes | Sum (%) |
| All [N] (%) | 67,377 (94.97) | 3,567 (5.03) | 70,944 (100.0) |
| Men [N] (%) | 36,975 (54.88) | 2,040 (57.19) | 39,015 (54.99) |
| Mean age [yrs.] (SD) | 72.8 (11.2) | 66.1 (10.1) | 72.5 (11.3) |

*P200, P201: subgingival debridement; P202, P203: open flap debridement.

**Table III.** Peripheral arterial occlusive disease stages in patients with and without periodontal treatment.

| | Stages | | |
|---|---|---|---|
| PD treatment | IC (%) | CLTI (%) | Sum (%) |
| No | 32,258 (45.47) | 35,119 (49.5) | 67,377 (96.08) |
| Yes | 2,541 (3.58) | 1,026 (1.45) | 3,567 (3.92) |
| Sum | 34,799 (49.05) | 36,145 (50.95) | 70,944 (100) |

IC: intermittent claudication, CLTI: chronic limb threatening ischaemia, PD: periodontal disease.

**Table IV.** Multivariate logistic regression model: odds for a patient to be in the chronic limb threatening ischaemia group.

| Effect | Odds ratio | 95% Wald Confidence limits | | p-value |
|---|---|---|---|---|
| Age[§] | 1.052 | 1.051 | 1.054 | <.0001 |
| PD treatment no vs yes* | 1.972 | 1.826 | 2.129 | <.0001 |
| Gender female vs male[#] | 0.989 | 0.958 | 1.021 | 0.49 |
| Diabetes yes vs no[&] | 2.102 | 2.011 | 2.196 | <.0001 |

[§]adjusted for PD treatment, gender, diabetes; *adjusted for age, gender, diabetes; [#]adjusted for age, PD treatment, diabetes; [&]adjusted for age, PD treatment, gender. PD: periodontal disease.

An independent association between periodontal treatment and PAD severity grades could be confirmed by multivariable methods after adjusting for age, gender, and diabetes.

The results are of special interest because cross-sectional data obtained from the NHANES study showed that PD and PAD are associated with each other [14], and that systemic markers of inflammation, like C-reactive protein, white blood cell count, and fibrinogen, are also associated with PAD [19] as well as with PD. In addition, a large prospective survey, which included 45,136 male health professionals free of cardiovascular disease at baseline, incident tooth loss, which is a frequent consequence of PD, was associated with an elevated risk of subsequent occurrence of PAD after controlling for traditional risk factors for cardiovascular disease. [15]. If causal, this association would be of great importance because preventing or treating PD could potentially be beneficial for patients with PAD.

The efficacy of periodontal treatment to reduce PAD has not yet been evaluated in an RCT. Performing such an RCT would be challenging because it would need to include a very large number of patients in order to detect plausible effects. Randomization and blinding would also be difficult, and a long-term approach would be needed to achieve a sustained improvement of periodontal health and a sufficient number of PAD incidences during the follow-up period. To circumvent these obstacles, we performed a retrospective analysis of insurance claims records of hospitalized PAD patients to obtain information on the potential effects of periodontal treatment on PAD. The PAD patients were stratified according to whether they had or had not received periodontal treatment based on the health insurer's claims records. The null hypothesis was that there was no association between periodontal treatment and PAD severity grades. The null hypothesis was rejected by the study results, which for the first time suggests that periodontal treatment is associated with severity of PAD.

Although, this result is only a first indication of a potential connection between periodontal treatment and PAD disease severity, it can be judged important for national healthcare systems because of the high prevalence of PD and PAD. According to the World Health Organization (WHO), 5–20 % of middle-aged (35–44 years) adults in Europe, and up to 40 % of older people (65–74 years) suffer from severe periodontal disease.

Health insurance data were previously used to study the impact of periodontal therapy on general health [20]. The study showed that periodontal therapy was associated with significant reductions in medical costs and the number of hospitalizations due to type-2-diabetes, cardiovascular disease, coronary artery disease, and pregnancy. Although data of an RCT on PAD are not available, one randomized trial, which included 301 patients with stable coronary artery disease, assessed the effects of periodontal treatment (a single full-mouth scaling and root planning) on major cardiovascular events over 6 to 25 months of follow-up [21]. The pilot study had low statistical power and, as expected, yielded inconclusive results on the impact of the intervention on cardiovascular outcomes. Other clinical studies could demonstrate that periodontal treatment had beneficial effects on carotid intima-media thickness, endothelial dysfunction, circulating levels of inflammatory biomarkers, and flow-mediated dilation [22–24].

It should be noted that according to the BARMER tooth report [25], only around one in four BARMER patients took periodontal diagnostic services in 2017. In our current study, only 5.03 % of the PAD patients had received therapeutic services for PD. Although this fraction is higher compared to the whole population insured by BARMER

 

(which is only about 2 %) [25], it is still considerably lower than one would expect based on the much higher prevalence of PD in this group of elderly patients. According to the population-based German Oral Health Survey (DMS V) [26, 27], 43.4 % of older adults are affected by moderate and 8.2 % by severe PD. These findings lead to the assumption indicate that a significant fraction of the PAD patients of our study which was affected by PD did not receive appropriate periodontal diagnostic services and treatment.

The approach used in this study has several advantages: (1) The analysis is based on a very high number of patient records, thus enabling a high sensitivity to test the null hypothesis. (2) all patients receiving periodontal treatment suffered from manifest severe PD that required treatment. (3) the diagnoses and grading of PD and PAD was based on standardized procedures in compliance with guidelines issued by the health insurer.

## Limitations

Besides several strengths, this study has limitations that need to be taken into account. Firstly, the primary purpose of the data collection should be considered in using it for secondary purposes, and all research data should undergo validation. Health insurance funds perform random cross-checks with patient files on a regular basis. While coding errors are possible, they would likely affect both study groups. Secondly, the complex interaction of PD and PAD introduces significant problems with confounding. This study could only take the most important observed confounders into account. Thirdly, it would be interesting to determine the course of patients with in-hospital treatment of PAD during the follow-up. If would be also interesting to analyse subgroups the current study did not stratify for. Although the current study included the most important predictors published in the available literature, other comorbidities, medications, and outcomes are also interesting and probably hypothesis generating. For instance, tobacco consumption would probably be an important predictor but is known to be not validly captured in administrative data. However, the results can generate hypotheses and support future research.

It is possible that the group of approximately 5 % of PAD patients receiving periodontal treatment differed from those who received no treatment. For example, the treated group could be a specific compliant group, which generally has better health-related behaviour than the untreated comparison group. Health-related behaviour is likely to affect PAD and its risk factors, which could have affected the age- and gender-adjusted rate of PAD severity because patients who received periodontal treatment may be more likely to also adhere to behaviours that will affect the prognosis for other diseases including PAD. It is well known that health-related behaviours related to diet, smoking, exercise and the use of health services tend to cluster in individuals [28]. On the other hand, the association between periodontal treatment and PAD severity remained after adjusting the regression model for diabetes, which is affected by similar health-related behaviours. Nevertheless, additional prospective studies such as the Hamburg City Health Study, are clearly warranted to further strengthen the potential influence of periodontal treatment on PAD severity [29].

## Conclusions

In this large-scale retrospective analysis of health insurance claims data comprising hospitalized PAD patients, periodontal treatment was associated with PAD independent of age, gender and diabetes. This potential benefit of periodontal treatment in relation to PAD will have to be proven in further prospective studies.

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Original communication

# Long-term incidence of cancer after index treatment for symptomatic peripheral arterial disease – a health insurance claims data analysis

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**Summary:** *Background*: Cancer as a concomitant condition in symptomatic peripheral arterial disease (PAD) patients could have an impact on further therapy and the long-term prognosis of these patients. Aim of this study was to investigate whether there is an increased incidence of cancer in PAD patients and to quantify the corresponding effect size. *Materials and methods*: Between January 1st, 2008 and December 31st, 2017, we analysed health insurance claims data from Germany's second-largest insurance fund, BARMER. Symptomatic PAD patients suffering from intermittent claudication (IC) or chronic limb-threatening ischaemia (CLTI) were stratified by gender at index treatment. PAD patients were then followed until an incident cancer diagnosis was recorded. To adjust for age and gender, standardized incidence ratios (SIR) were computed using the 2012 German standard population as reference. *Results*: 96,528 PAD patients (47% female, 44% IC, mean age 72 years) were included in the current study. When compared to the overall population, female and male PAD patients have a significantly increased risk of incident cancer of the lung (SIR 3.5 vs. 2.6), bladder (SIR 3.2 vs. 4.0), pancreas (SIR 1.4 vs. 1.6), and colon (SIR 1.3 vs. 1.3). During ten years of follow-up, some 7% of males and 4% of females developed lung cancer. For bladder, colon and pancreas cancer, the cumulative hazards were 1% vs. 3.2%, 2.2% vs. 2.8%, and 0.7% vs. 0.9%, respectively. *Conclusions*: Patients suffering from symptomatic PAD face a markedly higher risk for incident cancer in the long-term follow-up. The cancer risk increased continuously for certain types and PAD was strongly associated with cancer of the lung, bladder, pancreas, and colon. Taking these results into account, PAD patients could benefit from secondary and tertiary screening. These results also emphasize the impact of common risk factors such as tobacco smoke as target for health prevention.

**Keywords:** peripheral arterial disease, cancer, health services research, gender differences

## Introduction

More than 200 million patients worldwide and approximately 20% of German inhabitants aged over 70 years are affected by a peripheral arterial disease (PAD) leading to rapidly rising healthcare costs [1–3].

PAD patients have a substantially higher risk for major adverse cardiovascular and limb events when compared to the general population associated with an impaired life expectancy [4]. While cardiovascular outcomes have been extensively studied, concomitant malignant diseases have been neglected so far, despite they are known to be in general the second most frequent cause of death [5–7].

In Germany, more than 226,000 people died of cancer in 2015, which corresponds to around 25% of all deaths and is thus the second most frequent cause of death after diseases of the cardiovascular system [8].

The medical and economic relevance of both PAD and cancer is important and continues to increase [3, 9]. Whether PAD patients have an enhanced risk of malignant tumours compared to the general population has only been investigated in a comparatively small scale to date [10–15].

The diagnosis of PAD usually represents a considerable life restriction for affected patients [16]. The prognosis and further therapy depend decisively on other relevant concomitant diseases of the patient [17]. Hence, the early

detection of malignant tumours in these patients may be of clinical relevance. This study aimed to determine to what extent PAD patients have a different incidence of cancer when compared to the overall population in Germany. Furthermore, the corresponding effect size should be estimated. We hypothesize that there is an association between PAD and certain cancer entities known to be strongly caused by the same risk factors, notably tobacco smoke.



## Materials and methods

### Data source and study population

Health insurance claims data of Germany's second-largest insurance fund, BARMER, were used. This cohort includes the outpatient and inpatient medical care provided to approximately 9 million German citizens (10.8% of Germany's population) and is similar compared to the entire German population [18]. The study population consisted of fully inpatient patients aged 40 years and older treated for symptomatic PAD diagnosis (primary diagnosis, coding of the International Classification of Diseases in its German Modification [ICD-10-GM]) in accordance to Kreutzburg et al. [3] and Behrendt et al. [4] during the period January 1st, 2008 to December 31st, 2017.

To identify symptomatic PAD patients, the Fontaine classification [19] was used including disease stage II (intermittent claudication), stage III (ischaemic rest pain), and stage IV (ischaemic ulcer or gangrene).

Longitudinal data of PAD patients was subsequently analysed for cancer incidence. Cancer patients were grouped in accordance to following cancer types as primary or secondary inpatient diagnosis (ICD-10-GM coding): Breast (C50), colon (C18-C20), bladder (C67), lung (C33-C34), stomach (C16), melanoma (C43), ovaries (C56), pancreas (C25), prostate (C61), uterine (C54-C55) and other (C00-C97 without C77-79). PAD and cancer types with corresponding ICD-10-GM codes are listed in Table I in electronic supplementary material 1.

The index hospital stay was defined as the first diagnosis for PAD, respectively cancer. As a reference, age- and gender-specific cancer incidence rates and population counts from the overall population in Germany from 2012 (GSP, mean observation period of our study time frame) from the Robert Koch-Institute, Berlin, Germany (RKI) were used [20].

### Statistical analysis

Patients were described with numbers (n) and percentages (%) of the total numbers (for each subgroup) for age and gender. The age was grouped into 5-years intervals.

To estimate the time until cancer, cumulative hazard functions of the different cancer types with a 95% confidence interval (CI) were plotted.

Starting with the index PAD diagnosis, all patients were observed until cancer event, end of insurance (e.g., death) or censoring (December 31st, 2017). Patients with a history of cancer before index stay were excluded from the study.

Furthermore, standardized incidence ratios (SIRs) were calculated to compare the incidence of cancer in PAD patients with the German standard population of 2012. The term standard population was defined as the estimated cancer incidence of the Center for Registry Data of the RKI (https://www.krebsdaten.de) for the year 2012. SIRs, adjusted for age (5-year age groups), were calculated for all observed cancer types.

All analyses were stratified by gender as the prevalence of specific cancer types differs by gender (e.g. breast cancer, prostate cancer).

All analyses were performed with software SAS (SAS Institute Inc., North Carolina, United States of America) Version 9.04 for data processing and R version 3.1 for incidence estimation and visualization. Visualization was performed with software Adobe Illustrator version 24.1.2 (Adobe, California, United States).

## Results

### Patient characteristics

In the current study, we included 96,528 patients aged 40 years and older who were treated for symptomatic PAD (47% female) during the period January 1st, 2008 to December 31st, 2017. The most represented age group was between 70–74 years, including 15,524 patients (16.1%). The mean age of all patients in the PAD cohort was 72 years. 42,536 patients (44%) were admitted for intermittent claudication, 41,037 patients (42.5%) were admitted for ischaemic wound healing disorders, and 12,955 patients (13.4%) suffered from ischaemic rest pain.

### Incidence of cancer in the PAD cohort and the German overall population

Cancer incidence of the lung, bladder, pancreas, and colon were mostly increased with PAD, while the risk for cancer of melanoma, breast, uterine and prostate did not differ from the general population. Standardized incidences of the most common cancer entities for male and female patients by different age groups are presented in Figure 1. For lung cancer, there is an increased incidence in the PAD cohort in all age groups, except in the 85+ age group. The greatest difference among female is found in the age group 60–65 years (764 per 100,000 in PAD vs. 103 per 100,000 in GSP). For men, the most pronounced difference was found in the age group 65–70 years (902 per 100,000 in PAD vs. 279 per 100,000 in GSP) (Figure 1A).

For bladder cancer, both genders show an increased incidence in the PAD cohort in all age groups. The most pronounced difference for females was also found in the age

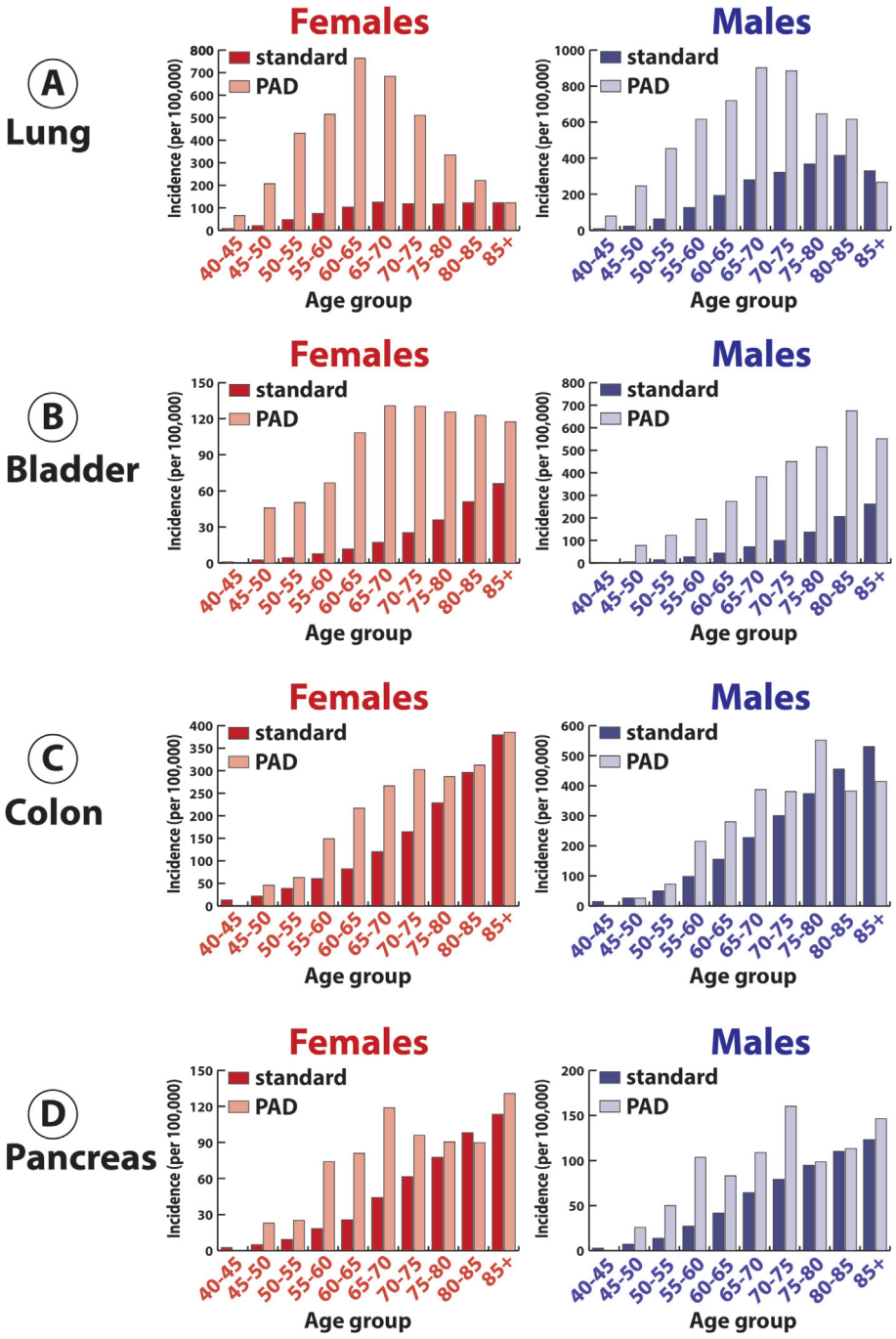


**Figure 1.** Gender-specific incidences of the three most common tumours by different age groups: A) Lung, B) Bladder, C) Colon, D) Pancreas. PAD: Peripheral arterial disease.

group 60–65 (108 per 100,000 in PAD vs. 12 per 100,000 in GSP). For males, the greatest difference was found in the age group of 80–85 years (675 per 100,000 in PAD vs. 207 per 100,000 in GSP) (Figure 1B).

For colon cancer, the greatest difference among females was found in the 65–70 age group (266 per 100,000 in PAD vs. 120 per 100,000 in GSP). Among males, the most pronounced difference was found in the age group of 75–80 years (552 per 100,000 in PAD vs. 373 per 100,000 in GSP) (Figure 1C).

For pancreas cancer, the greatest difference among females was found in the 65–70 age group (119 per 100,000 in PAD vs. 44 per 100,000 in GSP). Among males, the major difference was found in the age group of 70–75 years (160 per 100,000 in PAD vs. 79 per 100,000 in GSP) (Figure 1D).

## Sensitivity analyses stratified by disease severity

All calculations have been performed using subgroups stratified by different Fontaine stages. Sensitivity analyses confirmed the findings of the current study.

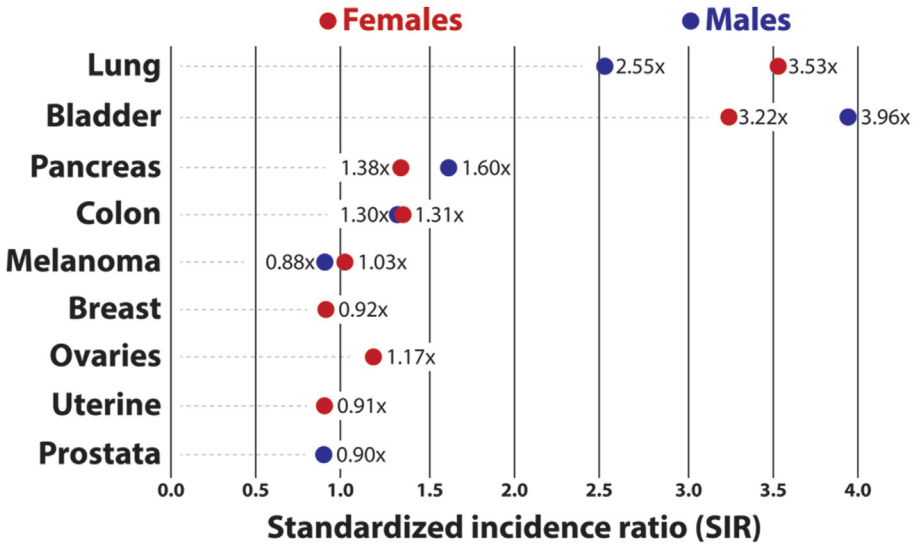


**Figure 2.** Standardized incidence ratio (SIR) of peripheral arterial disease (PAD) patients compared to the 2012 German standard population.

## Standardized incidence ratio (SIR) of peripheral arterial disease patients compared to German overall population

Figure 2 illustrates the SIRs for common cancer entities in PAD patients when compared to GSP stratified by gender. A strong association between symptomatic PAD and cancer in female and male patients, respectively, was found for cancer of the lung (SIR 3.5 vs. 2.6), bladder (SIR 3.2 vs. 4.0), pancreas (SIR 1.4 vs. 1.6), and colon (SIR 1.3 vs. 1.3). Whereas for ovaries cancer (SIR 1.2) and male melanoma (0.9) no strong association and female melanoma (SIR 0.9), breast (SIR 0.9), uterine (SIR 0.9) and prostate cancer (SIR 0.9) an opposite association was found.

## Incident cancer after treatment of symptomatic PAD

Figure 3 illustrates the cumulative hazards for incident cancer after index treatment for symptomatic PAD stratified by gender. In the entire study sample, some 8% of the patients were diagnosed for any common cancer (e.g., lung, breast, colon, bladder, prostate) during five years after the index treatment for symptomatic PAD. After a follow-up of five years, 4% of male patients and 2% of female patients were diagnosed for incident lung cancer (6.5% vs. 4% after ten years). For men, the cumulative hazards for prostate, bladder, colon, and pancreas were 2.2%, 1.8%, 1.7%, and 0.5% (3.7%, 3.1%, 2.5%, and 0.9% after ten years). For female, the cumulative hazards for breast, colon, bladder, and pancreas were 1.8%, 1.2%, 0.6%, and 0.5 (3%, 2.3%, 0.9%, and 0.7% after ten years) respectively.

# Discussion

To our knowledge, this is the first large-scale health insurance claims study determining incidences of cancer in the long-term after index treatment for symptomatic PAD. A large cohort insured by a nationwide insurance fund was used and compared to the German overall population. The analyses were stratified by age and gender and extensive sensitivity analyses have been conducted to address differences between disease severity groups. We observed a strong association between four common cancer entities and symptomatic PAD in both genders. Cancer incidence of the lung, bladder, pancreas, and colon were mostly increased with PAD, while the risk for cancer of melanoma, breast, uterine and prostate did not differ from the general population. Importantly, some 8% of the patients were diagnosed for any common cancer during five years after the index treatment for symptomatic PAD.

To date, only a few other studies have investigated this important research topic. A study from Pehrsson et al. [12] evaluated 63,921 patients below 80 years during 1972 and 1991 in Stockholm County regarding cancer incidence. While the current study found the highest SIRs for cancer of the lung, bladder, and pancreas, they reported in men larynx followed by pharynx and lung cancer. Andersson et al. [21] lists colon, lung and bladder cancer as the three most common tobacco smoke associated tumours in the Nordic countries. Therefore, we assume that the described differences from Pehrsson et al. are the result of a regional phenomenon, as the study population was limited to the Stockholm area. However, we do not have any valid data to support this assumption.

Onega et al. examined in a population-based cohort study in Denmark 53,762 patients with intermittent claudication. The three most frequently observed cancer entities in this patient cohort were lung followed by tongue and larynx cancer. Unfortunately, this study did not distinguish between genders, limiting their comparability.

Similar to the study by Pehrsson et al., oropharyngeal carcinomas are among the three most common cancers. However, this does not correspond to the observations for the most common tobacco smoke associated tumours for

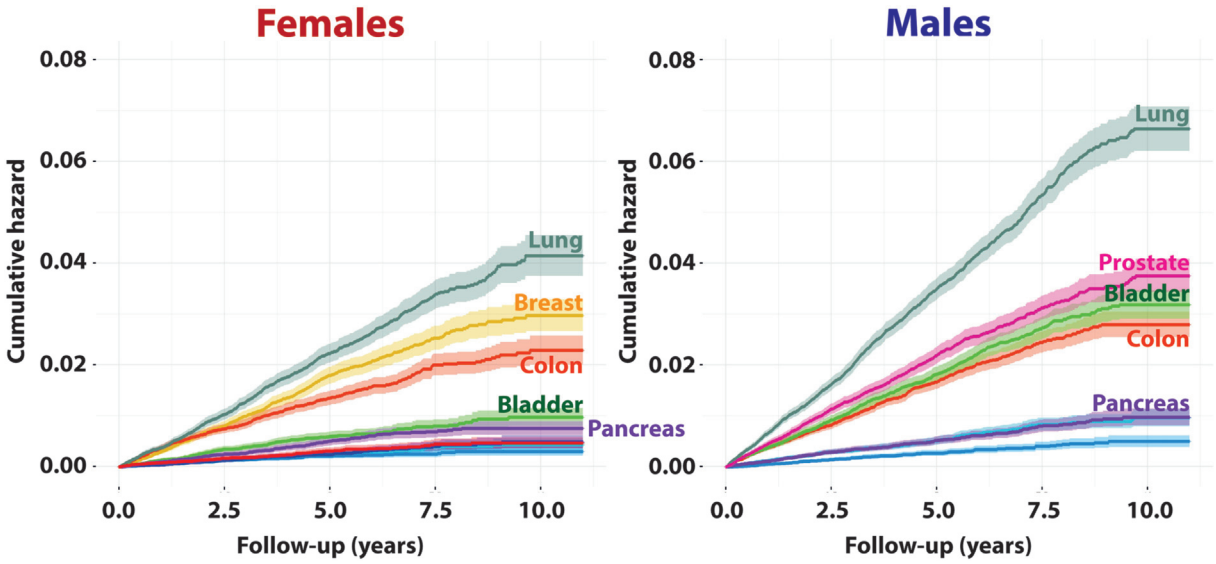


**Figure 3.** Cumulative hazards for incident cancer after index treatment of symptomatic peripheral arterial disease.



Nordic countries. We, therefore, assume that in Nordic countries other risk factors, especially in PAD patients, probably lead to an increased incidence of oropharyngeal tumours.

Further studies investigated a common occurrence of PAD and cancer. A recent prospective study from Rantner et al. [10] analysed results from the CAVASIC-study (CArdioVAScular disease in patients with Intermittent Claudication). In this study, 255 male patients with intermittent claudication were included and followed for 7 years. As one main result, the authors described that most of the patients died from cancer and not from vascular complications. Fiotti et al. [22] confirmed these results in their study.

In a related prospective study with a follow-up of 10 years, Taute et al. [11] investigated the possible risk of cancer in 109 patients with intermittent claudication. The main result of this study also was the observed high incidence of cancer (2.11 per 100 patient-years) and cancer mortality (1.05 per 100 patient-years) in patients with intermittent claudication. The mortality from cancer was almost as high as that from vascular events (36% cancer vs. 39% vascular events). The results of these studies were confirmed by the results of the current study. PAD patients exhibited a higher incidence of cancer when compared to the standard population.

In contrast to this Naschitz et al. [14] e.g. described in 1987 that the cancer incidence of patients with intermittent claudication is not significantly increased compared to the American urban, white population. Concerning this, a previous study by Jelnes et al. [23] from 1986 interestingly describes only mortality from the malignancy of 27% in patients with intermittent claudication.

When comparing the results of Rantner et al. [10], Taute et al. [11], Fiotti et al. [22] and the current study with these older studies, it is noticeable that cancer mortality in PAD appears to have increased over the last decades.

An explanation of the described differences in the mortality could be that modern vascular medicine has led to a higher survival rate of PAD, thus increasing the chance of developing cancer. However, to date, there is no study to prove this hypothesis.

Apart from the studies of Naschitz et al. [14] and Jelnes et al. [23], all other cited studies show an increased incidence of cancer in PAD patients compared to the normal population.

The most obvious explanation for this observation is certainly the presence of common risk factors, especially tobacco smoke. A significant association with tobacco smoke has been described both for PAD [24] as well as for the highest cancer incidences described in our study and other studies [25].

Another result of our study is the earlier development of certain cancers in PAD patients compared to the standard population. For example, male PAD patients show approximately 15 years earlier incidence-peak of lung cancer in comparison to the standard population. Although this effect is less pronounced in women, it is still noticeable (Figure 1A).

This phenomenon can also be explained by common risk factors such as tobacco smoke, as PAD patients are thought to have increased tobacco consumption compared to the standard population and, in conjunction with this, to be more likely to develop lung cancer.

Furthermore, we could show that the cumulative hazards for the development of cancer in PAD patients increase continuously linear within the first 10 years after index treatment. It can be assumed that common risk factors, primarily continued tobacco smoke, triggers the development. In this context, it remains to be seen whether specific smoking cessation programs, in addition to the prognosis of PAD, can also positively influence the incidence of cancer development.

In summary, the results of our study show that PAD patients are likely to benefit from timely cancer screening. However, the current guidelines for the treatment of PAD do not yet take this into account.

## Limitations

Firstly, health insurance claims data are not collected for scientific evaluation but rather for reimbursement purposes [26]. However, such claims are subject to increase awareness from scientific audience [27]. There is corroboration that there might be a progression toward upcoding of comorbidities and complications in claims [27]; while registry data are known to be affected by some degree of underreporting [28, 29]. Furthermore, a regular external cross-sample validation is performed by an independent service and peer-reviewed evidence is available showing excellent results for mortality and major outcomes in administrative data. We performed analyses separately for each cancer site and did not consider that cancer incidence and death are competing for events influencing each other. The insurance fund included in the current study only covered a proportion of the entire population in Germany. Besides statutorily insured, there is a small proportion (10%) of privately insured patients, and it remains unknown if there is a relevant selection bias. Hence, the current study used commonly accepted standardisation methods (age, gender) to address this issue, and the comparative study design makes it less affected by methodological challenges related to differences between insured cohorts.

In this study, only in-patients were included. However, it can be assumed that the proportion of symptomatic PAD patients treated outpatient in Germany is very low.

## Conclusions

Patients suffering from symptomatic PAD face a markedly higher risk for incident cancer in the long-term follow-up. The cancer risk increased continuously for certain types and PAD was strongly associated with cancer of the lung, bladder, pancreas, and colon. Taking these results into account, PAD patients could benefit from secondary and tertiary screening. These results also emphasize the impact of common risk factors such as tobacco smoke as a target for health prevention.

## Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at https://doi.org/10.1024/0301-1526/a000901

**ESM 1.** ICD codes for cancer types (Table).

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# Editor's Choice – Long Term Survival after Femoropopliteal Artery Revascularisation with Paclitaxel Coated Devices: A Propensity Score Matched Cohort Analysis

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**WHAT THIS PAPER ADDS**

In this retrospective cohort study of 37 914 patients and 21 546 propensity score matched patients having index revascularisation between 1 January 2010 and 31 December 2018, rapid adoption of paclitaxel coated devices and higher long term survival at five years was observed after their use for the treatment of symptomatic peripheral arterial occlusive disease. Among BARMER patients, no sign of increased all cause mortality following use of paclitaxel coated devices was found, emphasising differences between population based evidence and randomised trials.

**Objective:** The aim of this study was to determine the survival of patients after use of paclitaxel coated devices (PCX), as a recent meta-analysis of randomised trials reported higher mortality in patients treated with PCX balloons and stents

**Methods:** A retrospective health insurance claims analysis of patients covered by the second largest insurance fund in Germany, BARMER, was used to identify index femoropopliteal arterial interventions between 1 January 2010 and 31 December 2018. To ensure first PCX exposure, patients with prior deployment of PCX were excluded. The study cohort was stratified into patients with chronic limb threatening ischaemia (CLTI) and intermittent claudication (IC), then into balloons *vs.* stents cohorts. Within each stratum PCX were compared with uncoated devices. Propensity score matching was used to balance the study groups. Survival was evaluated using the Kaplan–Meier method and Cox regression.

**Results:** There were 37 914 patients (mean age 73.3 years; 48.8% female) included in the study. The annual proportion of PCX use increased from 3% to 39% during the study period for CLTI and from 4% to 48% for IC (both $p < .001$). Paclitaxel coated balloons and stents were associated with improved overall survival (hazard ratio [HR] 0.83, 95% confidence interval [CI] 0.77–0.90), amputation free survival (HR 0.85, 95% CI 0.78–0.91), and freedom from major cardiovascular events (HR 0.82, 95% CI 0.77–0.89) *vs.* uncoated devices at five years for CLTI. In IC cohort, mortality was significantly lower after using drug coated balloons (DCB) (HR 0.87, 95% CI 0.76–0.99) or combined DCB and drug eluting stents (HR 0.88, 95% CI 0.80–0.98).

**Conclusion:** In this large health insurance claims analysis, rapid adoption of PCX, higher long term survival, better amputation free survival, and lower rates of major cardiovascular events were seen after their use for the treatment of CLTI.

**Keywords:** Chronic limb threatening ischaemia, Drug coated balloon, Drug eluting stent, Intermittent claudication, Paclitaxel, Peripheral arterial occlusive disease

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## INTRODUCTION

Peripheral arterial occlusive disease (PAOD) affects more than 200 million patients worldwide.[1] Over 3.7 million patients worldwide underwent endovascular interventions in 2017, with the number expected to exceed 4.5 million by

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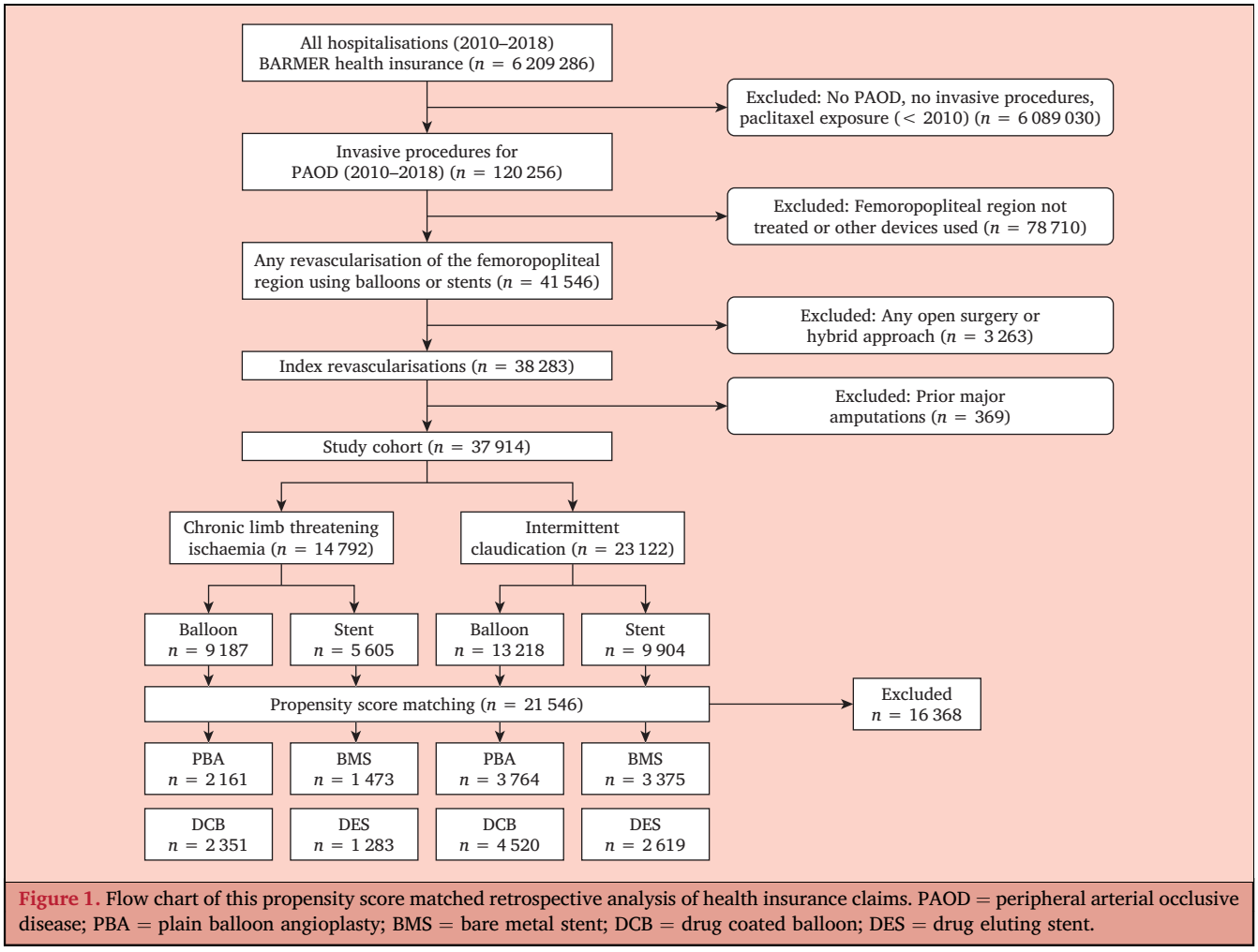


**Figure 1.** Flow chart of this propensity score matched retrospective analysis of health insurance claims. PAOD = peripheral arterial occlusive disease; PBA = plain balloon angioplasty; BMS = bare metal stent; DCB = drug coated balloon; DES = drug eluting stent.

2022.[2] Paclitaxel coated technology has become increasingly popular in the past decade for the treatment of PAOD in an effort to reduce the notoriously high restenosis rate. Practice guidelines from societies in the USA and Europe have recommended the use of drug eluting devices.[3,4] Moreover, the 2018 SCAI consensus guidelines recommended drug eluting stents (DES) or drug coated balloons (DCB) as first line treatments in the femoropopliteal segment, because of their perceived greater efficacy.[5,6] Recently, these recommendations have been heavily scrutinised after a systematic review and meta-analysis was published that involved data from 28 randomised controlled trials (RCTs) that enrolled 4663 patients with 12 different devices.[7] The authors found a higher risk of death at two and five years following the use of paclitaxel coated balloons and stents in the femoropopliteal artery. Following this report, a study in the USA using Medicare fee for service claims data to evaluate outcomes found no differences between paclitaxel coated and uncoated devices. The study was limited owing to its short follow up duration and inclusion of only patients aged >65 years.[8] The US Food and Drug Administration (FDA) conducted an independent review of trial data submitted to the FDA for device approval and confirmed the presence of a safety signal associated with paclitaxel coated devices (https://www.fda.gov/media/127698/download). These inconsistent findings between RCT and real world data have since been debated by physicians and regulators, highlighting the need for longer term patient level data, and device surveillance studies using population based data from registries and/or health insurance claims.[9–12] The aim of this study was to address concerns related to long term survival after treatment of the femoropopliteal artery with paclitaxel coated devices using a propensity score matched retrospective analysis of health insurance claims from Germany.

## PATIENTS AND METHODS

### *BARMER cohort*

The longitudinal data of Germany's second largest insurance fund, BARMER, includes the outpatient and inpatient medical care provided to approximately 9.4 million German citizens (13.2% of Germany's population) involving 6.2 million hospitalisations between 2010 and 2018. The BARMER cohort includes nationally generalisable data with comparable sex and age distribution to the entire German population, and has been widely used for cardiovascular research.[13,14] A regular random sample validation of internal and external validity is performed by the Medical

Service of the Health Funds in Germany, and various validation studies have been published previously.[15–18]

The International Classification of Diseases in its German Modification (ICD-10-GM) was used to identify diagnoses and Operations and Procedures Codes (OPS) to identify procedures. The German OPS coding is adapted to the International Classification of Procedures in Medicine. To identify medical prescriptions, the German version of the international Anatomical Therapeutic Chemical classification was used.

### Study population

A cohort of patients with symptomatic PAOD (intermittent claudication [IC], Fontaine stage II or chronic limb threatening ischaemia [CLTI], Fontaine stages III–IV) in the femoropopliteal segment was created. All patients aged ≥40 years with endovascular peripheral vascular intervention (PVI) stent/balloon revascularisation in the femoropopliteal artery were included. The index hospitalisation for PVI was from 1 January 2010 to 31 December 2018, with follow up until 31 December 2018. To create relevant comorbidities (available ICD-10-GM data going back to 2005) and to ensure first paclitaxel exposure (available procedure codes for drug coated devices going back to 2008), five year lookback in the BARMER data set was used.

In the analyses, separate cohorts for IC and CLTI were created (Fig. 1).[19] The primary diagnoses for inclusion were IC (I70.21 until 2014 and I70.21–22 since 2015) or CLTI (I70.22–24 until 2014 and I70.23–25 since 2015) with or without diabetic foot syndrome (E10.50–51, E10.7, E11.50–51, E11.7), other peripheral vascular diseases (I73), arterial embolism and thrombosis (I74), cellulitis of finger and toe, including acute lymphangitis (L03.01–02, L03.11), or chronic ulcer of skin and gangrene (L98.4, R02) using the ICD-10-GM.[20]

Patients who received at least one index DCB/DES during the study period were assigned to the paclitaxel group. If a patient received a stent and balloon at the same time, it was defined as a stent procedure. Additional information and coding criteria for DES or DCB can be found in Table S1 (see Supplementary Material). Patients with hybrid interventions (open surgical repair and PVI) exposed to paclitaxel before 2010 or patients who received a major amputation prior to the paclitaxel treatment and missing information on age, sex, and follow up (∼0.48%) were excluded using complete case deletion from the analyses. The non-paclitaxel group included plain balloon angioplasty and bare metal stent. Patients with plain balloon angioplasty or bare metal stent at index stay, but exposed to paclitaxel (e.g., DCB or DES) at a later revascularisation in the femoropopliteal artery of the lower limbs, were assigned to the paclitaxel group according to the date of the second procedure. If patients were exposed to consecutive treatments using paclitaxel coated devices during the study period, the initial application of paclitaxel (first exposure) was used as the index treatment.

For the baseline characteristics the comorbidity groups categorised by ICD-10 codes, separated into 30 Elixhauser comorbidity groups[21,22] for five years before the first PAOD diagnosis (lookback), were used. The linear van Walraven score is a validated weighted sum score ranging from −19 to +89 based on the Elixhauser groups; high scores represent a higher in hospital mortality risk.[23]

### Statistical analysis

Baseline patient characteristics were summarised as mean ± standard deviation for normally distributed variables and as median (interquartile range [IQR]) for non-normally distributed variables. For discrete variables, percentages and risk differences, including 95% Wald confidence interval (CI; significant if 0 outside the interval), were used.

The Student's *t*-test and Wilcoxon rank sum test were used to test for differences between exposure groups. The Cochrane Armitage trend test was used for the trend test of proportion of paclitaxel use. The discharge year; age; sex; number of prior hospital admissions and PAOD related outpatient admissions; number of different prescriptions during the prior year; prescription for antithrombotics, antihypertensives, lipid lowering drugs, antihypertensives, antidiabetics, analgesics, hypnotics and sedatives, antidementives, and antidepressives during the prior year; all the Elixhauser coding groups (except acquired immunodeficiency syndrome/human immunodeficiency virus); and prior stroke or transient ischaemic attack (TIA), dyslipidaemia, coronary artery disease, smoking, and prior myocardial infarction were used as variables for propensity score matching stratified by CLTI and IC.[21–23]

The primary outcome was all cause mortality; the end of follow up was in December 2018. Secondary outcomes were the composite end points of amputation free survival (AFS; major amputation or all cause mortality) and major cardiovascular events (myocardial infarction, stroke or TIA, and all cause mortality). Follow up times were censored after five years to compute robust five year rates. All outcomes were estimated using Cox proportional hazard models stratified by CLTI and IC for the full sample, and by subgroup stent and balloon. All Cox models were additionally adjusted for age; sex; Fontaine stage; prior myocardial infarction; van Walraven score; congestive heart failure; cardiac arrhythmias; valvular disease; hypertension; neurogenerative disorders; chronic pulmonary disease; hypothyroidism; renal failure; liver disease; metastatic cancer; solid tumour without metastasis; obesity; fluid and electrolyte disorders; deficiency anaemia; psychosis; depression; lipid lowering drugs in the year before admission; antithrombotics in the year before admission; antihypertensives in the year before admission; antidementives in the year before admission; number of different prescriptions in the year before admission; number of previous inpatient admissions total (including the index admission); and number of prior PAOD outpatient admissions entered

into the matching algorithm to account for residual confounding.

In the sensitivity analysis, patients experiencing events within 30 days after hospital discharge (landmark analysis) were excluded and Cox proportional hazards (PH) models without adjustment for residual confounding were computed (Table S2; see Supplementary Material). As an additional sensitivity analysis long term survival, including patients with IC and CLTI (unstratified), was calculated.

The primary exposure of interest was any index (first) paclitaxel coated device application. Disease severity specific propensity score matching (greedy 1:1 matching) was applied to adjust for observed confounding allowing for differences in confounding effects between IC and CLTI. To measure the validity of the matching algorithm, standardised differences (values $> 0.1$ or $< -0.1$ deemed to indicate meaningful differences) were used. Details of the logistic regression model and a comparison of quality for propensity score matching are reported in Tables S3 and S4 (see Supplementary Material).

All analyses were performed with SAS version 9.04 (SAS Institute, Cary, NC, USA). Results were reported using the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement,[24] the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement,[25] and following international recommendations on medical device evaluation studies.[24]

Cox regression models and visualisations were performed with R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

The trial was registered on the ClinicalTrials.gov website (NCT03909022).

## RESULTS

This study included a total of 37 914 patients hospitalised during the study period (mean age 73.33 ± 10.36 years; 48.8% females) and 21 546 propensity score matched patients undergoing PVI from 1 January 2010 to 31 December 2018. The cohort was stratified by CLTI *vs.* IC and then by balloon *vs.* stent use. Within each cohort, drug eluting device use was evaluated. The annual proportion of paclitaxel coated devices for CLTI increased from 3% in 2010 to 39% in 2018, ($p<.001$), and for IC from 4% in 2010 to 48% in 2018 ($p<0.001$).

### *Unmatched analyses for demographics and comorbidities*

The median length of follow up was 983 days (IQR 412—1777 days [4.9 years]). The longest follow up was eight years.

In the CLTI group, patients treated with paclitaxel coated devices were younger (75.8 *vs.* 77.4 years; $p < .001$), received a larger mean number of medications (13.6 *vs.* 13.0; $p < .001$), were hospitalised more often prior to their index revascularisation (5.9 *vs.* 5.0; $p < .001$), and had a shorter length of follow up (median 567 *vs.* 764 days) (Table 1). Furthermore, they were more likely to be smokers (15.8% *vs.* 12.7%), to have dyslipidaemia (62.1% *vs.* 51.5%), obesity (19.5% *vs.* 17.6%), hypertension (90.1% *vs.* 88.5%), and liver disease (6.9% *vs.* 5.5%). At the same time, patients treated with paclitaxel coated devices had less often had a prior stroke/TIA (11.3% *vs.* 12.9%).

In the IC group, patients treated with paclitaxel coated devices received a larger mean number of medications (9.9 *vs.* 9.2; $p < .001$), were hospitalised more often prior to their index revascularisation (4.1 *vs.* 3.5; $p < .001$), had a shorter follow up time (median 805 *vs.* 1398 days), were more often females (47.7% *vs.* 45.1%), and exhibited multiple comorbidities with a van Walraven score >9 (27.1% *vs.* 25.2%). They were also more likely to be smokers (21.0% *vs.* 19.7%), have dyslipidaemia (65.1% *vs.* 55.9%), hypertension (86.3% *vs.* 82.9%), coronary artery disease (37.4% *vs.* 35.0%), cardiac arrhythmias (20.2% *vs.* 18.9%), complicated diabetes (19.3% *vs.* 18.1%), and renal failure (27.3% *vs.* 23.6%).

### *Outcomes in matched cohorts*

Demographics and comorbidities of the comparison groups after propensity score matching are given in Table 2.

In the CLTI group, patients treated with paclitaxel coated devices less often experienced acute respiratory failure (0.6% *vs.* 1.1%), pneumonia (0.6% *vs.* 1.0%), and had a shorter length of stay (median 7.0 *vs.* 9.0 days) (Table 3).

The proportion of patients discharged to rehabilitation (0.6% *vs.* 1.0%) was lower in the paclitaxel coated devices group, when compared with uncoated devices for CLTI (Table 3).

A total of 2454 deaths occurred within five years of follow up. After treatment for CLTI, a lower mortality rate was observed in the paclitaxel coated device group at five years (31.8% *vs.* 35.8%) (Table 3).

In the IC group, patients treated with paclitaxel coated devices less often experienced stroke/TIA (0.1% *vs.* 0.2%), had a shorter length of stay (median 3.0 *vs.* 3.0 days, 8 + days: 6.5% *vs.* 8.9%), and died less often within five years of hospital discharge (9.4% *vs.* 10.5%).

### *Cox proportional hazards analyses in matched cohorts*

The results of the Cox proportional hazards models for survival after five years are given in Fig. 3. In propensity score matched cohorts, a paclitaxel related survival benefit was observed for patients with CLTI treated with DCB (hazard ratio [HR] 0.82, 95% CI 0.74—0.91), for those treated with a DES (HR 0.84, 95% CI 0.73—0.96), and in the combined DCB and DES analysis (HR 0.83, 95% CI 0.77—0.90).

For AFS and major cardiovascular events after treatment of patients with CLTI, there was also a benefit of paclitaxel coated devices (HR 0.85 [95% CI 0.78—0.91] and HR 0.82 [95% CI 0.77—0.88], respectively) (data not shown).

For the subgroup of patients with IC, survival was better for DCB (HR 0.87, 95% CI 0.76—0.99) and combining DCB and DES (HR 0.88, 95% CI 0.80—0.98), but similar for DES (HR 0.91, 95% CI 0.77—1.08) (Fig. 3).

For AFS and major cardiovascular events following treatment of patients with IC, no benefit of paclitaxel coated devices was detected (HR 0.91 [95% CI 0.82—1.00] and HR 0.93 [95% CI 0.87—1.00], respectively) (data not shown).

### *Additional sensitivity analysis using cox proportional hazards in the unstratified matched cohort*

Sensitivity analyses estimated the Cox proportional hazards for the unstratified matched cohort including both patients with CLTI and IC. DCB (HR 0.83, 95% CI 0.77—0.90), DES (HR 0.86, 95% CI 0.77—0.96), and combined DCB/DES (HR 0.85, 95% CI 0.80—0.90) added significantly to the model.

## DISCUSSION

In this propensity score matched retrospective analysis of health insurance claims, comprising a rapidly increasing proportion of paclitaxel coated devices in the treatment of PAOD, higher long term survival, AFS, and adverse cardiovascular event free survival after the treatment of CLTI with paclitaxel coated devices (both balloon and stent) was found, when compared with the uncoated control group. In patients with IC, paclitaxel coated devices were associated with higher long term survival only, visible in the group where balloons and stents were combined and for balloons but not for stents. Unlike any other prior analysis, a persistent, robust, and positive association of paclitaxel exposure and survival is documented for a wide range of subgroups.

**Table 1. Baseline characteristics of the entire unmatched study cohort of patients treated endovascularly with a paclitaxel coated device (PCX) or other device protocol (control) for chronic limb threatening ischaemia (CLTI) or intermittent claudication (IC)**

| | CLTI | | | | IC | | | |
|---|---|---|---|---|---|---|---|---|
| **Unmatched characteristics** | **PCX ($n$ = 3 634)** | **Control ($n$ = 11 158)** | ***p* value** | **RD (95% CI)** | **PCX ($n$ = 7 139)** | **Control ($n$ = 15 983)** | ***p* value** | **RD (95% CI)** |
| Age − years | 75.8 ± 10.5 | 77.4 ± 10.5 | <.001* | | 70.93 ± 9.5 | 71.03 ± 9.6 | .47 | |
| No. of prescriptions prior to admission† | 13.61 ± 6.8 | 13.0 ± 6.8 | <.001* | | 9.9 ± 5.6 | 9.2 ± 5.4 | <.001* | |
| No. of prior hospitalisations | 5.9 ± 4.5 | 5.0 ± 4.0 | <.001* | | 4.1 ± 3.3 | 3.5 ± 3.0 | .001* | |
| Follow up time − d | 567 (236−1094) | 763.5 (255−1531) | <.001* | | 805 (383−1383) | 1398 (708−2205) | .001* | |
| Female sex | 1 969 (54.2) | 5 918 (53.0) | | 1.14 (−0.72−3.01) | 3 407 (47.7) | 7 210 (45.1) | | 2.61 (1.22−4.01)* |
| vWS > 9 | 2 064 (56.8) | 6 274 (56.2) | | 0.57 (−1.29−2.42) | 1 936 (27.1) | 4 024 (25.2) | | 1.94 (0.71−3.17)* |
| Prior stroke or TIA | 411 (11.3) | 1 441 (12.9) | | −1.6 (−2.81− −0.40)* | 478 (6.7) | 1 092 (6.8) | | −0.14 (−0.84−0.56) |
| Smoking | 574 (15.8) | 1 417 (12.7) | | 3.1 (1.76−4.43)* | 1 498 (21.0) | 3 144 (19.7) | | 1.31 (0.18−2.44)* |
| Dyslipidaemia | 2 257 (62.1) | 5 744 (51.5) | | 10.63 (8.8−12.46)* | 4 649 (65.1) | 8 936 (55.9) | | 9.21 (7.86−10.56)* |
| Obesity | 707 (19.5) | 1 961 (17.6) | | 1.88 (0.41−3.35)* | 970 (13.6) | 2 121 (13.3) | | 0.32 (−0.64−1.27) |
| Prescription of lipid lowering drugs prior to admission† | 1 986 (54.7) | 4 908 (44.0) | | 10.66 (8.80−12.53)* | 4 570 (64.0) | 8 883 (55.6) | | 8.44 (7.08−9.79)* |
| Hypertension | 3 273 (90.1) | 9 879 (88.5) | | 1.53 (0.39−2.67)* | 6 159 (86.3) | 13 252 (82.9) | | 3.36 (2.37−4.35)* |
| CAD | 1 654 (45.5) | 4 889 (43.8) | | 1.7 (−0.16−3.56) | 2 668 (37.4) | 5 588 (35.0) | | 2.41 (1.07−3.75)* |
| Prior MI | 566 (15.6) | 1 695 (15.2) | | 0.38 (−0.97−1.74) | 834 (11.7) | 1 771 (11.1) | | 0.6 (−0.29−1.49) |
| CHF | 1 529 (42.1) | 4 652 (41.7) | | 0.38 (−1.46−2.23) | 1 339 (18.8) | 2 867 (17.9) | | 0.82 (−0.27−1.90) |
| Valvular disease | 683 (18.8) | 2 064 (18.5) | | 0.3 (−1.16−1.76) | 621 (8.7) | 1 345 (8.4) | | 0.28 (−0.50−1.07) |
| Cardiac arrhythmias | 1 419 (39.0) | 4 433 (39.7) | | −0.68 (−2.51−1.15) | 1 445 (20.2) | 3 024 (18.9) | | 1.32 (0.21−2.43)* |
| Prescription of antithrombotics prior to admission† | 2 206 (60.7) | 5 845 (52.4) | | 8.32 (6.48−10.16)* | 3 784 (53.0) | 6 973 (43.6) | | 9.38 (7.99−10.77)* |
| Prescription of antiplatelets prior to admission† | 1 656 (45.6) | 3 920 (35.1) | | 10.44 (8.59−12.28)* | 3 270 (45.8) | 5 610 (35.1) | | 10.7 (9.33−12.08)* |
| Prescription of oral anticoagulation prior to admission† | 962 (26.5) | 2 599 (23.3) | | 3.18 (1.54−4.81)* | 885 (12.4) | 1 698 (10.6) | | 1.77 (0.87−2.67)* |
| Prescription of antiplatelets and of oral anticoagulation prior to admission† | 365 (10.0) | 699 (6.3) | | 3.78 (2.70−4.86)* | 355 (5.0) | 471 (2.9) | | 2.03 (1.46−2.59)* |
| Chronic pulmonary disease | 712 (19.6) | 2 147 (19.2) | | 0.35 (−1.13−1.83) | 1 072 (15.0) | 2 263 (14.2) | | 0.86 (−0.13−1.85) |
| Diabetes, complicated | 1 607 (44.2) | 4 766 (42.7) | | 1.51 (−0.35−3.36) | 1 376 (19.3) | 2 893 (18.1) | | 1.17 (0.08−2.27)* |
| Prescription of antidiabetics prior to admission† | 1 608 (44.2) | 4 630 (41.5) | | 2.75 (0.90−4.61)* | 2 074 (29.1) | 4 391 (27.5) | | 1.58 (0.32−2.84)* |
| Renal failure | 1 825 (50.2) | 5 434 (48.7) | | 1.52 (−0.35−3.39) | 1 952 (27.3) | 3 768 (23.6) | | 3.77 (2.54−4.99)* |
| Liver disease | 251 (6.9) | 610 (5.5) | | 1.44 (0.51−2.37)* | 293 (4.1) | 601 (3.8) | | 0.34 (−0.20−0.89) |

Data are mean ± standard deviation, n (%), or median (interquartile range). RD = risk difference; CI = confidence interval; vWS = van Walraven score; TIA = transient ischaemic attack; CAD = coronary artery disease; MI = myocardial infarction; CHF = congestive heart failure.
* Denotes statistically significant result.
† Within one year prior to admission.

The cohort was population based and comparable to current European populations. To date, 15 DCBs and two DESs have been approved for the European market; three DCBs and two DES have been approved by the FDA in the USA.[9] In the midst of the widespread adoption of this new technology, a recent meta-analysis led to a global debate concerning possible harms of paclitaxel coated devices, which has led to regulatory actions in the USA and Europe.[7] The most recent 2019 Global Vascular Guidelines for the treatment of CLTI contain a distinct statement concerning the indeterminate risk and efficacy of these devices, emphasising the need to exercise appropriate caution until data from controlled prospective studies are available.[26] Moreover, ongoing trials, such as BASIL-3 (Balloon *vs.* Stenting in Severe Ischaemia of the Leg 3) or SWEDEPAD (Swedish Drug Elution Trial in Peripheral Arterial Disease), have temporarily stopped recruitment until this critical issue is resolved.[27] Meanwhile, several arguments have been raised by the proponents of the meta-analysis, mostly concerning the lack of patient level data available to the authors, and insufficient stratification of non-homogeneous subgroups (e.g., CLTI *vs.* IC, stent *vs.* balloon angioplasty).[9,28] Most importantly, several RCTs included in the recently published meta-analyses did not have a long enough follow up to determine long term survival, and most were underpowered. Only three of 28 RCTs reported mortality rates at least three years after inclusion.[10,29–31] The five year all cause mortality rates in the Zilver Paclitaxel (PTX)[10,29] and THUNDER (Local Taxan With Short Time Contact for Reduction of Restenosis in Distal Arteries)[30] trials were 16.9% (25.0%) for the paclitaxel group and 10.2% (14.8%) for the PTA group.[10,29] At three years after

**Table 2. Baseline characteristics of the matched study cohort of patients treated endovascularly with a paclitaxel coated device (PCX) or other device (control) for chronic limb threatening ischaemia (CLTI) or intermittent claudication (IC)**

| | CLTI | | | | IC | | | |
|---|---|---|---|---|---|---|---|---|
| **Matched characteristics** | **PCX (*n* = 3 634)** | **Control (*n* = 3 634)** | ***p* value** | **RD (95% CI)** | **PCX (*n* = 7 139)** | **Control (*n* = 7 139)** | ***p* value** | **RD (95% CI)** |
| Age − years | 75.7 ± 10.5 | 76.0 ± 10.3 | .27 | | 70.93 ± 9.48 | 71.19 ± 9.51 | .10 | |
| No. prescriptions prior to admission† | 13.61 ± 6.8 | 13.6 ± 6.8 | .81 | | 9.85 ± 5.56 | 9.63 ± 5.45 | .02* | |
| No. of prior hospitalisations | 5.9 ± 4.5 | 5.6 ± 4.6 | .02* | | 4.13 ± 3.28 | 3.88 ± 3.35 | <.001* | |
| Follow up time − d | 567 (236–1 094) | 508 (193–1 026) | <.001* | | 805 (383–1 383) | 839 (406–1 377) | .01* | |
| Female sex | 1 969 (54.2) | 1 968 (54.2) | | 0.03 (−2.26–2.32) | 3 407 (47.7) | 3 325 (46.6) | | 1.15 (−0.49–2.79) |
| vWS > 9 | 2 064 (56.8) | 2 035 (56.0) | | 0.80 (−1.48–3.08) | 1 936 (27.1) | 1 918 (26.9) | | 0.25 (−1.2–1.71) |
| Prior stroke or TIA | 411 (11.3) | 409 (11.3) | | 0.06 (−1.4–1.51) | 4 78 (6.7) | 501 (7.0) | | −0.32 (−1.15–0.51) |
| Smoking | 574 (15.8) | 552 (15.2) | | 0.61 (−1.06–2.27) | 1 498 (21.0) | 1 432 (20.1) | | 0.92 (−0.4–2.25) |
| Dyslipidaemia | 2 257 (62.1) | 2 256 (62.1) | | 0.03 (−2.2–2.26) | 4 649 (65.1) | 4 522 (63.3) | | 1.78 (0.21–3.35)* |
| Obesity | 707 (19.5) | 708 (19.5) | | −0.03 (−1.85–1.79) | 970 (13.6) | 950 (13.3) | | 0.28 (−0.84–1.4) |
| Prescription of lipid lowering drugs prior to admission† | 1 986 (54.7) | 1 956 (53.8) | | 0.83 (−1.47–3.12) | 4 570 (64.0) | 4 447 (62.3) | | 1.72 (0.14–3.31)* |
| Hypertension | 3 273 (90.1) | 3 264 (89.8) | | 0.25 (−1.14–1.63) | 6 159 (86.3) | 6 104 (85.5) | | 0.77 (−0.37–1.91) |
| CAD | 1 654 (45.5) | 1 689 (46.5) | | −0.96 (−3.25–1.33) | 2 668 (37.4) | 2 663 (37.3) | | 0.07 (−1.52–1.66) |
| Prior MI | 566 (15.6) | 578 (15.9) | | −0.33 (−2.00–1.34) | 834 (11.7) | 841 (11.8) | | −0.10 (−1.15–0.96) |
| CHF | 1 529 (42.1) | 1 535 (42.2) | | −0.17 (−2.44–2.11) | 1 339 (18.8) | 1 342 (18.8) | | −0.04 (−1.32–1.24) |
| Valvular disease | 683 (18.8) | 689 (19.0) | | −0.17 (−1.96–1.63) | 621 (8.7) | 621 (8.7) | | 0 (−0.92–0.92) |
| Cardiac arrhythmias | 1 419 (39.0) | 1 444 (39.7) | | −0.69 (−2.93–1.56) | 1 445 (20.2) | 1 455 (20.4) | | −0.14 (−1.46–1.18) |
| Prescription of antithrombotics prior to admission† | 2 206 (60.7) | 2 189 (60.2) | | 0.47 (−1.78–2.72) | 3 784 (53.0) | 3 668 (51.4) | | 1.62 (−0.01–3.26) |
| Prescription of antiplatelets prior to admission† | 1 656 (45.6) | 1 469 (40.4) | | 5.15 (2.87–7.42)* | 3 270 (45.8) | 2 942 (41.2) | | 4.59 (2.97–6.22)* |
| Prescription of oral anticoagulation prior to admission† | 962 (26.5) | 1 007 (27.7) | | −1.24 (−3.28–0.81) | 885 (12.4) | 934 (13.1) | | −0.69 (−1.78–0.41) |
| Prescription of antiplatelets and of oral anticoagulation prior to admission† | 365 (10.0) | 293 (8.1) | | 1.98 (0.66–3.30)* | 355 (5.0) | 275 (3.9) | | 1.12 (0.45–1.79)* |
| Chronic pulmonary disease | 712 (19.6) | 728 (20.0) | | −0.44 (−2.27–1.39) | 1 072 (15.0) | 1 044 (14.6) | | 0.39 (−0.77–1.56) |
| Diabetes, complicated | 1 607 (44.2) | 1 579 (43.5) | | 0.77 (−1.51–3.05) | 1 376 (19.3) | 1 339 (18.8) | | 0.52 (−0.77–1.81) |
| Prescription of antidiabetics prior to admission† | 1 608 (44.2) | 1 586 (43.6) | | 0.61 (−1.68–2.89) | 2 074 (29.1) | 2 048 (28.7) | | 0.36 (−1.12–1.85) |
| Renal failure | 1 825 (50.2) | 1 812 (49.9) | | 0.36 (−1.94–2.66) | 1 952 (27.3) | 1 909 (26.7) | | 0.60 (−0.85–2.06) |
| Liver disease | 251 (6.9) | 240 (6.6) | | 0.30 (−0.85–1.46) | 293 (4.1) | 296 (4.1) | | −0.04 (−0.69–0.61) |

Data are mean ± standard deviation, *n* (%), or median (interquartile range). RD = risk difference; CI = confidence interval; vWS = van Walraven score; TIA = transient ischaemic attack; CAD = coronary artery disease; MI = myocardial infarction; CHF = congestive heart failure.
* Denotes statistically significant result.
† Within one year prior to admission.

**Table 3. Peri-operative (in hospital) outcomes and long term survival of the matched study group of patients treated endovascularly with a paclitaxel coated device (PCX) or other device (control) for chronic limb threatening ischaemia (CLTI) or intermittent claudication (IC)**

| | CLTI | | | | IC | | | |
|---|---|---|---|---|---|---|---|---|
| Matched outcomes | PCX ($n$ = 3 634) | Control ($n$ = 3 634) | $p$ value | RD (95% CI) | PCX ($n$ = 7 139) | Control ($n$ = 7 139) | $p$ value | RD (95% CI) |
| Length of stay − d | 7.0 (4.0–14.0) | 9.0 (4.0–17.0) | <.001* | | 3.0 (2.0–4.0) | 3 (2.0–4.0) | <.001* | |
| Length of stay ≥ 8 d | 1 767 (48.6) | 2 089 (57.5) | | −8.86 (−11.15– −6.58)* | 462 (6.5) | 637 (8.9) | | −2.45 (−3.32– −1.58)* |
| ALI | 253 (7.0) | 251 (6.9) | | 0.06 (−1.11–1.22) | 346 (4.8) | 349 (4.9) | | −0.04 (−0.75–0.66) |
| Bleeding | 123 (3.4) | 142 (3.9) | | −0.52 (−1.38–0.34) | 51 (0.7) | 59 (0.8) | | −0.11 (−0.4–0.17) |
| Acute MI | 18 (0.5) | 29 (0.8) | | −0.30 (−0.67–0.07) | 17 (0.2) | 19 (0.3) | | −0.03 (−0.19–0.14) |
| Acute renal failure | 105 (2.9) | 106 (2.9) | | −0.03 (−0.8–0.74) | 24 (0.3) | 23 (0.3) | | 0.01 (−0.17–0.20) |
| Acute respiratory failure | 20 (0.6) | 41 (1.1) | | −0.58 (−1– −0.16)* | 11 (0.2) | 13 (0.2) | | −0.03 (−0.16–0.11) |
| Post-operative delirium | 31 (0.9) | 46 (1.3) | | −0.41 (−0.88–0.06) | 7 (0.1) | 13 (0.2) | | −0.08 (−0.21–0.04) |
| Pneumonia | 20 (0.6) | 37 (1.0) | | −0.47 (−0.87– −0.06)* | 3 (0.0) | 3 (0.0) | | 0.0 (−0.07–0.07) |
| Stroke or TIA | 6 (0.2) | 6 (0.2) | | 0 (−0.19–0.19) | 5 (0.1) | 14 (0.2) | | −0.13 (−0.25– −0.01)* |
| Sepsis or SIRS | 18 (0.5) | 18 (0.5) | | 0 (−0.32–0.32) | 2 (0.0) | 1 (0.0) | | 0.01 (−0.03–0.06) |
| In hospital death | 65 (1.8) | 82 (2.3) | | −0.47 (−1.11–0.18) | 5 (0.1) | 7 (0.1) | | −0.03 (−0.12–0.07) |
| Discharged to rehabilitation | 20 (0.6) | 36 (1.0) | | −0.44 (−0.84– −0.04)* | 4 (0.1) | 8 (0.1) | | −0.06 (−0.15–0.04) |
| Discharged to nursing home | 78 (2.1) | 98 (2.7) | | −0.55 (−1.26–0.16) | 6 (0.1) | 10 (0.1) | | −0.06 (−0.17–0.05) |
| Death within 30 days | 108 (3.0) | 130 (3.6) | | −0.61 (−1.42–0.21) | 10 (0.1) | 16 (0.2) | | −0.08 (−0.22–0.06) |
| Death within five years | 1 154 (31.8) | 1 300 (35.8) | | −4.02 (−6.19– −1.85)* | 673 (9.4) | 753 (10.5) | | −1.12 (−2.1– −0.14)* |
| Amputation after five years | 226 (6.2) | 226 (6.2) | | 0 (−1.11–1.11) | 70 (1.0) | 57 (0.8) | | 0.18 (−0.13–0.49) |
| MI after five years | 318 (8.8) | 348 (9.6) | | −0.83 (−2.15–0.5) | 593 (8.3) | 602 (8.4) | | −0.13 (−1.03–0.78) |
| Stroke/TIA after five years | 275 (7.6) | 301 (8.3) | | −0.72 (−1.96–0.53) | 429 (6.0) | 433 (6.1) | | −0.06 (−0.84–0.73) |

Data are median (interquartile range) or $n$ (%). RD = risk difference; CI = confidence interval; ALI = acute limb ischaemia; MI = myocardial infarction; TIA = transient ischaemic attack; SIRS = systemic inflammatory response syndrome.
* Denotes statistically significant result.

inclusion in the IN.PACT SFA (IN.PACT Admiral® Drug Coated Balloon *vs.* Standard PTA for the Treatment of SFA and Proximal Popliteal Arterial Disease) trial, deaths were reported in 10.7% of the paclitaxel group *vs.* 1.9% of the PTA group.[31] For the latter, the authors discussed the significantly higher all cause death rate among patients receiving DCB *vs.* uncoated balloons, underlining that all events occurred late after therapy and none of the deaths was determined to be related to the balloon treatment.[31] The updated meta-analysis recently reported no differences in mortality, which also illuminates possible problems with RCT data pooling, with a fine line between methodological validity and possible selection bias.[28] Owing to a large sample size and high internal and external validity of death ascertainment, longitudinal data from the present study can complement the evidence base and at least partially fill the knowledge gap.[32]

Interestingly, the results of the current study are inconsistent with the central findings and conclusions of a meta-analysis in 2018.[7] Higher rates of amputations following the application of paclitaxel coated devices possibly responsible for survival differences could not be confirmed. In addition, a delayed effect leading to long term differences was not observed. In fact, the differences in survival were immediately noticeable one year after the index procedure (Fig. 2).

Recently, a German health insurance claims analysis using the same database was published concerning a similar research question. The authors used a heterogeneous sample using a relatively flexible model with multiple collinearities and only moderate adjustment for confounding (Table S5; see Supplementary Material).[32] Interestingly, differences in the median length of follow up are explained by the fact that the present study included more up to date treatments with short term follow up lowering this estimate. Correspondingly, the study by Freisinger *et al.*[32] included only 177 DESs and 61 DCBs implanted before 2010 (0.5% of all devices). The authors concluded that no evidence for increased mortality after drug eluting devices was found over a follow up of 11 years. The present study confirmed the findings using a more robust model. Aiming to add to the existing evidence, the current approach rested on a rigorous study design involving a more homogeneous study population (only femoropopliteal segment, no prior major amputation), with a lookback period of up to five years and follow up periods (left and right censoring) of five years, stratified propensity score matching and adjustment

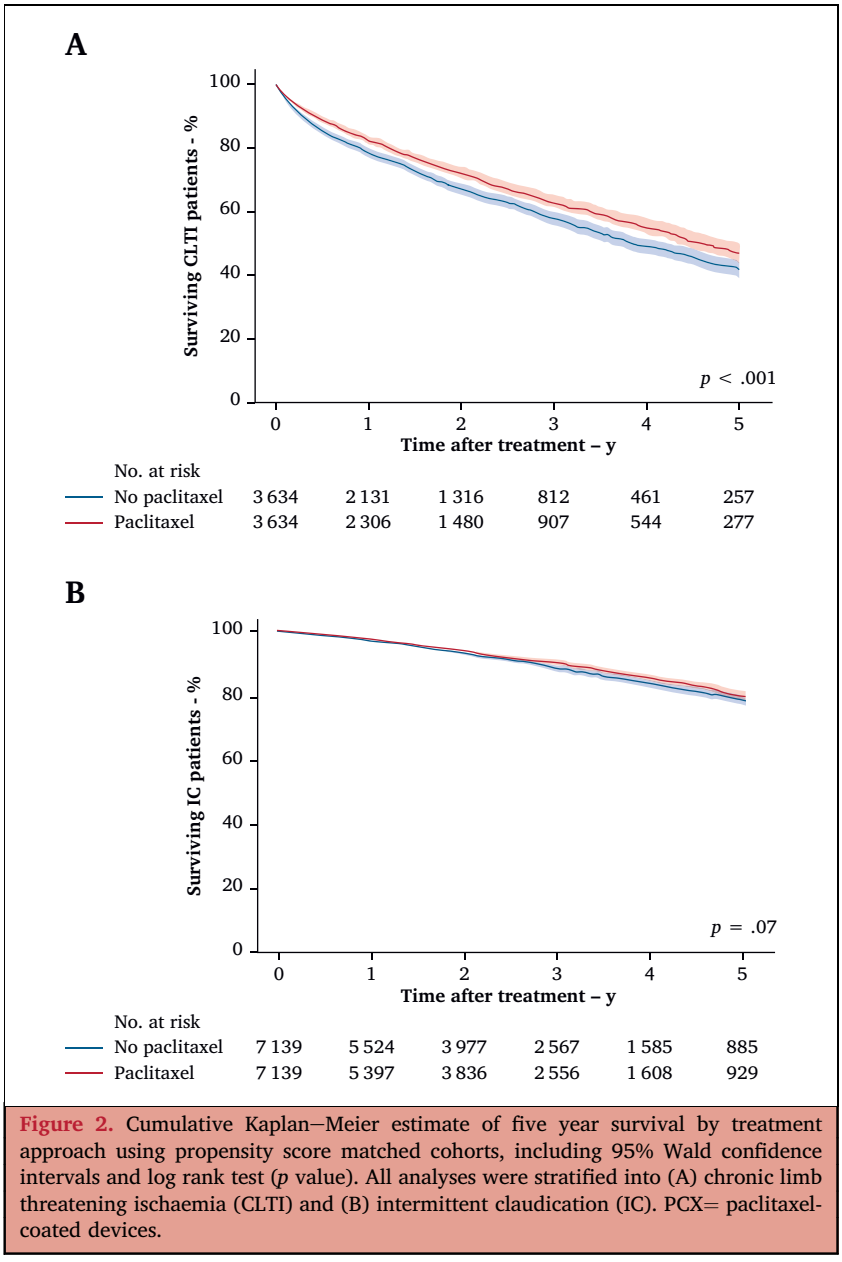


**Figure 2.** Cumulative Kaplan–Meier estimate of five year survival by treatment approach using propensity score matched cohorts, including 95% Wald confidence intervals and log rank test (*p* value). All analyses were stratified into (A) chronic limb threatening ischaemia (CLTI) and (B) intermittent claudication (IC). PCX= paclitaxel-coated devices.

for residual confounding based on the most up to date information, and extensive sensitivity analyses to ensure the robustness of the findings.

The present study has limitations. It is possible that the experience of the centre performing the procedures and the follow up of those patients play a major role increasing the overall survival of the target population. Follow up studies can determine the impact of optimal medical treatment, especially the effect of statins, and a possible clustering of patients in high volume paclitaxel trial centres. Furthermore, information on specific devices, doses of paclitaxel delivered, or paclitaxel applied during coronary or cancer treatment could not be collected validly. There is a very small proportion of coatings other than paclitaxel, making some of the codings used, less specific. In addition, the primary purpose of the data collection should be considered when using the data for secondary purposes, and all research data should undergo validation. Health insurance funds in Germany perform random cross checks with patient files on a regular basis. Prior validation studies revealed high major outcomes validity such as mortality in health insurance claims data.[15–18] Patients with CLTI have competing risks for mortality that may mask the mortality effects of devices. Known confounders were controlled for in an effort to minimise this possibility. However, there are probably remaining confounders not available in health insurance claims data. It must be highlighted that retrospective observational studies are merely hypothesis generating. Only a properly powered RCT would be suitable to confirm or refute the signal identified in the recently published meta-analysis. Lastly, although the fee for service reimbursement system in Germany probably motivates interventionalists to perform inpatient procedures rather than outpatient procedures, there might be another target

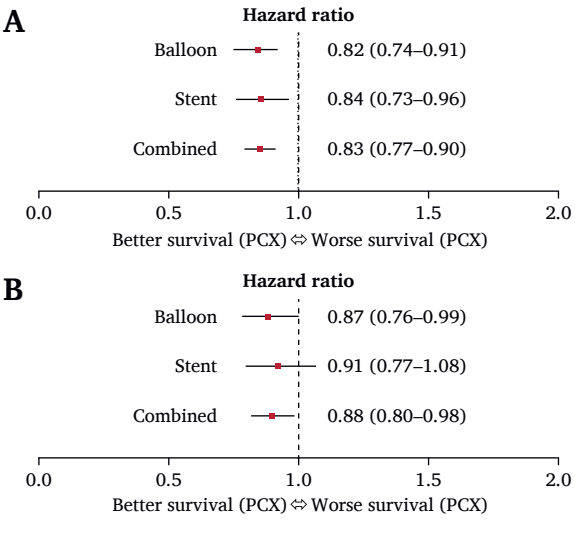


**Figure 3.** Forest plots of five year survival by treatment approach using propensity score matched cohorts with hazard ratios and 95% confidence intervals (balloon *vs.* stent *vs.* both approaches merged together). All analyses were stratified in (A) chronic limb threatening ischaemia and (B) intermittent claudication. PCX = paclitaxel-coated devices.

population not included in this study. The same limitation is valid for patients insured by other insurance providers or patients changing their health insurance company during the study period, although this is known to occur seldomly in the target population. However, it is believed that paclitaxel distribution is comparable and that there is no relevant selection bias limiting the results of this study.

The current results significantly differ between CLTI and IC, and between balloons and stents, indicating that studies should stratify their analyses accordingly. However, it remains unclear if there is a varying effect in different subgroups, or if these differences are caused by a longer time delay between index treatment for IC until major adverse outcomes.

As patients with paclitaxel coated devices were fundamentally different from those without paclitaxel coated devices in the unmatched cohort, the possibility that unmeasured confounding may partly explain the findings should be considered. A possible explanation may be that patients revascularised with DCB or DES are more likely to be treated in highly experienced trial centres with a clear follow up protocol. A higher proportion of statin prescriptions and strict surveillance for cardiac diseases might explain some of the differences observed in the current study. Further studies should exploit quasi-experimental research designs, for example randomised blinded studies or instrumental variables, to explore this in greater detail.[16,33–35]

The results of this study provide important information for physicians caring for patients with PAOD, which should be considered in addition to data from RCTs. It also adds significantly to the knowledge base by including patients with CLTI *vs.* IC who were not sufficiently covered by the recently published meta-analysis.

## CONCLUSIONS

Using a propensity score matched retrospective analysis of paclitaxel coated devices in the treatment of PAOD, higher long term survival, AFS, and freedom from major cardiovascular events after treatment of CLTI and IC with paclitaxel coated devices was found when compared with the uncoated control group. These results emphasise the differences between population based evidence and meta-analyses of trials, prompting future research and reflection by policy makers.

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## CONFLICTS OF INTEREST

MS has done consultancy work (medical advisory board) for Abbott, Cook, and Medtronic. TiK received travel and research grants, speaking fees, IP, royalties, and proctoring with Cook Medical. He is shareholder of Mokita Medical GmbH. ESD has received funding from Bayer and Terumo. The other authors declare no conflicts of interest.

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## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2019.12.034.

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# Long Term Outcomes After Revascularisations Below the Knee with Paclitaxel Coated Devices: A Propensity Score Matched Cohort Analysis

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**WHAT THIS PAPER ADDS**

In this retrospective cohort study of 14 738 patients and 6 568 propensity score matched patients with index revascularisation below the knee between 1 January 2010 and 31 December 2018, a reduction was observed in long term all cause mortality and the combined endpoints of amputation or death and cardiovascular event or death five years after the use of paclitaxel coated devices when compared with uncoated devices for the treatment of chronic limb threatening ischaemia. The study addressed a key question in vascular medicine and using long term real world evidence does not confirm the potential harm reported in randomised controlled trials.

**Objective:** Endovascular revascularisation has become a standard approach for below knee lesions and paclitaxel coated devices have been widely used in patients with chronic limb threatening ischaemia. A recent meta-analysis reported higher mortality in paclitaxel coated devices compared with uncoated devices in femoropopliteal lesions. This study aimed to determine long term outcomes in below the knee interventions using paclitaxel coated devices in routine vascular care using a large and contemporary cohort.

**Methods:** A large cohort was created using all inclusive health insurance claims data of patients covered by the second largest insurance fund in Germany. The cohort included patients with index revascularisation of arteries below the knee performed from 1 January 2010, to 31 December 2018. Only patients with first paclitaxel coated device exposure were included. The study cohort was stratified into balloon *vs.* stent treatment and patients with paclitaxel coated devices were matched with uncoated devices using propensity score. Outcomes were evaluated using the Kaplan—Meier method and Cox regression.

**Results:** There were 14 738 patients (mean age 77.6 years, 43.6% female) and 6 568 matched patients included in the study. Increasing use of paclitaxel coated devices was observed during the study period (6% in 2010 *vs.* 31% in 2018, $p < .001$), and a total of 2 611 (39.8%) deaths occurred within five years of follow up. In the propensity score matched Cox model, a paclitaxel related reduction of five year mortality (hazards ratio, HR 0.84, 95% confidence interval, CI 0.78—0.91), amputation or death (HR 0.87, 95% CI 0.81—0.94), and cardiovascular event or death (HR 0.86, 95% CI 0.80—0.92) were observed.

**Conclusion:** In this propensity score matched cohort, reduced long term all cause mortality, reduced rates of amputation or death and cardiovascular event or death were observed at five years after the use of paclitaxel coated devices when compared with uncoated devices for the treatment of chronic limb threatening ischaemia.

**Keywords:** Chronic limb threatening ischaemia, Drug coated balloon, Drug eluting stent, Paclitaxel, Peripheral arterial occlusive disease
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## INTRODUCTION

More than 200 million patients worldwide and 40 million in Europe are affected by peripheral arterial occlusive disease (PAOD).[1] Chronic limb threatening ischaemia (CLTI) marks the end stage of PAOD or diabetic foot syndrome leading to high amputation rates, morbidity, and mortality, and is commonly caused by severe multilevel atherosclerosis including the below knee (BK) segment. Endovascular revascularisation for infrapopliteal disease has evolved as a

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primary approach in high risk CLTI patients.[2,3] Nevertheless, outcomes of percutaneous transluminal angioplasty (PTA) with or without bare metal stenting (BMS) remain suboptimal,[4,5] especially in BK lesions, because of the high incidence of restenosis and occlusion caused by neointimal hyperplasia. To diminish the restenosis rate, drug eluting balloons (DEB) and stents (DES) have been invented using the antiproliferative effect of paclitaxel on vascular smooth muscle and endothelial cell proliferation.[6]

Since the first publications in the early 2000s, several randomised controlled trials (RCT) on paclitaxel coated devices (PCX) in peripheral vascular interventions (PVI) have been conducted. They involved mainly femoropopliteal[7–9] but also BK lesions,[10–12] giving promising results regarding target lesion revascularisation and major amputation rate. Interestingly, there were more complications in the drug eluting arm of one trial leading to serious concerns over higher amputation rates.[11] The remarkable rise of paclitaxel coated balloons and stents was shattered in 2018 by a meta-analysis of summary level trial data presenting increased all cause mortality two and five years following application of PCX in femoropopliteal arteries.[13] While the FDA analyses confirmed the findings of the meta-analysis, several studies using real world data from registries or health insurance claims data either reported none or even a positive influence of PCX on long term outcomes.[14–17] More recently, a second meta-analysis of summary level trial data reiterated safety concerns of PCX for BK application in patients suffering from chronic limb threatening ischaemia.[18] Against the backdrop of this discussion, another controversy concerned a possible association between PCX and increased amputation rates in BK CLTI patients.[11] However, neither the involved RCT nor the meta-analysis was initially powered to investigate this issue in the longer term.

The current study sought to determine the long term outcomes of BK interventions using PCX in CLTI patients with large scale population based health insurance claims data. The study hypothesis was that PCX is associated with an increase in long term overall mortality, amputation, or death, and cardiovascular events or death in real world data from Germany.

## METHODS

### *BARMER cohort*

The longitudinal data of Germany's second largest insurance fund, BARMER, includes the outpatient and inpatient medical care provided to approximately 9.4 million German citizens (13.2% of Germany's population) involving 6.2 million hospitalisations between 2010 and 2018. The BARMER cohort includes nationally generalisable data with comparable gender and age distribution to the entire German population and has been widely used for cardiovascular research. The database contains longitudinal information for each person including date of birth, start and end of insurance episodes, and date of death until 31 December 2018. A regular random sample validation of internal and external validity is performed by the Medical Service of the Health Funds (MDK) in Germany, and various validation studies have been published before.[19–22]

The International Classification of Diseases in its German Modification (ICD-10-GM) was used to identify diagnoses and Operations and Procedures Codes (OPS) coding to identify procedures. The German OPS code is adapted to the International Classification of Procedures in Medicine (ICPM). For identifying medical prescriptions, the German version of the international Anatomical Therapeutic Chemical (ATC) classification was used. This study is part of a larger project on outcomes of PAOD patients after revascularisation. Further details regarding this cohort can be found in a published study protocol on optimal pharmacological treatment and the ongoing claims study (clinicaltrials.gov NCT03909022).[23] The precise analyses in this paper were not pre-specified.

### *Study population*

A cohort of patients with CLTI (Fontaine stages III to IV) in the crural segment below the knee was created. All patients aged $\geq$ 40 years were included with an endovascular PVI comprising stent/balloon revascularisation in the crural arteries. The index hospitalisation for PVI was from 1 January 2010 to 31 December 2018, with follow up until 31 December 2018. Five year lookback was used in the BARMER dataset to create relevant comorbidities (available ICD-10-GM data going back to 2005) and to ensure first paclitaxel exposure (available procedure codes for drug coated devices going back to 2008).

Patients were included whose primary diagnosis was CLTI (I70.22—24 until 2014 and I70.23—25 since 2015) or CLTI as secondary diagnosis in combination with a primary diagnosis of diabetic foot syndrome (E10.50—51, E10.7, E11.50—51, E11.7), other peripheral vascular diseases (I73), arterial embolism and thrombosis (I74), cellulitis of finger and toe including acute lymphangitis (L03.01—02, L03.11), or chronic ulcer of skin and gangrene (L98.4, R02) using the ICD-10-GM.

Patients who received at least one index drug coated balloon/stent during the study period were assigned to the paclitaxel group. If the patient received a stent and balloon at the same time, this was defined as a stent procedure. Additional information and coding criteria for DES or DCB and identification of CLTI patients by Fontaine stage can be found in the Table S1. Patients with hybrid interventions (open surgical repair [OSR] and PVI) exposed to paclitaxel before 2010 or patients who received a major amputation prior to the index stay or patients with missing information on age, sex, and follow up ($\sim$0.48%) were excluded using complete case deletion. The non-paclitaxel group included plain balloon angioplasty (PBA) and bare metal stent (BMS). Patients with PBA or BMS at index stay but exposed to paclitaxel (e.g., DCB or DES) at later revascularisation of the lower limbs were assigned to the paclitaxel group according to the date of the second procedure. If patients were exposed to consecutive treatments using paclitaxel coated

devices during the study period, the initial application of paclitaxel (first exposure) was used as index treatment.

For the baseline characteristics, the comorbidity groups were categorised by ICD-10-GM codes separated into 30 Elixhauser comorbidity groups[24,25] during five years before the first PAOD diagnosis (lookback). The linear van Walraven score (vWS) is a weighted sum score ranging from −19 to +89 based on the Elixhauser groups and has been validated, wherein high scores represent a higher risk of in hospital death.[26]

### *Statistical analysis*

Baseline characteristics of the patients were summarised with means and standard deviations (SD) for normally distributed variables, and medians and interquartile ranges (IQR) for non-normally distributed variables. For discrete variables, percentages and relative risk differences were used including 95% Wald CI (significant if 0 outside the interval).

The t test and Wilcoxon rank sum tests were used to test for differences between exposure groups, and the Cochrane Armitage test was used for trend test of the proportion of paclitaxel usage. The discharge year, age, sex, number of prior hospital admissions and PAOD related outpatient admissions, number of different prescriptions during the prior year, and prescription for antithrombotics, antiplatelets, oral anticoagulants, dual antithrombotic therapy (antiplatelet and anticoagulant), lipid lowering drugs, antihypertensives, antidiabetics, analgesics, hypnotics and sedatives, antidementia, antidepressives during the prior year, all the Elixhauser coding groups (except AIDS/HIV), and prior stroke or transient ischaemic attack (TIA), dyslipidaemia, coronary artery disease, smoking, and prior myocardial infarction were used as variables for propensity score (PS) matching.

The primary outcome was all cause mortality with the end of the follow up in December 2018. Secondary outcomes were the composite endpoints amputation or death (major amputation or all cause mortality) and cardiovascular event or death (myocardial infarction, stroke or TIA, and all cause mortality). Follow up times were censored after five years to compute robust five year rates. All outcomes were estimated using Cox proportional hazards models stratified by stent and balloon treatment. All Cox models were additionally adjusted for age, sex, Fontaine stage, prior myocardial infarction, congestive heart failure, cardiac arrhythmias, valvular disease, hypertension, neurodegenerative disorders, chronic pulmonary disease, hypothyroidism, renal failure, liver disease, metastatic cancer, solid tumour without metastasis, obesity, fluid and electrolyte disorders, deficiency anaemia, psychosis, depression, lipid lowering drugs, antithrombotics, antiplatelets, oral anticoagulants, dual antithrombotic therapy (antiplatelet and anticoagulant), antihypertensives, antidiabetics, antidementia during year before admission, number of different prescriptions during year before admission, number of previous inpatient admissions total (incl. index), and number of prior PAOD outpatient admissions.

As a sensitivity analysis, Cox models were computed without additional regression adjustment, used an intention to treat approach for assigning study groups based on the first revascularisation only, excluded patients switching from non-paclitaxel revascularisation to paclitaxel revascularisation during follow up, excluded patients experiencing any outcome events within 30 days after hospital discharge (landmark analysis), and adjusting also for post-discharge medication therapy (Tables S4 and S5). Further sensitivity models excluded patients with concomitant PCX devices in the femoropopliteal or abdominal and pelvic arteries, excluded patients treated in centres with mean annual revascularisation volume above 200 cases, adjusted the model also for log mean annual revascularisation volume, stratified the sample by low and high volume at the median of 68 cases annually and stratified the sample by low and high rate of PCX (ratio of all PCX cases and all cases) using 0.14 as the threshold (Table S6).

The primary exposure of interest was any index (first) PCX application. PAOD severity specific PS matching (greedy 1:1 matching) was applied to adjust for observed confounding. To measure the validity of the matching algorithm, standardised differences were used (values above 0.1 or below −0.1 deemed to indicate meaningful differences). Details of the logistic regression model and a comparison of quality for PS matching are reported in Tables S2 and S3.

All analyses were performed with software SAS version 9.04 (SAS Institute, NC, USA). Results were reported using the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) statement,[27] the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement,[28] and following international recommendations on medical device evaluation studies.[29]

Cox regression models and visualisations were performed with software R version 3.3.3 (The R Foundation for Statistical Computing, Vienna, Austria). Illustrations were designed using Adobe Illustrator version 24.0.1 (Adobe Systems Software Ireland Ltd., Dublin, Republic of Ireland).

## RESULTS

This study included a total of 14 738 patients with CLTI hospitalised for BK revascularisation during the study period with average age 77.6 ± 9.9 years (43.6% females), and 6 568 PS matched patients undergoing PVI from 1 January 2010 to 31 December 2018 (Fig. 1). An increasing proportion of PCX was observed during the study period (6% in 2010 *vs.* 31% in 2018, $p < .001$).

### *Unmatched analyses for demographics and comorbidities*

The median follow up was 606 days (interquartile range from 214 to 1 295 days, 3.5 years). The longest follow up was 8 years. Among all CLTI patients, 2 192 (14.9%) suffered from rest pain and 12 546 (85.1%) had been revascularised for wound healing disorders. There was a prior diagnosis of stroke or TIA in 1934 patients (13.1%), 6 792 patients (46.1%) had a prior diagnosis of coronary artery disease, 2

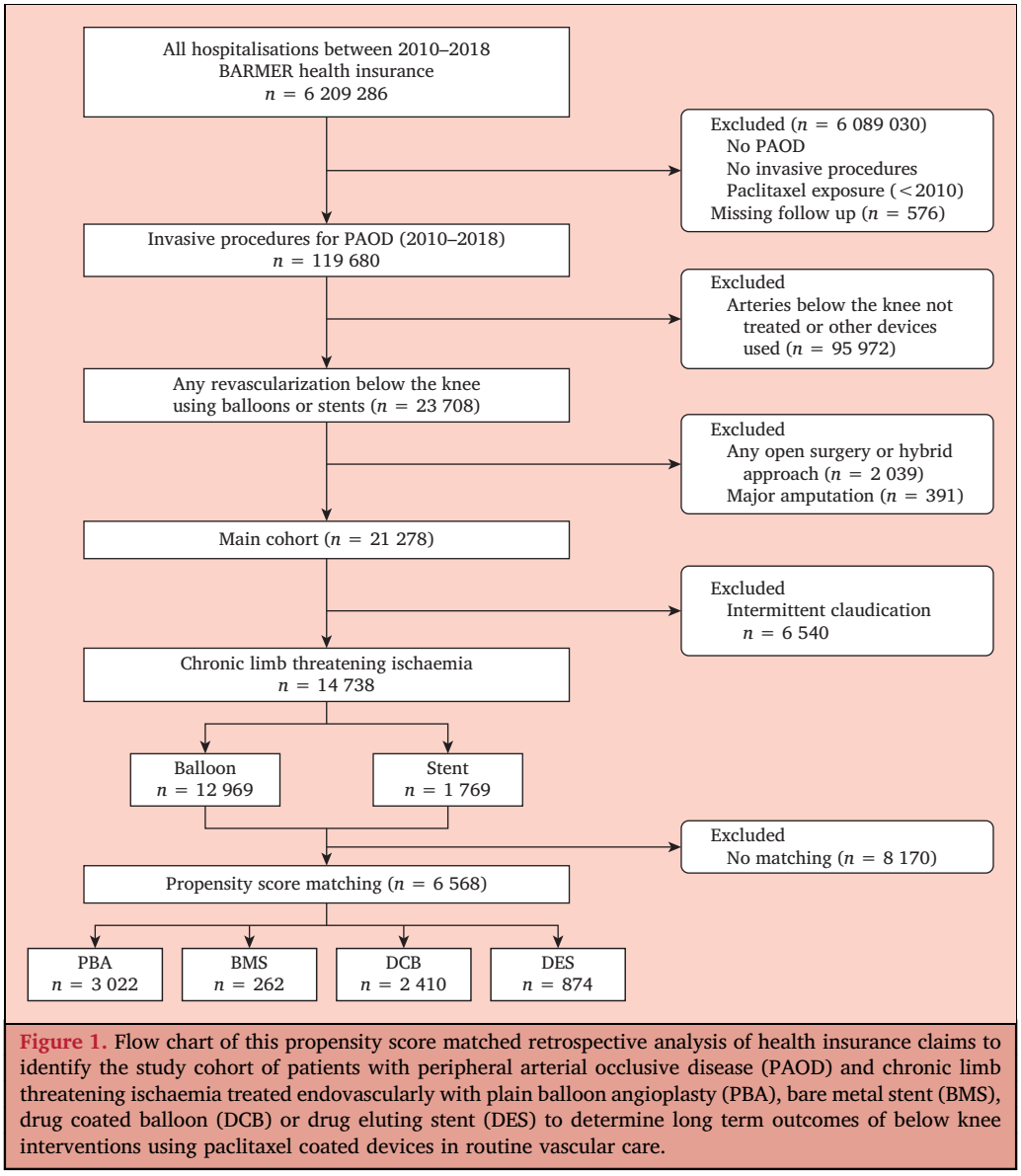


**Figure 1.** Flow chart of this propensity score matched retrospective analysis of health insurance claims to identify the study cohort of patients with peripheral arterial occlusive disease (PAOD) and chronic limb threatening ischaemia treated endovascularly with plain balloon angioplasty (PBA), bare metal stent (BMS), drug coated balloon (DCB) or drug eluting stent (DES) to determine long term outcomes of below knee interventions using paclitaxel coated devices in routine vascular care.

283 (15.5%) patients had prior myocardial infarction, and 9 319 (63.2%) had previously been diagnosed with diabetes. The median van Walraven comorbidity score was 12 (5—21) and the median length of hospital stay was 11 days (5—20). The baseline characteristics of the entire unmatched cohort are presented in Table 1. When compared with the control group, patients exposed to PCX received a higher mean number of medical prescriptions during one year before admission (14.5 *vs.* 13.8, $p < .001$), including the prescription of any antithrombotic medication (62.5% *vs.* 57.1%), and lipid lowering drugs (49.7% *vs.* 43.7%).

### *Demographics in matched cohorts*

Demographics and comorbidities of the comparison groups after PS matching are presented in Table 2. The median follow up was longer in the paclitaxel group compared with the controls (540 *vs.* 472 days, $p < .001$).

### *Primary and secondary outcome in matched cohorts*

The short and long term outcomes are presented in Table 3. Only the length of stay was significantly different between the comparison groups. Patients exposed to PCX experienced a shorter median length of hospital stay (9 *vs.* 10 days, $p < .001$). A total of 2 611 (39.8%) deaths occurred within the five years of follow up in the matched cohort.

### *Cox proportional hazards analyses in matched cohorts*

The results of the Cox proportional hazards models for all cause mortality, major amputation or death, and cardiovascular events or death after five years are reported in Fig. 2. In PS matched cohorts, a paclitaxel related reduction of five year all cause mortality was observed for patients treated with PCX in the combined DCB and DES analysis (HR 0.84, 95% CI 0.78—0.91) but also separately for DCB (HR 0.84, 95% CI 0.77—0.92) and DES (HR 0.76, 95% CI 0.61—0.94).

**Table 1. Baseline characteristics of the entire unmatched study cohort of this retrospective analysis of health insurance claims of patients with chronic limb threatening ischaemia (CLTI) treated endovascularly for arterial lesions below the knee. The patients were assigned to the paclitaxel (PCX) group if they were treated with drug eluting devices *vs.* control patients never exposed to drug eluting devices during the observational period**

| Characteristics of the unmatched study cohorts | PCX ($n$ = 3 284) | Control ($n$ = 11 454) | $p$ value* or RD (95% CI) |
|---|---|---|---|
| Age − y | 77.37 ± 9.77 | 77.66 ± 9.94 | .14 |
| No. of prescriptions during one year prior to admission | 14.50 ± 6.96 | 13.81 ± 6.73 | <.001 |
| No. of prior hospitalisations | 5.91 ± 4.50 | 5.31 ± 4.14 | <.001 |
| Median follow up time (IQR) − d | 539.50 (213.00, 1112.50) | 627.00 (214.25, 1346.00) | <.001 |
| Female sex | 1 529 (46.6) | 4 901 (42.8) | −3.77 (−5.7 − −1.84)† |
| van Walraven Score > 9 | 2 009 (61.2) | 7 032 (61.4) | 0.22 (−1.67−2.11) |
| Prior stroke or TIA | 411 (12.5) | 1 523 (13.3) | 0.78 (−0.51−2.07) |
| Smoking | 314 (9.6) | 957 (8.4) | −1.21 (−2.33 − −0.08)† |
| Dyslipidaemia | 1 902 (57.9) | 5 967 (52.1) | −5.82 (−7.74 − −3.9)† |
| Obesity | 658 (20.0) | 2 335 (20.4) | 0.35 (−1.21−1.9) |
| Prescription of lipid-lowering drugs during one year prior to admission | 1 632 (49.7) | 5 003 (43.7) | −6.02 (−7.95 − −4.08)† |
| Hypertension | 3 000 (91.4) | 10 273 (89.7) | −1.66 (−2.77 − −0.55)† |
| Coronary artery disease | 1 577 (48.0) | 5 215 (45.5) | −2.49 (−4.43 − −0.55)† |
| Prior myocardial infarction | 540 (16.4) | 1 743 (15.2) | −1.23 (−2.65−0.2) |
| Congestive heart failure | 1 503 (45.8) | 5 269 (46.0) | 0.23 (−1.7−2.17) |
| Valvular disease | 678 (20.6) | 2 293 (20.0) | −0.63 (−2.19−0.94) |
| Cardiac arrhythmias | 1 537 (46.8) | 5 265 (46.0) | −0.84 (−2.77−1.1) |
| *Antithrombotic drug prescriptions during one year prior to admission* | | | |
| Antithrombotics | 2 052 (62.5) | 6 543 (57.1) | −5.36 (−7.25 − −3.47)† |
| Antiplatelets | 1 464 (44.6) | 4 008 (35.0) | −9.59 (−11.5 − −7.68)† |
| Oral anticoagulation | 1 035 (31.5) | 3 327 (29.0) | −2.47 (−4.26 − −0.68)† |
| Antiplatelets and oral anticoagulation | 378 (11.5) | 812 (7.1) | −4.42 (−5.61 − −3.23)† |
| Chronic pulmonary disease | 545 (16.6) | 2 038 (17.8) | 1.2 (−0.26−2.65) |
| Diabetes, complicated | 1 718 (52.3) | 6 235 (54.4) | 2.12 (0.18−4.06) |
| Prescription of antidiabetics during one year prior to admission | 1 632 (49.7) | 5 853 (51.1) | 1.4 (−0.54−3.34) |
| Renal failure | 1 859 (56.6) | 6 204 (54.2) | −2.44 (−4.37 − −0.52)† |
| Liver disease | 208 (6.3) | 767 (6.7) | 0.36 (−0.59−1.31) |

Data are provided as $n$ (%) or mean ± standard deviation unless stated otherwise. CLTI = chronic limb threatening ischaemia; PCX = paclitaxel coated devices; RD = risk difference with 95% Wald confidence intervals (CI); IQR = interquartile range; TIA = transient ischaemic attack.
* $p$ values at $\alpha = .05$ were considered statistically significant.
† Significant values at $\alpha = .05$.

Treatment with DCB was associated with a lower risk of cardiovascular events or death (HR 0.86, 95% CI 0.79—0.93) also seen in the combined DCB and DES analysis (HR 0.86, 95% CI 0.80—0.92) but not for DES alone.

Amputation or death occurred significantly less often in PCX in the combined analysis (HR 0.87, 95% CI 0.81—0.94) but also separately for DCB (HR 0.89, 95% CI 0.82—0.96) and DES (HR 0.74, 95% CI 0.60—0.92) (Fig. 2).

The Kaplan—Meier curves and log rank test results for all cause mortality, major amputation or death, and cardiovascular events or death after five years are presented in Fig. 3. In these analyses using PS matched cohorts, treatment with paclitaxel coated devices was significantly associated with better outcomes when compared with treatment with uncoated devices.

### *Sensitivity analysis*

The results were robust throughout the sensitivity analyses (see Tables S5 and S6). Effect size was generally smaller and less often significant in the intention to treat design perhaps as a result of the smaller sample size ($n$ = 4 830) and less strict assignment of study groups according to PCX exposure. The same was true when stratifying the sample by hospital volume and PCX rate. Estimates for balloons and stents combined varied between HR 0.83 and HR 0.94 for all cause mortality, HR 0.85 and 0.96 for amputation or death, and between 0.86 and 0.97 for cardiovascular event or death.

## DISCUSSION

In this PS matched retrospective analysis of health insurance claims, an overall high long term mortality was observed after five years but no indication of increased risk of mortality, amputation or death and cardiovascular events or death after treatment with PCX when compared with uncoated devices.

In Cox proportional hazards models, a paclitaxel related reduction of all cause mortality, amputation, or death, and cardiovascular event or death could be observed in the unstratified analyses involving both DCB and DES. In stratified analyses, only DES was not associated with a reduction in cardiovascular event or death.

**Table 2. Baseline characteristics of the matched study cohort of this retrospective analysis of health insurance claims of patients with chronic limb threatening ischaemia (CLTI) treated endovascularly for arterial lesions below the knee. The patients were assigned to the paclitaxel (PCX) group if they were treated with drug eluting devices *vs.* control patients never exposed to drug eluting devices during the observational period**

| Characteristics of the matched study cohorts | PCX ($n$ = 3 284) | Control ($n$ = 3 284) | $p$ value* or RD (95% CI) |
|---|---|---|---|
| Age − y | 77.37 ± 9.77 | 77.30 ± 9.90 | .79 |
| No. prescriptions during one year prior to admission | 14.50 ± 6.96 | 14.34 ± 6.77 | .37 |
| No. of prior hospitalisations | 5.91 ± 4.50 | 5.84 ± 4.73 | .50 |
| Median follow up time (IQR) − d | 539.50 (213.00, 1112.50) | 471.50 (175.00, 995.00) | <.001 |
| Female sex | 1 529 (46.6) | 1 502 (45.7) | −0.82 (−3.23–1.59) |
| van Walraven Score > 9 | 2 009 (61.2) | 2 003 (61.0) | −0.18 (−2.54–2.18) |
| Prior stroke or TIA | 411 (12.5) | 430 (13.1) | 0.58 (−1.04–2.19) |
| Smoking | 314 (9.6) | 318 (9.7) | 0.12 (−1.3–1.55) |
| Dyslipidaemia | 1 902 (57.9) | 1 920 (58.5) | 0.55 (−1.84–2.93) |
| Obesity | 658 (20.0) | 666 (20.3) | 0.24 (−1.7–2.18) |
| Prescription of lipid lowering drugs during one year prior to admission | 1 632 (49.7) | 1 582 (48.2) | −1.52 (−3.94–0.9) |
| Hypertension | 3 000 (91.4) | 3 013 (91.7) | 0.4 (−0.95–1.74) |
| Coronary artery disease | 1 577 (48.0) | 1 567 (47.7) | −0.3 (−2.72–2.11) |
| Prior myocardial infarction, | 540 (16.4) | 516 (15.7) | −0.73 (−2.51–1.05) |
| Congestive heart failure | 1 503 (45.8) | 1 523 (46.4) | 0.61 (−1.8–3.02) |
| Valvular disease | 678 (20.6) | 656 (20.0) | −0.67 (−2.62–1.28) |
| Cardiac arrhythmias | 1 537 (46.8) | 1 477 (45.0) | −1.83 (−4.24–0.58) |
| *Antithrombotic drug prescriptions during one year prior to admission* | | | |
| Antithrombotics | 2 052 (62.5) | 2 020 (61.5) | −0.97 (−3.32–1.37) |
| Antiplatelets | 1 464 (44.6) | 1 468 (44.7) | 0.12 (−2.28–2.53) |
| Oral anticoagulation | 1 035 (31.5) | 1 000 (30.5) | −1.07 (−3.3–1.17) |
| Antiplatelets and oral anticoagulation | 378 (11.5) | 366 (11.1) | −0.37 (−1.9–1.17) |
| Chronic pulmonary disease | 545 (16.6) | 537 (16.4) | −0.24 (−2.04–1.55) |
| Diabetes, complicated | 1 718 (52.3) | 1 723 (52.5) | 0.15 (−2.26–2.57) |
| Prescription of antidiabetics during one year prior to admission | 1 632 (49.7) | 1 624 (49.5) | −0.24 (−2.66–2.17) |
| Renal failure | 1 859 (56.6) | 1 847 (56.2) | −0.37 (−2.76–2.03) |
| Liver disease | 208 (6.3) | 222 (6.8) | 0.43 (−0.77–1.62) |

Data are provided as $n$ (%) or mean ± standard deviation unless stated otherwise. CLTI = chronic limb threatening ischaemia; PCX = paclitaxel coated devices; RD = risk difference with 95% Wald confidence intervals (CI); TIA = transient ischaemic attack.
* $p$ values at $\alpha = .05$ were considered statistically significant. No data analysed for RD reached statistical significance.

This non-specific benefit of PCX was confirmed by Kaplan–Meier analyses. These results emphasise that PCX is safe both for DES and DCB.

After the implementation of PCX for PAOD treatment, various prospective trials led to their widespread use in the United States (US) and Europe.[30] This trend was confirmed in this cohort as the proportion of PCX use significantly increased during the study period (30% PCX use in 2018). In 2018, a meta-analysis of PCX in femoropopliteal lesion reported increased all cause mortality in summary level data, which unleashed a global debate on possible harms with consecutive regulatory actions in the US and Europe. One major point of criticism concerning this meta-analysis, besides an insufficient involvement of CLTI and BK treatment, was that several RCTs included in the meta-analysis were underpowered and had no adequate long term follow up. To overcome this limitation, various real world studies have been published and the results in this field remain diametrically opposed.[14,31–33]

For PCX in BK lesions and CLTI, there currently are only a few RCTs available with low participant numbers and almost completely missing long term data, leading to a larger gap of evidence when compared with the treatment of femoropopliteal lesions. The RCTs comparing paclitaxel coated balloons with standard PTA were BIOLUX P-II,[10] IN.PACT DEEP,[11] DEBATE-BTK,[12] Lutonix BTK,[34] as well as a trial by Haddad *et al.* including a total of 1097 patients.[35] Twelve month mortality was reported as 9.4% *vs.* 6.0% (DEB *vs.* PTA, $p = .58$) in BIOLUX P-II, 10.1% *vs.* 8.1% (DEB *vs.* PTA, $p = .55$) in IN.PACT DEEP, and 7.7% *vs.* 4.5% (DEB *vs.* PTA, $p = .40$) in DEBATE-BTK. Lutonix BTK reported a freedom from all cause mortality at 180 days of 96.8% *vs.* 96% (DEB *vs.* PTA, $p = .70$), whereas all cause mortality presented by Haddad *et al.* was 20.8% *vs.* 13.3% for DEB vs. PTA 2016. A meta-analysis of RCTs showed no significant difference regarding major adverse events (29.0% in DEB *vs.* 38.8% in PTA, $p = .48$) at 12 month follow up.[36] Similarly, a Cochrane analysis from 2016 including femoropopliteal and BK interventions did not find any significant difference for amputation or death in a subgroup analysis of BK and CLTI patients at 12 month follow up.[37]

In contrast, this PS matched cohort revealed a PCX related reduction of all cause mortality, lower risk of amputation or death, and lower risk of cardiovascular

**Table 3. Peri-operative (in hospital) outcomes and long term event rates (death, myocardial infarction, major amputation) of the matched study cohort of this retrospective analysis of health insurance claims of patients with chronic limb threatening ischaemia (CLTI) treated endovascularly for arterial lesions below the knee. The patients were assigned to the paclitaxel (PCX) group if they were treated with drug eluting devices *vs.* control patients never exposed to drug eluting devices during the observational period**

| Peri-operative and long term outcomes | PCX ($n$ = 3 284) | Control ($n$ = 3 284) | $p$ value* or RD (95% CI) |
|---|---|---|---|
| Median length of stay (IQR) − d | 9.00 (5.00, 17.00) | 10.00 (5.00, 19.00) | <.001 |
| Length of stay ≥ 8 d | 1 919 (58.4) | 2 137 (65.1) | 6.64 (4.29–8.98)† |
| Acute limb ischaemia | 258 (7.9) | 228 (6.9) | −0.91 (−2.18–0.35) |
| Bleeding | 282 (8.6) | 260 (7.9) | −0.67 (−2 − 0.66) |
| Acute myocardial infarction | 34 (1.0) | 40 (1.2) | 0.18 (−0.33–0.69) |
| Acute renal failure | 241 (7.3) | 241 (7.3) | 0 (−1.26–1.26) |
| Acute respiratory failure | 87 (2.6) | 101 (3.1) | 0.43 (−0.38–1.23) |
| Post-operative delirium | 64 (1.9) | 81 (2.5) | 0.52 (−0.19–1.23) |
| Pneumonia | 73 (2.2) | 81 (2.5) | 0.24 (−0.49–0.98) |
| Stroke or TIA | 13 (0.4) | 9 (0.3) | −0.12 (−0.4–0.16) |
| Sepsis or SIRS | 39 (1.2) | 49 (1.5) | 0.3 (−0.25–0.86) |
| In hospital death | 71 (2.2) | 90 (2.7) | 0.58 (−0.17–1.33) |
| Discharged to rehabilitation | 29 (0.9) | 40 (1.2) | 0.33 (−0.16–0.83) |
| Discharged to nursing home | 103 (3.1) | 114 (3.5) | 0.33 (−0.53–1.2) |
| Death within 30 d | 155 (4.7) | 181 (5.5) | 0.79 (−0.27–1.86) |
| Death within 5 y | 1 256 (38.2) | 1 355 (41.3) | 3.01 (0.65–5.38)† |
| Major amputation within 5 y | 251 (7.6) | 214 (6.5) | −1.13 (−2.37–0.11) |
| Myocardial infarction within 5 y | 325 (9.9) | 332 (10.1) | 0.21 (−1.24–1.66) |
| Stroke or TIA within 5 y | 303 (9.2) | 286 (8.7) | −0.52 (−1.9–0.86) |

Data are provided as $n$ (%) unless stated otherwise. CLTI = chronic limb threatening ischaemia; PCX = paclitaxel coated devices; RD = risk difference with 95% Wald confidence intervals (CI); TIA = transient ischaemic attack; SIRS = systemic inflammatory response syndrome.
* $p$ values at $\alpha = .05$ were considered statistically significant.
† Significant values at $\alpha = .05$.

events or death during long term follow up. Besides non-random assignment to treatment, a reason for these conflicting results when compared with RCT data and meta-analyses might be the larger sample size and consequently higher statistical power to determine longer term outcomes after PCX interventions comprised in the current analysis. The observed long term survival benefit in the PCX group *vs.* uncoated devices could be explained by the different quality of medical therapy or other unobserved variables. Against that backdrop, the positive impact of statins is well known as one of the main pillars in optimal medical treatment with a positive impact on long term outcomes.[38–40] Hence, valid societal guidelines clearly recommend the permanent prescription of statins after lower limb revascularisations.[5,41] In this study, higher rates of statin use and other important drugs groups were observed (see Table S4) among PCX cases both during the year before admission and during the month after. Adjustments were made only for these differences before admission and at 30 days after discharge in the landmark cohort to avoid correlation of medical therapy and outcome. Future studies may tackle the hypothesis of whether better long term management with respect to medical therapy may explain the advantage of PCX cases using a time dependent design.

Besides, PCX might have a positive impact on survival of unknown cause, that is first seen after more than 12 months and currently, there are no further long term data available comparing uncovered devices with PCX BK.

The overall mortality after five years reported in the current study, independent of the device, is remarkably high and most probably an expression of advanced age, severe multisite artery disease, and multiple comorbidities including coronary and cerebrovascular disease in CLTI patients. Estimated five year survival rates in the PADI trial,[42] which compared BK BMS *vs.* DES in 137 CLTI patients were comparable to the current study results (37.0% BMS *vs.* 37.7% in the DES group).

Besides severe comorbidities, amputation itself is a relevant risk factor for death in PAOD patients. Klaphake *et al.* found overall mortality after major amputation to be 44%, 66%, and 85% after one, three, and five years.[43] Interestingly, the current analysis found a significantly better amputation free survival after five years in the PCX group compared with uncoated devices. Correspondingly, the PADI trial also reported a higher amputation free survival in the DES group (31.8% *vs.* 20.4%, $p = .043$).[42] In stratified analysis, DES but not DCB was associated with a lower risk of cardiovascular events or death and amputation or death. Literature comparing paclitaxel coated balloons with paclitaxel coated stents in BK lesions is scarce. While the meta-analysis by Katsanos *et al.* did not detect a relationship between paclitaxel and amputation risk,[44] a more recent review reported a harm signal with respect to amputation free survival (13.7% *vs.* 9.4%, $p = .080$).[18] The authors presumed that major adverse events, that is limb and also systemic, might be caused by non-target paclitaxel embolisation. The results of the current study do not

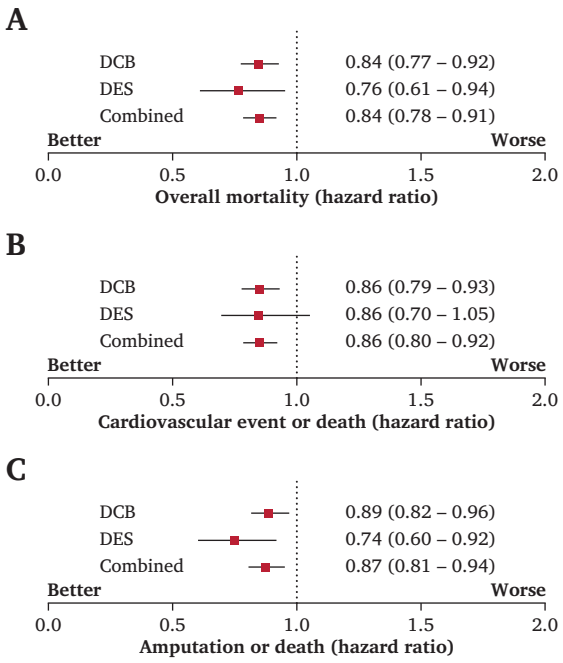


**Figure 2.** Forest plots of all cause mortality (A), cardiovascular events or death (B), and amputation or death (C) after five years by treatment approach by drug coated balloon (DCB) or drug eluting stent (DES) in patients with chronic limb threatening ischaemia in the below knee arteries using propensity score matched cohorts with hazards ratios and 95% confidence intervals (balloon *vs.* stent *vs.* both approaches merged together).

confirm this safety concern for more general or for more specific outcomes.

In summary, the current study could demonstrate that PCX in BK lesions is associated with a reduction in long term all cause mortality, amputation, or death, and cardiovascular event or death in CLTI patients. Further prospective trials with appropriate statistical power are needed to illuminate the various technical and morphological aspects of BK revascularisations and their impact on long term outcomes in a more detailed way.

This study has limitations. It is possible that the experience of the centre performing the procedures and the follow up of those patients play a major role in increasing the overall survival of the target population. It cannot be ruled out that a considerable proportion of the improved outcomes in paclitaxel exposed patients are explained by unobserved patient differentials or other aspects of healthcare. Furthermore, it was not possible to validly collect information regarding specific devices, doses of paclitaxel delivered, or paclitaxel applied during coronary or cancer treatment. There is a very small proportion of coatings other than paclitaxel, making a few of the codings used less specific. In addition, the primary purpose of the data collection should be considered when using it for secondary purposes, and all research data should undergo validation. Health insurance funds in Germany perform random cross checks with patient files on a regular basis.

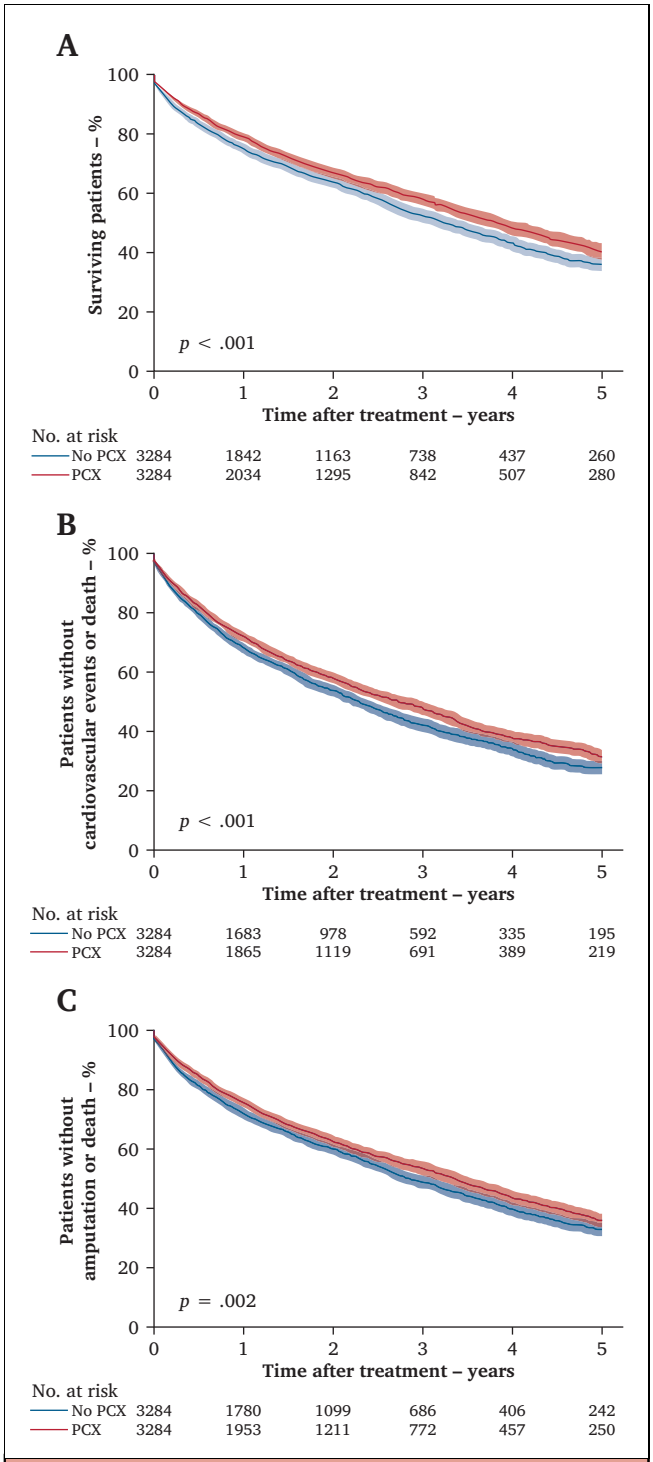


**Figure 3.** Cumulative Kaplan–Meier estimates of all cause mortality (A), cardiovascular events or death (B), and amputation or death (C) after five years by endovascular treatment approach with (red line) or without (blue line) paclitaxel (PCX) containing device in patients with chronic limb threatening ischaemia of the below knee arteries using propensity score matched cohorts including 95% Wald confidence interval and log rank test (*p* value).

Prior validation studies revealed high validity of major outcomes such as mortality in health insurance claims data.[19–22] In the current analysis, 53.8% of PCX cases were also revascularised at other sites than the infrapopliteal

arteries during their index stay. Yet, the results were robust to the exclusion of these patients during sensitivity analyses. Further, patients with CLTI have competing risks for mortality that may mask the mortality effects of devices. Known confounders were controlled for in an effort to minimise this possibility. However, there are probably additional confounders not available in health insurance claims data, for example, more detailed information about disease severity or quality of medical therapy. Residual unobserved confounding might be a reason for the conflicting results between RCTs and observational studies. It must be highlighted that retrospective observational studies are merely hypothesis generating. Only a properly powered RCT would be suitable to validly confirm or refute signals for causative effects. Lastly, although the fee for service reimbursement system in Germany probably motivates interventionalists to perform inpatient procedures rather than outpatient procedures, there might be another target population not included in this study. The same limitation is valid for patients insured by other insurance providers or patients changing their health insurance company during the study period, although this is known to be uncommon in the target population of interest. However, it is believed that paclitaxel distribution is comparable.

## CONCLUSIONS

In this PS matched cohort, a reduction was observed in long term all cause mortality, amputation, or death, and cardiovascular event or death five years after the use of PCX when compared with uncoated devices for the treatment of CLTI.

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST

ESD has received funding by Bayer and Terumo. The other authors declare no conflicts of interest.

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## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2020.06.033.

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# Sex Disparities in Long-Term Mortality after Paclitaxel Exposure in Patients with Peripheral Artery Disease: A Nationwide Claims-Based Cohort Study

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**Abstract:** Background: Randomized controlled trials have reported excess mortality in patients treated with paclitaxel-coated devices versus uncoated devices, while observational studies have reported the opposite. This study aims to determine the underlying factors and cohort differences that may explain these opposite results, with specific focus on sex differences in treatment and outcomes. Methods: Multicenter health insurance claims data from a large insurance fund, BARMER, were studied. A homogeneous sample of patients with an index of endovascular revascularization for symptomatic peripheral arterial occlusive disease between 2013 and 2017 was included. Adjusted logistic regression and Cox regression models were used to determine the factors predicting allocation to paclitaxel-coated devices and sex-specific 5-year all-cause mortality, respectively. Results: In total, 13,204 patients (54% females, mean age 74 ± 11 years) were followed for a median of 3.5 years. Females were older (77 vs. 71 years), and had less frequent coronary artery disease (23% vs. 33%), dyslipidemia (44% vs. 50%), and diabetes (29% vs. 41%), as well as being less likely to have a history of smoking (10% vs. 15%) compared with males. Mortality differences were mostly attributable to the female subgroup who were revascularized above the knee (hazard ratio, HR 0.78, 95% CI: 0.64–0.95), while no statistically significant differences were observed in males. Conclusions: This study found that females treated above the knee benefited from paclitaxel-coated devices, while no differences were found in males. Ongoing and future registries and trials should take sex disparities into account.

**Keywords:** peripheral arterial occlusive disease; chronic limb-threatening ischemia; drug-eluting stent; drug-coated balloon; paclitaxel



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## 1. Introduction

In 2018, a systematic review and meta-analysis of summary-level data from randomized controlled trials (RCT) revealed an association between treatment with paclitaxel-coated devices and increased overall mortality among patients with peripheral arterial

occlusive disease (PAOD) [1]. This association was later confirmed in a patient-level meta-analysis and a separate meta-analysis concerning amputation-free survival after below-the-knee treatment [2,3]. During this ongoing controversy, multiple studies that used either real-world data from large administrative and clinical registries [4–9] or interim analyses from a large RCT [10] were not able to replicate this unsettling safety signal. Strikingly, analyses using observational datasets found an opposite signal, with improved survival in patients exposed to paclitaxel when compared with those not exposed [5,6]. Ever since, the global scientific community, numerous task forces, and regulatory bodies have discussed the possible factors and cohort differences driving these contrasting results (Supplementary Table S1).

Meanwhile, there is clear evidence of striking differences between the sexes concerning various aspects of PAOD treatments (including prevention, best medical treatment, and revascularization procedures) and outcomes [11–15].

The current study aimed to determine the interaction of sex and corresponding differences in risk profiles on long-term mortality in patients treated with paclitaxel-coated devices, with particular attention given to the role of pharmacological therapy.

A large, unselected, all-comer administrative registry covering more than 13% of the insured cohort in Germany was used for the current study. To minimize the risk of bias caused by heterogeneity among the study groups, we tailored the cohort to a sample of homogenous patients with first endovascular interventions.

## 2. Materials and Methods

### 2.1. BARMER Cohort

The longitudinal data of Germany's second-largest insurance fund, BARMER, include the outpatient and inpatient medical care provided to approximately 9.4 million German citizens (13.2% of Germany's insured population), involving 9.5 million hospitalizations between 2013 and 2017. Furthermore, comprehensive information on pharmacological treatments is available in the same database. The BARMER cohort includes nationally generalizable data with comparable sex and age distributions to the entire German population and has been widely used for cardiovascular research [16]. The database contains longitudinal information for each person, including date of birth, start and end of insurance episodes, and date of death, through to 31 December 2019. A regular random sample validation of internal and external validity was performed by the Medical Service of the Health Funds (MDK) in Germany, and various validation studies have been published [17–20].

We used the International Classification of Diseases in its German Modification (ICD-10-GM) to identify diagnoses and the Operations and Procedures Codes (OPS) coding to identify procedures. The German OPS code is adapted to the International Classification of Procedures in Medicine (ICPM). For identifying medical prescriptions, the German version of the international Anatomical Therapeutic Chemical (ATC) classification was used. The study protocol was published a priori on 24 December 2020 (clinicaltrials.gov NCT04683458) (accessed on 1 June 2021) [21].

### 2.2. Study Population

We included patients with a primary diagnosis of intermittent claudication (IC) (I70.22 until 2014 and I70.21-22 since 2015), chronic limb-threatening ischemia (CLTI) (I70.22-24 until 2014 and I70.23-25 since 2015), or IC and CLTI as secondary diagnosis, in combination with a primary diagnosis of diabetic foot syndrome (E10.50-51, E10.7, E11.50-51, E11.7), other peripheral vascular diseases (I73), arterial embolism and thrombosis (I74), cellulitis of the fingers and toes including acute lymphangitis (L03.01-02, L03.11), or chronic ulcers of the skin and gangrene (L98.4, R02) using the ICD-10-GM (Supplementary Table S2).

The index admission for symptomatic PAOD, denoted as "index stay", was identified between 1 January 2005 and 31 December 2017, with follow-up through 31 December 2019.

Exclusion criteria were an index stay before 2013, an age below 40, hybrid surgery, revascularization at other levels outside of the femoropopliteal or crural arteries, previ-

ous endovascular intervention, surgical revascularization, coronary angioplasty, major amputation of the lower limbs, or any other exposure to paclitaxel or cancer diagnoses during the five years before the index procedure. We also excluded patients who were not continuously insured at BARMER during the 5 years before the index stay. These selection criteria were aimed at tailoring the study to a cohort as homogenous as possible with respect to prior diagnoses and interventions, but also to prior paclitaxel exposure due to coronary intervention or cancer treatment. There were a few cases with missing information on age, sex, and follow-up (~0.5%), and these were excluded.

Patients who received at least one index drug-coated balloon/stent at the index stay were assigned to the paclitaxel group. If the patient received a stent and a balloon at the same time, we defined it as a stent procedure. Additional information and coding criteria for drug-eluting stent or drug-coating balloon can be found in Supplementary Table S2.

### 2.3. Baseline Characteristics

Primary and secondary diagnoses reported during the index stay or during inpatient admissions up to five years prior to the index stay (the lookback period) were used to measure comorbidities, including coronary artery disease, dyslipidemia, frailty, a history of myocardial infarction, a history of stroke or transient ischemic attack (TIA), and the Elixhauser comorbidity groups (i.e., congestive heart failure, cardiac arrhythmias, hypertension, neurodegenerative disorders, chronic pulmonary disease, uncomplicated diabetes, complicated diabetes, hypothyroidism, obesity, weight loss, and depression) [22,23]. The linear van Walraven score (vWS), a weighted sum score, ranged from −19 to +89 based on the Elixhauser groups (wherein high scores represent a higher risk for in-hospital mortality) was also calculated [22,23]. We evaluated the validity of these comorbidities over time thoroughly in an earlier study [24]. Smoking was defined as ICD-10-GM code F17: either noted during an outpatient visit one year prior to the index stay or during an inpatient visit within five years of the index stay. Further, we measured the number of inpatient visits, PAOD-related outpatient visits, and optimal pharmacological treatment (consisting of lipid-lowering, antithrombotic, and antihypertensive drugs) [25], oral anticoagulation, and the number of different prescriptions during the year before the index stay. At the index stay, we ascertained age, hospital volume (lower or higher than median), the number of invasive revascularizations at index, the length of hospital stay, IC vs. CLTI at presentation, discharge year (2013–14 vs. 2015–17), patient residence (West or East Germany), whether a stent was placed (vs. a balloon angioplasty), and whether below-the-knee arteries were involved (vs. above-the-knee arteries).

### 2.4. Statistical Analysis

The baseline characteristics are presented as proportions for categorial variables, means (with standard deviation) for normally distributed variables, and medians (with interquartile ranges) for non-normally distributed variables. We computed standardized mean differences (SMD), where values greater than or equal to 0.1 denote meaningful differences between males and females. In observational studies, which usually involve large numbers of participants, the use of SMD instead of *p*-values is highly recommended to avoid false-positive findings.

Logistic regression was applied for modelling the relation between the baseline variables and the odds of receiving a paclitaxel-coated device versus receiving a non-coated device during the index procedure. This was expressed as an odds ratio with 95% confidence intervals. The top five predictors were identified using the variable importance metric suggested by Breiman [26].

The primary outcome was a 5-year, all-cause mortality with the end of the follow-up in December 2019. Follow-up times longer than five years were censored to ensure robust estimations. There was no exclusion of patients with a shorter follow-up. Cox proportional hazard regression models were utilized to estimate the impact of paclitaxel exposure mortality for the total cohort and the subgroups of paclitaxel-coated device type

(balloon vs. stent), affected level (above vs. below the knee), hospital volume (low vs. high), patient residence (West vs. East Germany), Fontaine stage (CLTI vs. IC), history of diabetes (no vs. yes), van Walraven score (<5 vs. ≥5), prior PAOD diagnosis (no vs. yes), and history of coronary artery disease (no vs. yes). Each model was estimated separately for the total cohort and each subgroup was adjusted for all baseline variables, resulting in point estimates of the hazard ratio (HR) of the impact of paclitaxel exposure on 5-year, all-cause mortality with 95% confidence intervals. An interaction of each binary subgroup variable and binary paclitaxel exposure was entered into each model to compute separate confidence intervals for both subgroups. If the confidence intervals of females and males were non-overlapping, we tested sex differences using the three-way interactions of sex, paclitaxel, and the variable of interest. The proportional hazards assumption was checked using graphical diagnostics based on Schoenfeld residuals, and the test suggested by Grambsch and Therneau [27]. This is an explanatory analysis not adjusting for multiple testing.

A landmark analysis (removing all deaths up to one year after the index stay) was applied for assessing the role of optimal pharmacological treatment (OPT) during the year after discharge from the index stay (Supplementary Table S3).

Data management was performed with the software SAS, version 9.04 (SAS Institute, NC, USA). We reported results using the reporting of studies conducted using the observational routinely-collected health data (RECORD) statement [28] and the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement [29].

The statistical analyses and visualizations were performed with software R version 3.6.2 (The R Foundation for Statistical Computing, Vienna, Austria). Illustrations were designed using Adobe Illustrator version 24.0.1 (Adobe Systems Software Ireland Ltd., Dublin, Republic of Ireland).

## 3. Results

A total of 13,204 patients (54% females, mean age 74.4 ± 10.7 years) met the inclusion criteria between 2013 and 2017. Female and male patients were followed for a median of 1274 (IQR 846-1798) and 1302 (IQR 874-1817) days, respectively (Figure 1 and Table 1).

### *3.1. Baseline Characteristics by Sex*

The baseline characteristics of the entire study cohort by sex with standardized mean differences (SMD) are presented in Table 1. While females were selected for first endovascular interventions at a higher age (77 vs. 71 years, SMD = 0.549), they exhibited a favorable cardiovascular risk profile in terms of coronary artery disease (23% vs. 33%, SMD = 0.241), dyslipidemia (44% vs. 50%, SMD = 0.110), diabetes (29% vs. 41%, SMD = 0.255), and smoking (10% vs. 15%, SMD = 0.149) when compared with their male counterparts. Females were more often diagnosed with depression (10% vs. 6%, SMD = 0.142) and hypothyroidism (22% vs. 8%, SMD = 0.391) relative to males.

During the year before the index admission, females had less often experienced an outpatient visit for PAOD (55% vs. 60%, SMD = 0.112) and were less often treated with optimal pharmacological treatment (19% vs. 27%, SMD = 0.190), but had an overall higher mean number of different pharmacological prescriptions (10 vs. 9, SMD = 0.144).

The five strongest predictors increasing the odds of being treated with paclitaxel-coated devices in females were a discharge year later than 2014, high center volume, intermittent claudication, and uncomplicated diabetes, while a higher van Walraven score decreased the odds accordingly. In males, a discharge year later than 2014, high center volume, intermittent claudication, and residency in East Germany were associated with higher odds of being treated with paclitaxel-coated devices, while older age decreased the odds accordingly (Supplementary Table S4).

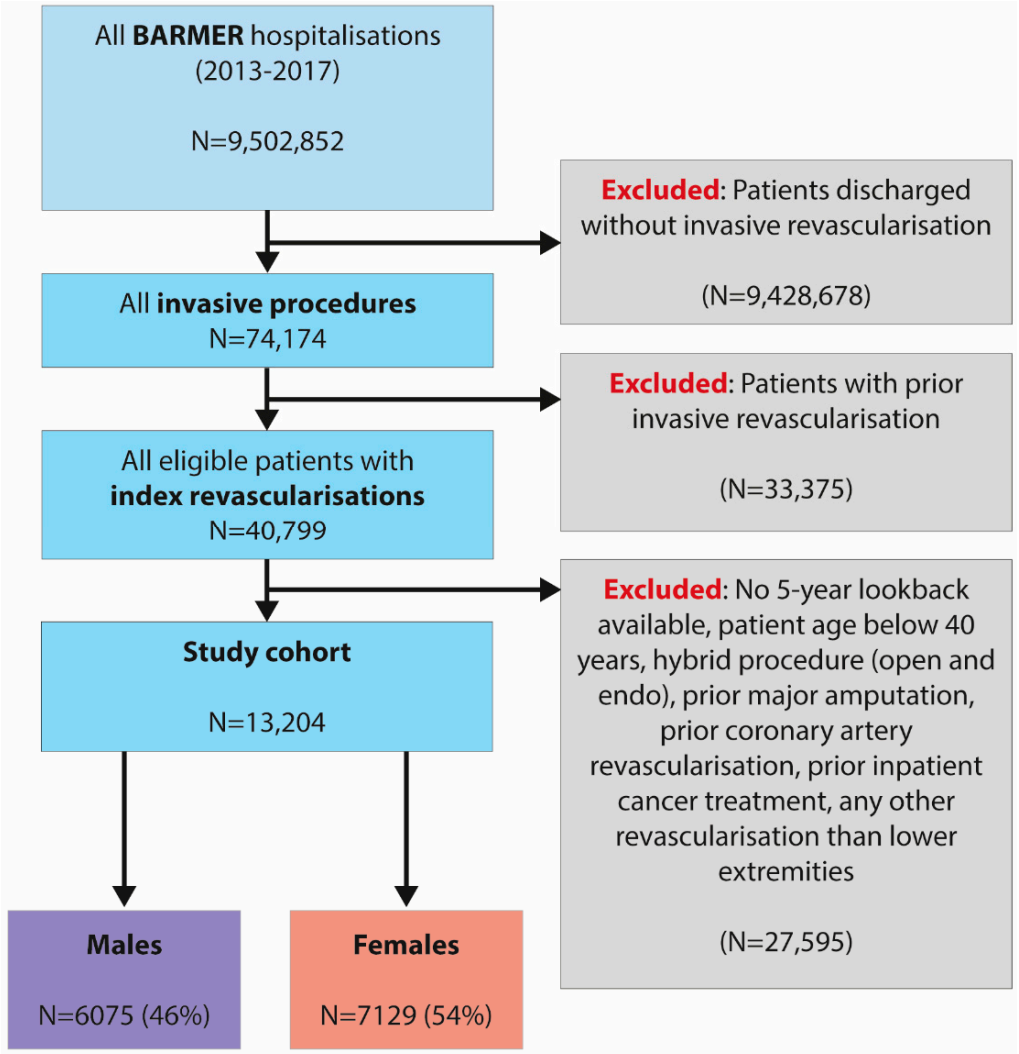


**Figure 1.** Flow chart of the current analysis of health insurance claims data from Germany.

**Table 1.** Baseline characteristics by female vs. male sex in this retrospective analysis of health insurance claims data from Germany.

| | *N* | % Females | *N* | % Males | SMD |
|---|---|---|---|---|---|
| No of patients | 7129 | 100 | 6075 | 100 | |
| Paclitaxel exposure at index | 1611 | 22.6 | 1324 | 21.8 | 0.017 |
| Stent at index | 3030 | 42.5 | 2643 | 43.5 | 0.020 |
| Crural arteries involved | 2509 | 35.2 | 2254 | 37.1 | 0.038 |
| Intermittent claudication | 3949 | 55.4 | 3639 | 59.9 | 0.091 |
| Discharge year >2014 | 4434 | 62.2 | 3791 | 62.4 | 0.005 |
| High hospital volume | 3736 | 52.4 | 3177 | 52.3 | 0.001 |
| Patient residence East Germany | 1355 | 19.0 | 1361 | 22.4 | 0.086 |
| Prior outpatient PAOD visit | 3907 | 54.8 | 3663 | 60.3 | 0.112 # |
| Van Walraven score >5 | 3593 | 50.4 | 2855 | 47.0 | 0.069 |
| Coronary artery disease | 1611 | 22.6 | 2023 | 33.3 | 0.241 # |

**Table 1.** *Cont.*

| | *N* | % Females | *N* | % Males | SMD |
|---|---|---|---|---|---|
| Dyslipidemia | 3151 | 44.2 | 3019 | 49.7 | 0.110 # |
| History of myocardial infarction | 364 | 5.1 | 377 | 6.2 | 0.046 |
| History of stroke or TIA | 549 | 7.7 | 504 | 8.3 | 0.021 |
| Congestive heart failure | 1576 | 22.1 | 1318 | 21.7 | 0.011 |
| Cardiac arrhythmias | 1739 | 24.4 | 1567 | 25.8 | 0.034 |
| Hypertension | 6003 | 84.2 | 4878 | 80.3 | 0.102 # |
| Neurodegenerative disorders | 428 | 6.0 | 413 | 6.8 | 0.033 |
| Chronic pulmonary disease | 984 | 13.8 | 778 | 12.8 | 0.030 |
| Diabetes, uncomplicated | 1668 | 23.4 | 1895 | 31.2 | 0.177 # |
| Diabetes, complicated | 1112 | 15.6 | 1458 | 24.0 | 0.214 # |
| Diabetes, total | 2082 | 29.2 | 2509 | 41.3 | 0.255 # |
| Hypothyroidism | 1547 | 21.7 | 486 | 8.0 | 0.391 # |
| Obesity | 763 | 10.7 | 796 | 13.1 | 0.074 |
| Weight loss | 349 | 4.9 | 164 | 2.7 | 0.115 # |
| Depression | 713 | 10.0 | 377 | 6.2 | 0.142 # |
| Smoking | 741 | 10.4 | 936 | 15.4 | 0.149 # |
| Optimal pharmacological therapy during the prior year | 1355 | 19.0 | 1640 | 27.0 | 0.190 # |
| Oral anticoagulation during the prior year | 1119 | 15.7 | 1027 | 16.9 | 0.030 |
| Age, mean (SD) | N/A | 77.01 (10.15) | N/A | 71.34 (10.51) | 0.549 # |
| Prior hospital visits, mean (SD) | N/A | 0.76 (1.21) | N/A | 0.76 (1.27) | <0.001 |
| No of different prescriptions during the prior year, mean (SD) | N/A | 10.03 (5.75) | N/A | 9.19 (5.85) | 0.144 # |
| Number of surgeries at index, mean (SD) | N/A | 1.76 (1.41) | N/A | 1.78 (1.69) | 0.007 |
| Hospital length of stay, mean (SD) | N/A | 5.85 (8.48) | N/A | 5.54 (9.01) | 0.036 |
| Follow-up time, median [Q1, Q3] | N/A | 1274 [846.0, 1798.0] | N/A | 1302 [874.0, 1816.5] | 0.047 |

Footnote: PAOD = peripheral arterial occlusive disease; SMD = standardized mean differences; TIA = transient ischemic attack; SD = standard deviation; N/A = not applicable. # denotes meaningful differences.

### *3.2. Impact of Paclitaxel Exposure on 5-Year Mortality among Subgroups*

The sex-stratified impact of paclitaxel exposure in the total cohort and different subgroups using variables available until index admission is presented in Figure 2. No statistically significant effect was apparent in males. In females, paclitaxel exposure was associated with a lower mortality in the following subgroups: revascularization of lesions above the knee (HR 0.78, 95% CI: 0.64–0.95), higher center volume (HR 0.83, 95% CI: 0.69–0.99), lower van Walraven score < 5 (HR 0.72, 95% CI: 0.53–0.97), no prior history of PAOD during the outpatient course (HR 0.81, 95% CI: 0.68–0.96), and no history of coronary artery disease (HR 0.85, 95% CI: 0.72–0.99). No statistically significant effect was apparent in males.

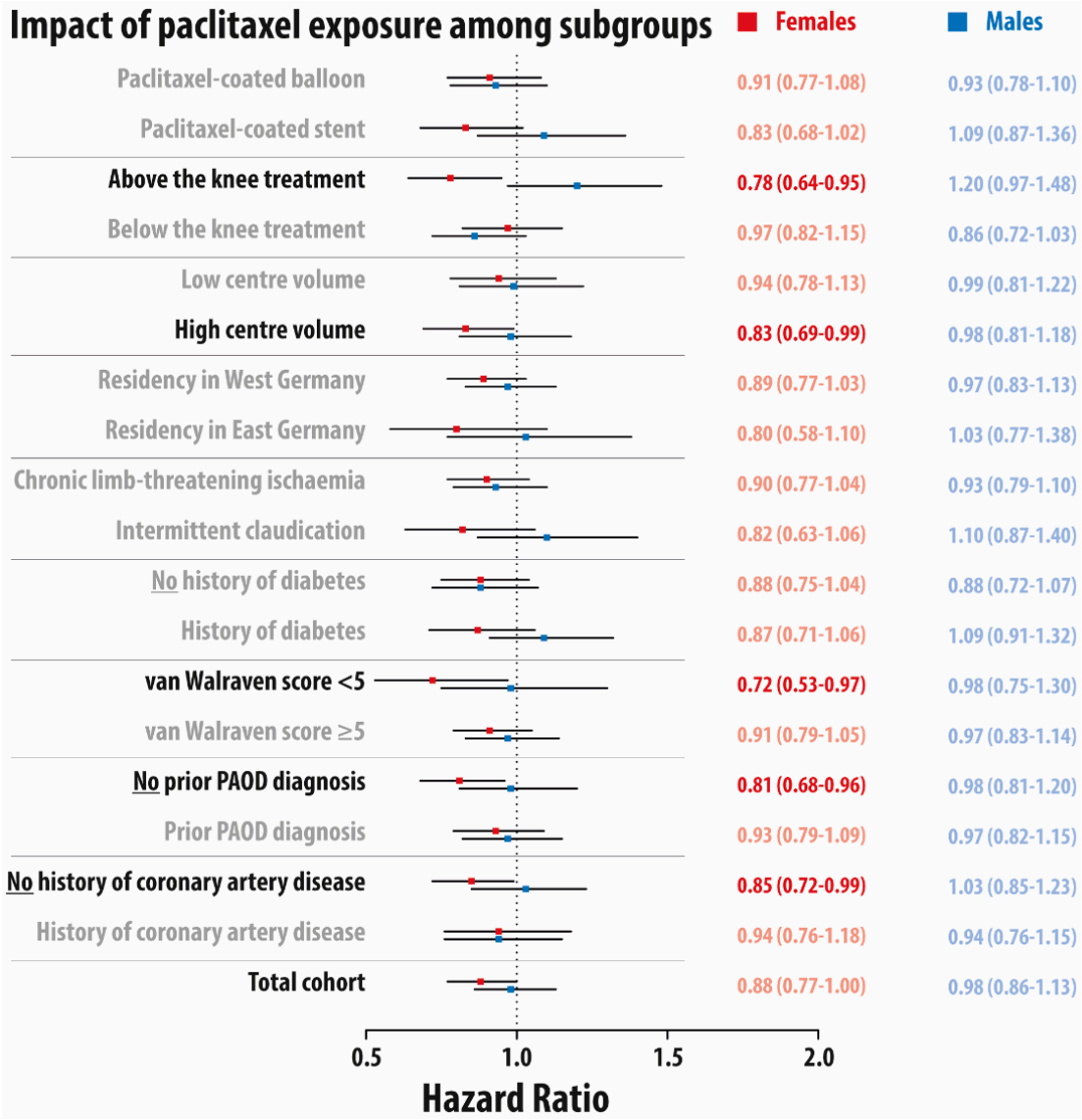


**Figure 2.** Forest plot for the adjusted impact of paclitaxel exposure on 5-year overall mortality among different subgroups stratified by sex (full cohort). Hazard ratio and 95% confidence interval in red for females and in blue for males. PAOD: peripheral arterial occlusive disease. All models were adjusted for all baseline characteristics using Cox models with regression adjustment.

### *3.3. Interaction of Treatment Level, Sex, and Paclitaxel Exposure on 5-Year Mortality*

The interaction between treatment level (above the knee vs. below the knee), dichotomized sex, and paclitaxel exposure on the 5-year mortality hazard ratio are presented in Figure 3. While no statistically significant differences were observed in the subgroup treated below the knee, a significantly lower 5-year mortality was observed in females (HR 0.79, 95% CI: 0.65–0.96) when compared with males (HR 1.20, 95% CI: 0.98–1.48) ($p$-value for interaction between males and females = 0.003) in the subgroup treated above the knee.

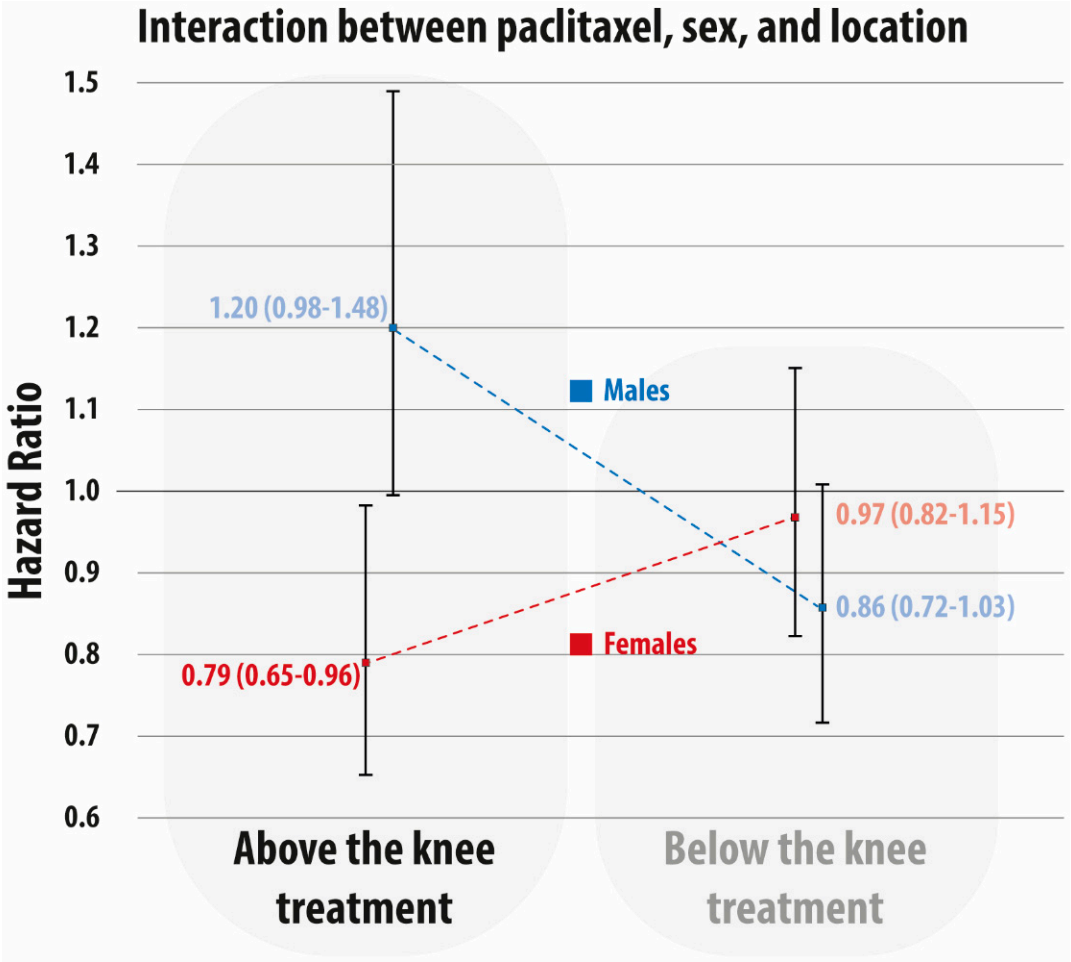


**Figure 3.** Interaction between paclitaxel exposure (yes vs. no), sex (female vs. male), and level (above-the-knee treatment vs. below-the-knee treatment). Hazard ratio and 95% confidence interval are in red for females and in blue for males.

## 4. Discussion

This analysis of unselected all-comer administrative data from Germany aimed to further determine the underlying factors that were driving the observed improvement in mortality associated with the use of paclitaxel-coated devices. Our design, focusing on first endovascular interventions in a cohort which was as homogenous as possible, revealed that the mortality differences were mostly attributable to the female subgroup treated above the knee, while no statistically significant differences were observed in males.

These novel findings emphasize the results from a recent patient-level meta-analysis of a drug-coated balloon [30]. Indeed, it appears difficult to imagine how the application of an endovascular device could directly improve or worsen the long-term outcomes years after the index treatment. Hence, paclitaxel exposure may instead serve as proxy for the underlying confounders related to the post-discharge surveillance. That said, the interesting fact that females with no prior history of PAOD were especially positively impacted by paclitaxel exposure further generates hypotheses related to post-discharge management. If females were systematically underdiagnosed and undertreated before their first hospital admission, they would likely benefit from an evidence-based surveillance strategy including all aspects of best medical treatment after discharge. Interestingly, these differences occurred even though we made all attempts to minimize the influence of interventions occurring before the index stay or differences in treatment at the index. For instance, prior coronary interventions and related adverse events, but also optimal pharmacological therapy, were more common among males than females before excluding patients with hybrid surgery, prior cancer diagnosis, and prior coronary or peripheral

interventions. Consequently, the observed survival benefit associated with paclitaxel exposure in females might be a sign of improved management in a subgroup of patients who exhibited insufficient prior care. This explanation would be in line with the well-known concept in health behavior research called the "teachable moment of the first in-hospital intervention".

The surveillance and patients' compliance in following pharmacological prescriptions beyond discharge was likely different between the sexes. A striking underrepresentation of females in RCT and varying outcomes between sexes were reported before the paclitaxel controversy was initiated in December 2018 [15,31–35]. Interestingly, neither RCT nor real-world studies during the ongoing paclitaxel controversy studied a possible interaction of sex and lesion level with outcomes after paclitaxel exposure. While females treated above the knee benefited from paclitaxel exposure, no statistically significant differences were seen if procedures were applied below the knee. This may indicate that these two groups are fundamentally different. Although the clinical symptoms had no impact, a comparable trend was observed in the subgroup of patients with intermittent claudication. In sum, it appears likely that females selected in an earlier disease stage will benefit most from secondary prevention. Although the proportion of females may not have an impact on central conclusions in appropriately powered RCT, the vulnerable aspects of trial design and power calculation in subgroups may still be affected by underrepresented subgroups. Even the most recent RCTs are likely affected by relevant bias. For instance, in a subgroup analysis of the VOYAGER PAD trial, the observed benefit of the investigational treatment on the primary efficacy endpoint was only driven by the male subgroup (HR 0.82, 95% CI: 0.71–0.94) while no differences were observed in females (HR 0.97, 95% CI: 0.76–1.23) [36]. Interestingly, the authors recently presented a subgroup analysis of that trial concluding that there was no mortality difference in patients exposed to paclitaxel-coated devices vs. those not exposed.

While 28 RCTs in the first meta-analysis enrolled 33% females [1] and 8 RCT in the second meta-analysis enrolled 29% females [2], the current study was undertaken within a dataset more representative of everyday clinical practice that included 54% females. The latter seems more representative for the disease under study since a recent comparison of more than 1 million hospitalizations in 11 countries revealed that females represent approximately 40% (between 23% in Portugal and 46% in Sweden) of the cohort treated with both open-surgical and endovascular revascularizations [11]. A recent systematic review of 69 PAOD trials in the USA showed that females were appropriately represented in less than 16% of these trials, while the percentage of females in the underlying PAOD population was 53.1% [34].

Regulatory bodies and societies issued still-existing safety warnings concerning the use of paclitaxel-coated devices for the treatment of PAOD [37]. Interventionists, patients, and the medical device industry face a huge challenge to interpret an evidence base which is hardly comprehensible or understandable [38]. The current study from the Medical Device Epidemiology Network (MDEpiNet) aims to support the ongoing discussion and regulatory decision-making.

A particular merit of our study is the rigorous design focussing on first endovascular intervention and excluding patients with either prior interventions or a potential paclitaxel exposure due to coronary intervention or cancer treatment. Mimicking an intention-to-treat approach known in pharmacoepidemiology, this enabled the study to avoid distortions due to prevalent user bias and immortal time bias, caused by including patients with reinterventions or at different stages of severity of atherosclerotic disease progression. The current discussion and the careful analysis of underlying real-world data can probably serve as an example to illustrate two central conclusions. First, there was no evidence for excess mortality in any of the subgroups studied. Moreover, females revascularized above the knee along with an optimal pharmacological post-discharge treatment likely benefitted from being exposed to paclitaxel-coated devices. Second, while the community is currently discussing marginal differences concerning primary efficacy endpoints in

recently completed trials on new medical devices and cardiovascular protective drugs, we tend to neglect that an evidence-based and cost-effective basic optimal pharmacological treatment could significantly improve outcomes by 30% [12,39,40]. Furthermore, the complementary interaction between all therapeutic modalities including best medical treatment, invasive revascularization, and supervised exercise therapy, deserves a more thorough consideration [41].

This study had limitations. First, there is an ongoing discussion concerning the comprehensive value of administrative registries for research. Indeed, health insurance claims are primarily collected for the reimbursement and administration of medical care. However, they are universally used to monitor healthcare services and quality improvement [16]. There is growing data of their good internal and external validity, especially regarding outcomes with major health impacts [42]. Nevertheless, a selection bias with possible impacts on the intervention-outcome relationship cannot be ruled out by design (e.g., through excluded patients) and by the fact that currently, no health insurance fund in Germany can claim to cover the entire insured population. Second, the granularity of the study data limits its use. No information was available on anatomical details or lesion severity. Furthermore, the specific devices were not collected. Collaborations such as the Medical Device Epidemiology Network (www.mdepinet.net, accessed on 1 June 2021) can help to develop pragmatic ways to collect device identifiers in routinely collected data. Lastly, even though the current study used robust statistical methods and numerous confirmative sensitivity analyses, the issue of residual confounding in observational research remains unsolved to date. Therefore, due to the non-random assignment, the current study can only generate hypotheses and reveal associations. Yet, appropriately powered and independent RCTs are still not available to further determine causal exposure–outcome relationships [43].

## 5. Conclusions

This study found that females treated above the knee benefit from paclitaxel-coated devices, while no differences were found in males. Ongoing and future registries and trials should take sex disparities into account.

**Supplementary Materials:** The following are available online at https://www.mdpi.com/article/10.3390/jcm10132978/s1: Table S1: Baseline characteristics of randomised controlled trials included in two systematic reviews in 2018 and 2020 vs. the current study; Table S2: International classification of diseases (ICD) 10th revision, operational and procedure coding (OPS), and anatomical-therapeutical-chemical (ATC) classification used for this study; Table S3: Top five strongest predictors increasing or decreasing the odds of being treated with paclitaxel coated devices; Table S4: Baseline characteristics by male vs. female sex of landmark sample.

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# A health insurance claims analysis on the effect of female sex on long-term outcomes after peripheral endovascular interventions for symptomatic peripheral arterial occlusive disease

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## ABSTRACT

**Objective:** Several reports have addressed sex disparities in peripheral arterial occlusive disease (PAOD) treatment with inconclusive or even conflicting results. However, most previous studies have neither been sufficiently stratified nor used matching or weighting methods to address severe confounding. In the present study, we aimed to determine the disparities between sexes after percutaneous endovascular revascularization (ER) for symptomatic PAOD.

**Methods:** Health insurance claims data from the second-largest insurance fund in Germany, BARMER, were used. A large cohort of patients who had undergone index percutaneous ER of symptomatic PAOD from January 1, 2010 to December 31, 2018 were included in the present study. The study cohort was stratified by the presence of intermittent claudication, ischemic rest pain, and wound healing disorders. Propensity score matching was used to adjust for confounding through differences in age, treated vessel region, comorbidities, and pharmacologic treatment. Sex-related differences regarding cardiovascular event-free survival, amputation-free survival, and overall survival within 5 years of surgery were determined using Kaplan-Meier time-to-event curves, log-rank test, and Cox regression analysis.

**Results:** In the present study, 50,051 patients (47.2% women) were identified and used to compose a matched cohort of 35,232 patients. Among all strata, female patients exhibited lower mortality (hazard ratio [HR], 0.69-0.90), fewer amputations or death (HR, 0.70-0.89), and fewer cardiovascular events or death (HR, 0.78-0.91). The association between female sex and improved long-term outcomes was most pronounced for the patients with intermittent claudication.

**Conclusions:** In the present propensity score-matched analysis of health insurance claims, we observed superior cardiovascular event-free survival, amputation-free survival, and overall survival during 5 years of follow-up after percutaneous ER in women with symptomatic PAOD. Future studies should address sex disparities in the open surgical treatment of PAOD to illuminate whether the conflicting data from previous reports might have resulted from insufficient stratification of the studies. (J Vasc Surg 2021;74:780-7.)

**Keywords:** Endovascular techniques; Health services research; Outcomes; Peripheral arterial disease; Sex

More than 200 million people worldwide experience peripheral arterial occlusive disease (PAOD), which is the third most common cause of death from cardiovascular disease.[1] PAOD in women remains underrecognized and undertreated, although some studies have suggest that the prevalence might be greater in women than in men, especially at older ages.[2-5] An expression of undertreatment is the sex disparity in evidence-based statin therapy for all cardiovascular diseases, including PAOD.[6,7] Various studies have demonstrated that women do present at an older age, will more often be treated on an emergency basis[8] and for advanced

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disease stages, including ischemic rest pain.[9-12] The most recently reported VASCUNET study on PAOD revascularization practices in 11 countries containing ~1.2 million hospitalizations revealed marked sex differences and provided evidence for a more rigorous selection of women for invasive treatment in some countries.[13]

Endovascular revascularization (ER) has evolved to be the treatment of first choice for symptomatic PAOD according to current guidelines.[14,15] Sex-specific differences are known in the outcomes after ER and open treatment of PAOD; however, the relationship between sex and outcomes has remained unclear. Some studies have reported greater mortality for women undergoing endovascular treatment of PAOD,[8,11,16] and others found no differences[17-19] Furthermore, the data on the association between sex and amputation-free survival (AFS) and perioperative morbidity are incongruent. Although representing one half of the population, women are known to be underrepresented in PAOD studies.[20]

In the present study, we aimed to determine the sex disparities in long-term outcomes after ER of symptomatic PAOD using largescale, population-based, health insurance claims data.

## METHODS

The present study was a retrospective observational study of health insurance claims data.

**BARMER cohort.** Longitudinal data from Germany's second-largest insurance fund, BARMER, include the outpatient and inpatient medical care provided to ~9 million German citizens (10.8% of Germany's population) involving >24 million hospitalizations from 2008 to 2020. In Germany, invasive revascularization for patients with PAOD are largely performed on an inpatient basis (including all cases reimbursed to a hospital). Hence, nearly all procedures were included in the present analysis. The BARMER cohort included nationally generalizable data with a sex and age distribution comparable to that in Western European Countries and has been widely used for cardiovascular research.[21-24] A regular random sample validation of internal and external validity is performed by the Medical Service of the Health Funds in Germany, and various peer-reviewed validation studies have been previously reported.[21-24]

We used the International Classification of Diseases, 10th revision, in its German modification (ICD-10-GM) to identify the diagnosis and the Operations and Procedures Codes to identify the procedures. The German Operations and Procedures Codes are adapted to the International Classification of Procedures in Medicine. To identify medical prescriptions, the German version of the international Anatomical Therapeutic Chemical Classification was used.[25]

**Study population.** The present study was a retrospective analysis of longitudinal inpatient and outpatient data.

### ARTICLE HIGHLIGHTS

- **Type of Research:** A multicenter, retrospective, nonrandomized propensity score-matched cohort study
- **Key Findings:** Among 50,051 patients with index percutaneous endovascular revascularization of symptomatic peripheral arterial occlusive disease from 2010 to 2018, female patients exhibited better overall survival, amputation-free survival, and cardiovascular event-free survival at 5 years after treatment.
- **Take Home Message:** The results of our study emphasize the relevance of sex-specific recommendations in future guidelines.

Patients aged ≥40 years with an index hospital stay and percutaneous ER for symptomatic PAOD from January 1, 2010 to December 30, 2018 were eligible for inclusion in the present study. The index stay denotes the first admission in the hospital within 5 years (lookback period).

Patients with symptomatic PAOD were identified using the primary or secondary diagnosis (ICD-10-GM) during the inpatient stay. As the primary diagnosis, the present study used intermittent claudication (code I70.21 until 2014 and code I70.21-22 since 2015), rest pain (code I70.22 until 2014 and code I70.23 since 2015), and ischemic ulcer or gangrene (code I70.23-24 until 2014 and code I70.24-25 since 2015) with or without diabetic foot syndrome (codes E10.50-51, E10.7, E11.50-51, E11.7), other peripheral vascular diseases (code I73), arterial embolism and thrombosis (code I74), cellulitis of finger and toe, including acute lymphangitis (codes L03.01-02, L03.11), or chronic ulcer of skin and gangrene (codes L98.4, R02) using the ICD-10-GM. If PAOD was coded as a secondary diagnosis only, the requirement for inclusion also included a primary diagnosis of diabetes with peripheral vascular complications to include patients with diabetic foot syndrome who had not been coded with chronic limb threatening ischemia. The sample was stratified by intermittent claudication (Fontaine stage II) vs ischemic rest pain (Fontaine stage III) vs wound healing disorders (Fontaine stage IV; Supplementary Table I, online only).

All percutaneous endovascular procedures, including balloon and stent angioplasty of the aortoiliac and infrainguinal arteries above and below the knee, were included. Patients with any open surgical procedures (including hybrid procedures), previous vascular interventions, or major amputations above the ankle level were excluded from the present study.

**Study variables.** The primary study endpoints were cardiovascular event-free survival (CVEFS), including freedom from stroke, myocardial infarction, and all-cause death, AFS (freedom from incident major amputation and all-cause death), and overall survival.

**Table I.** Baseline characteristics of propensity score-matched cohort

| Characteristic | Fontaine stage II | | | Fontaine stage III | | | Fontaine stage IV | | |
|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | SMD | Men | Women | SMD | Men | Women | SMD |
| Patients, No. | 11,298 | 11,298 | NA | 1676 | 1676 | NA | 4642 | 4642 | NA |
| Age, years | 69.30 ± 9.36 | 69.58 ± 9.87 | 0.048 | 72.10 ± 10.84 | 72.58 ± 11.41 | 0.075 | 77.45 ± 9.35 | 77.97 ± 10.25 | 0.058 |
| Follow-up, days | 1241.00 (601.00-1826.00) | 1290.00 (639.00-1826.00) | 0.029 | 1071.00 (456.75-1826.00) | 1160.50 (495.00-1826.00) | 0.043 | 641.00 (208.25-1312.75) | 690.00 (233.25-1401.75) | 0.053 |
| Van Walraven score | 2367 ± 21.0 | 2357 ± 20.9 | 0.002 | 603 ± 36.0 | 617 ± 36.8 | 0.017 | 2695 (58.1) | 2714 (58.5) | 0.008 |
| Congestive heart failure | 1595 (14.1) | 1595 (14.1) | <0.001 | 427 (25.5) | 423 (25.2) | 0.005 | 1993 (42.9) | 1988 (42.8) | 0.002 |
| Cardiac arrhythmias | 1803 (16.0) | 1796 (15.9) | 0.002 | 476 (28.4) | 473 (28.2) | 0.004 | 1984 (42.7) | 1990 (42.9) | 0.003 |
| Valvular disease | 748 (6.6) | 777 (6.9) | 0.010 | 216 (12.9) | 210 (12.5) | 0.011 | 867 (18.7) | 897 (19.3) | 0.016 |
| Pulmonary circulation disorders | 266 (2.4) | 284 (2.5) | 0.010 | 82 (4.9) | 90 (5.4) | 0.022 | 392 (8.4) | 415 (8.9) | 0.018 |
| Hypertension | 8859 (78.4) | 8904 (78.8) | 0.010 | 1363 (81.3) | 1372 (81.9) | 0.014 | 4063 (87.5) | 4065 (87.6) | 0.001 |
| Paralysis | 367 (3.2) | 384 (3.4) | 0.008 | 113 (6.7) | 118 (7.0) | 0.012 | 522 (11.2) | 530 (11.4) | 0.005 |
| Neurodegenerative disorders | 428 (3.8) | 422 (3.7) | 0.003 | 118 (7.0) | 123 (7.3) | 0.012 | 493 (10.6) | 516 (11.1) | 0.016 |
| Chronic pulmonary disease | 1483 (13.1) | 1505 (13.3) | 0.006 | 293 (17.5) | 289 (17.2) | 0.006 | 850 (18.3) | 835 (18.0) | 0.008 |
| Diabetes, uncomplicated | 2438 (21.6) | 2421 (21.4) | 0.004 | 479 (28.6) | 461 (27.5) | 0.024 | 1962 (42.3) | 1949 (42.0) | 0.006 |
| Diabetes, complicated | 1569 (13.9) | 1523 (13.5) | 0.012 | 343 (20.5) | 340 (20.3) | 0.004 | 2209 (47.6) | 2179 (46.9) | 0.013 |
| Renal failure | 2225 (19.7) | 2217 (19.6) | 0.002 | 534 (31.9) | 536 (32.0) | 0.003 | 2325 (50.1) | 2308 (49.7) | 0.007 |
| Liver disease | 368 (3.3) | 357 (3.2) | 0.006 | 57 (3.4) | 58 (3.5) | 0.003 | 292 (6.3) | 294 (6.3) | 0.002 |
| Peptic ulcer disease | 62 (0.5) | 65 (0.6) | 0.004 | 14 (0.8) | 12 (0.7) | 0.014 | 54 (1.2) | 55 (1.2) | 0.002 |
| Lymphoma | 35 (0.3) | 37 (0.3) | 0.003 | 6 (0.4) | 5 (0.3) | 0.010 | 42 (0.9) | 39 (0.8) | 0.007 |
| Metastatic cancer | 140 (1.2) | 143 (1.3) | 0.002 | 36 (2.1) | 32 (1.9) | 0.017 | 100 (2.2) | 104 (2.2) | 0.006 |
| Solid tumor without metastasis | 736 (6.5) | 701 (6.2) | 0.013 | 138 (8.2) | 141 (8.4) | 0.006 | 388 (8.4) | 378 (8.1) | 0.008 |
| Rheumatoid arthritis/collagen vascular disease | 274 (2.4) | 288 (2.5) | 0.008 | 59 (3.5) | 71 (4.2) | 0.037 | 249 (5.4) | 253 (5.5) | 0.004 |
| Coagulopathy | 454 (4.0) | 463 (4.1) | 0.004 | 145 (8.7) | 142 (8.5) | 0.006 | 665 (14.3) | 665 (14.3) | <0.001 |
| Obesity | 1240 (11.0) | 1220 (10.8) | 0.006 | 233 (13.9) | 234 (14.0) | 0.002 | 865 (18.6) | 855 (18.4) | 0.006 |
| Weight loss | 197 (1.7) | 196 (1.7) | 0.001 | 65 (3.9) | 70 (4.2) | 0.015 | 325 (7.0) | 319 (6.9) | 0.005 |
| Fluid and electrolyte disorders | 1770 (15.7) | 1832 (16.2) | 0.015 | 466 (27.8) | 469 (28.0) | 0.004 | 2251 (48.5) | 2278 (49.1) | 0.012 |
| Blood loss anemia | 91 (0.8) | 83 (0.7) | 0.008 | 28 (1.7) | 23 (1.4) | 0.024 | 119 (2.6) | 125 (2.7) | 0.008 |
| Deficiency anemia | 232 (2.1) | 248 (2.2) | 0.010 | 67 (4.0) | 61 (3.6) | 0.019 | 419 (9.0) | 425 (9.2) | 0.004 |
| Drug abuse | 95 (0.8) | 95 (0.8) | <0.001 | 19 (1.1) | 16 (1.0) | 0.018 | 76 (1.6) | 75 (1.6) | 0.002 |
| Psychosis | 48 (0.4) | 45 (0.4) | 0.004 | 6 (0.4) | 7 (0.4) | 0.010 | 44 (0.9) | 44 (0.9) | <0.001 |
| Depression | 666 (5.9) | 717 (6.3) | 0.019 | 128 (7.6) | 138 (8.2) | 0.022 | 505 (10.9) | 543 (11.7) | 0.026 |
| Previous stroke or transient ischemic attack | 653 (5.8) | 678 (6.0) | 0.009 | 159 (9.5) | 162 (9.7) | 0.006 | 618 (13.3) | 624 (13.4) | 0.004 |
| Smoking | 2346 (20.8) | 2299 (20.3) | 0.010 | 290 (17.3) | 282 (16.8) | 0.013 | 461 (9.9) | 440 (9.5) | 0.015 |
| Previous myocardial infarction | 1038 (9.2) | 1028 (9.1) | 0.003 | 221 (13.2) | 204 (12.2) | 0.030 | 658 (14.2) | 654 (14.1) | 0.002 |
| Dyslipidemia | 5889 (52.1) | 5904 (52.3) | 0.003 | 859 (51.3) | 853 (50.9) | 0.007 | 2254 (48.6) | 2214 (47.7) | 0.017 |
| History of coronary artery disease | 3259 (28.8) | 3187 (28.2) | 0.014 | 643 (38.4) | 610 (36.4) | 0.041 | 1913 (41.2) | 1881 (40.5) | 0.014 |
| Aortoiliac lesion treated | 4395 (38.9) | 4316 (38.2) | 0.014 | 429 (25.6) | 398 (23.7) | 0.044 | 461 (9.9) | 481 (10.4) | 0.016 |

**Table I.** Continued.

| Characteristic | Fontaine stage II | | | Fontaine stage III | | | Fontaine stage IV | | |
|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | SMD | Men | Women | SMD | Men | Women | SMD |
| Femoropopliteal lesion treated | 5344 (47.3) | 5410 (47.9) | 0.014 | 649 (38.7) | 659 (39.3) | 0.044 | 1311 (28.2) | 1319 (28.4) | |
| Crural lesion treated | 1559 (13.8) | 1572 (13.9) | 0.014 | 598 (35.7) | 619 (36.9) | 0.044 | 2870 (61.8) | 2842 (61.2) | |
| Previous (1-year) antihypertensive medication | 9108 (80.6) | 9152 (81.0) | 0.010 | 1397 (83.4) | 1403 (83.7) | 0.010 | 4181 (90.1) | 4190 (90.3) | 0.007 |
| Previous (1-year) lipid-lowering medication | 5949 (52.7) | 5940 (52.6) | 0.002 | 794 (47.4) | 803 (47.9) | 0.011 | 1919 (41.3) | 1868 (40.2) | 0.022 |
| Previous (1-year) antithrombotic medication | 4801 (42.5) | 4738 (41.9) | 0.011 | 845 (50.4) | 831 (49.6) | 0.017 | 2632 (56.7) | 2655 (57.2) | 0.010 |
| Previous medications, No. | 7.00 (4.00-11.00) | 8.00 (5.00-11.00) | 0.017 | 9.00 (5.00-13.00) | 9.00 (6.00-13.00) | 0.022 | 12.00 (8.00-17.00) | 12.00 (8.00-17.00) | 0.007 |
| Previous hospital admissions, No. | 2.00 (1.00-4.00) | 2.00 (1.00-4.00) | 0.003 | 3.00 (1.00-5.00) | 3.00 (1.00-5.00) | 0.001 | 4.00 (2.00-6.00) | 4.00 (2.00-6.00) | 0.005 |
| Previous outpatient visits, No. | 2.00 (1.00-8.00) | 1.00 (0.00-8.00) | 0.027 | 1.00 (0.00-10.00) | 1.00 (0.00-10.00) | 0.021 | 2.00 (0.00-12.00) | 1.00 (0.00-12.00) | 0.017 |

*NA*, not applicable; *SMD*, Standardized mean difference.
Data presented as mean ± standard deviation, median (interquartile range), or number (%), unless noted otherwise.

The comorbidity groups categorized using the ICD-10-GM codes were separated into 30 Elixhauser comorbidity groups during the 5 years before the first PAOD diagnosis (lookback) and were used to define the baseline characteristics.[26,27] In 1998, Elixhauser et al[27] introduced a systematic classification to identify relevant comorbidities among the primary and secondary diagnoses at discharge.[26] Major comorbidities, such as congestive heart failure, cardiac arrhythmia, chronic pulmonary disease, diabetes, and chronic renal failure, were categorized into 30 commonly accepted groups. The lookback period was 1 year for medication. The linear van Walraven score is a weighted sum score that ranges from −19 to +89 using the Elixhauser groups and has been validated.[28] A higher score indicates an increased risk of in-hospital mortality.

**Declaration of Helsinki.** The present study complied with the Declaration of Helsinki. Owing to the nature of the data, no ethics committee approval and no patient informed consent was necessary.

**Statistical analysis.** Continuous variables are presented as the mean ± standard deviation for normally distributed data and the median and interquartile range for non-normally distributed data. Discrete variables are presented as percentages. Standardized mean differences were used for a comparison of prevalence between the groups, with values >0.1 indicating a meaningful difference.

To adjust for baseline differences between the sexes, we performed propensity score matching as described in detail previously.[29] The scores were calculated and matched using nearest neighbor matching and strictly chosen within the range of 0.1 standard deviations of the distance measure. The performance and quality of the matching were assessed using standardized mean differences (Supplementary Table II, online only).

We analyzed the long-term outcomes CVEFS, AFS, and overall survival. Cox proportional hazards models stratified by indication group were used. Patients were censored after 5 years to compute robust rates. The short-term outcomes of in-hospital mortality were estimated using odds ratios and 95% confidence intervals. All analyses were conducted separately for each Fontaine stage.

For a sensitivity analysis, we conducted a landmark analysis to exclude patients with events during the hospital stay or within 30 days after discharge, and Cox proportional hazards regressions on the matched cohort (Supplementary Table III, online only). The baseline characteristics of the unmatched cohort are listed in Supplementary Table IV (online only). The baseline characteristics of the excluded patients (unmatched patients) are listed in Supplementary Table V (online only).

The statistical analysis was performed using SAS, version 9.4 (SAS Institute, Cary, NC) and R, version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

A total of 50,051 patients (47.2% women) were eligible for inclusion, and 35,232 patients (70.4%) were matched. The baseline characteristics of the matched cohort

**Table II.** Results of logistic regression using propensity score-matched cohort for in-hospital mortality

| Fontaine stage | OR | 95% CI |
|---|---|---|
| II (intermittent claudication) | 1.83 | 0.91-3.71 |
| III (ischemic rest pain) | 0.77 | 0.41-1.46 |
| IV (wound healing disorders) | 0.85 | 0.67-1.09 |

*CI*, Confidence interval; *OR*, odds ratio.

**Table III.** Results of Cox proportional hazards regression using propensity score-matched cohort for primary study endpoints of overall survival, amputation-free survival, and cardiovascular event-free survival

| Fontaine stage | HR | 95% CI |
|---|---|---|
| II | | |
| Overall mortality | 0.69 | 0.64-0.74 |
| Amputation or death | 0.70 | 0.65-0.76 |
| Cardiovascular event or death | 0.78 | 0.74-0.82 |
| III | | |
| Overall mortality | 0.77 | 0.67-0.88 |
| Amputation or death | 0.79 | 0.70-0.91 |
| Cardiovascular event or death | 0.81 | 0.73-0.91 |
| IV | | |
| Overall mortality | 0.90 | 0.85-0.96 |
| Amputation or death | 0.89 | 0.84-0.94 |
| Cardiovascular event or death | 0.91 | 0.87-0.97 |

*CI*, Confidence interval; *HR*, hazard ratio.

stratified by indication for treatment are presented in Table I.

**Short-term outcomes (matched cohort).** No statistically significant differences between the female and male patients were observed in in-hospital mortality (Table II).

**Long-term outcomes (matched cohort).** The results of the propensity score-matched and adjusted Cox proportional hazards regression analysis are presented in Table III. For all indication groups, stratified by Fontaine stage, the women had better mortality (hazard ratio [HR], 0.69-0.90), lower rates of amputation or death (HR, 0.70-0.89), and lower rates of cardiovascular events or death (HR, 0.78-0.91). The association between female sex and better long-term outcomes was most pronounced for patients with intermittent claudication.

The results of the Kaplan-Meier survival analysis using matched cohorts are presented in the Fig. Significantly better CVEFS, AFS, and overall survival were observed for the women among all strata.

**Long-term outcomes (landmark analysis and sensitivity analyses).** In the landmark analysis, which excluded patients experiencing events within 30 days after hospital discharge, all results were confirmed completely (change in HR, ±0.01). The results from additional sensitivity analyses, including unmatched Cox proportional hazards regression methods adjusted for sex, age, van Walraven score, region of treated vessels, discharge year, and Fontaine stages, were confirmative.

## DISCUSSION

In the present matched health insurance claims analysis addressing sex disparities after percutaneous ER for symptomatic PAOD, female patients showed better overall survival, AFS, and CVEFS during a follow-up of 5 years after index treatment across all Fontaine stages. A large population-based sample was stratified into the most relevant indication groups, and propensity score matching was applied to address the most relevant confounders.

Several previous studies have addressed the differences between women and men undergoing treatment for PAOD. It had been reported that the female patients were older and had had more severe, or even atypical, symptoms when being selected for treatment.[9,12] Using the multicenter Vascular Quality Initiative registry,[30] Ramkumar et al[12] included 58,247 patients (41% women) and 66,045 ERs were performed from 2010 to 2016 in the United States. In their unmatched retrospective observational study, worse reintervention-free survival and occlusion-free survival were observed for the women during a median follow-up of 376 days.[12] In line with other reports, the investigators concluded that sex-sensitive guideline recommendations were needed.[12] The multicenter K-VIS ELLA (Korean Vascular Intervention Society Endovascular Therapy in Lower Limb Artery Disease) registry included 3073 patients undergoing ER. Only 17.9% of the cohort were female patients. A significantly worse outcome for women after 2 years was reported using a composite endpoint of death, myocardial infarction, and major amputation (14.8% vs 9.8%).[16] Using data from the Nationwide Inpatient Sample in the United States, Lo et al[11] analyzed ~1.8 million patients (44% women) who had undergone open surgical revascularization and ER from 1998 to 2009. Worse survival was observed for women compared with men; however, the follow-up duration was limited to the hospital stay.[11] Other studies have reported either inconclusive or, even, disparate results. Hess et al[31] used the multicenter Premier Healthcare Database in the United States with 381,415 patients (41.7% women) treated from 2009 to 2014. Just as in the present study, they found lower major adverse limb event rates after 1 year in the female patients.[31] Krishnamurthy et al[32] analyzed 4459 patients (46% women) treated from 2008 to 2011 and reported improved amputation and death rates for female patients at 6 months of follow-up. When reviewing the existing real-world evidence on sex disparities in PAOD treatment, only a few studies with 118,545 patients had

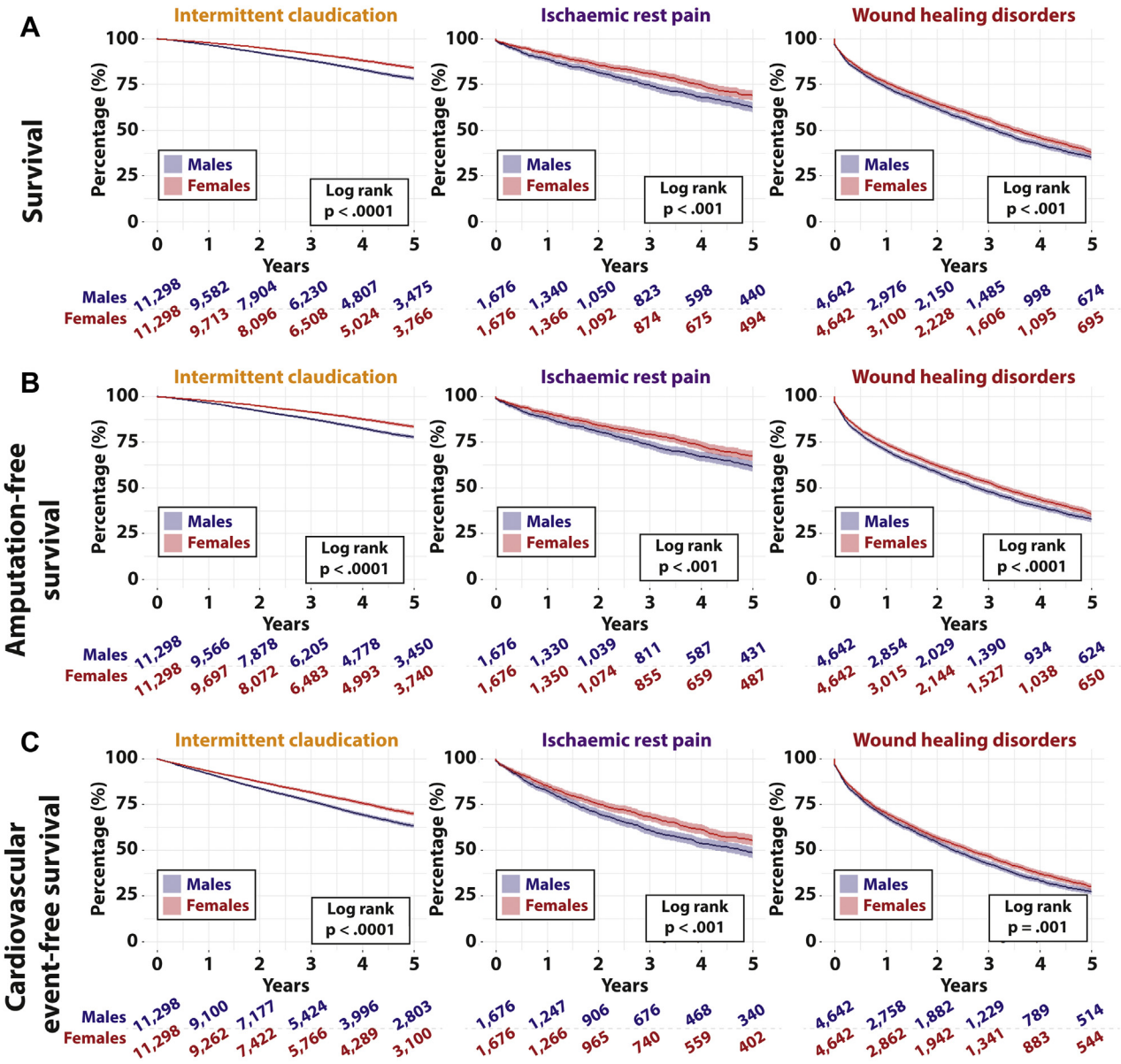


**Fig.** Kaplan-Meier survival curves stratified by sex and corresponding *P* values (log-rank test) for overall survival **(A)**, amputation-free survival (AFS; **B)**, and cardiovascular event-free survival (CVEFS; **C)** stratified by three indication groups (from left to right). A propensity score-matched cohort of patients undergoing percutaneous endovascular revascularization (ER) for symptomatic peripheral arterial occlusive disease (PAOD) from 2010 to 2018 was analyzed in the present retrospective observational study of health insurance claims in Germany.

used propensity score matching or alternative methods to sufficiently address the problem of severe confounding.[17,18,33-35] Among those studies, only three had sought to determine long-term outcomes beyond discharge, with inconclusive results.[33-35] Numerous confounders have been reported to have possible effects on the sex–outcome relationship. In 2018, women aged 65 had an average life expectancy of 21.2 years, with their male counterparts dying ~3 years earlier.[36] Also, it is common knowledge that male sex is a risk factor for diabetes.[37] Various other cardiovascular risk factors are also known to be more prevalent in male patients.

To sufficiently address confounding and selection bias, the present study included only percutaneous ER and stratified the patients by presentation: intermittent claudication (Fontaine stage II) vs ischemic rest pain (Fontaine stage III) vs wound healing disorders (Fontaine stage IV). In all strata, we matched for age, Elixhauser comorbidities, treated vessel region, and evidence-based medication (including lipid-lowering drugs, antithrombotic agents, and antihypertensive agents).

The association between sexes and improved outcomes in the long term was also confirmed by comprehensive sensitivity analyses emphasizing the robustness of the

present study design. In another study, we aim to determine the survival after open surgical and hybrid revascularizations to complement the present results.[29]

In addition to several strengths, the present study also had limitations. First, discussion concerning the value of administrative data is currently ongoing.[38] We believe the internal and external validity of insurance claims is better than that in unvalidated registries. An independent random sample and risk-based validation of data are performed on a regular basis by a service provider in Germany. Peer-reviewed validation studies of this data source have been performed, proving good validity, especially for major outcomes (eg, mortality, myocardial infarction, stroke, amputation). Second, the long-term outcomes are influenced by several factors, and as yet, no method to neutralize residual confounding has been accepted for an observational study design. We applied a robust design with restricted inclusion and exclusion criteria, stratification, and matching to address this challenge in a sophisticated manner. Furthermore, sensitivity analyses were confirmative. By excluding patients aged <40 years who had been selected for invasive revascularization, it appears possible that pre-, peri-, and postmenopausal women had been included in the study population. The chosen cutoff value and limited availability of information concerning sex hormones have made it challenging to adequately address this aspect, although significant debate has also ensued regarding its effects on the development and progression of vascular disease. The present study aimed to determine the commonly accepted major adverse events, including death, amputation, myocardial infarction, and stroke. In contrast, other studies addressed different outcomes, including reintervention. Although the composite endpoints used in the present study have been frequently used by randomized and nonrandomized studies, the incidence of these components and how they influence the event rates can vary considerably. Although major amputations were more frequent for the patients with ischemic wound healing disorders, major amputations were less for patients with intermittent claudication.

The cardiovascular community has been highlighting the importance of sex-sensitive research and treatment for years. The question arises of how the results from the present study can be translated into improvements in vascular care. It can be hypothesized that female sex is associated with improved outcomes after endovascular techniques in the long term. The question arises how peripheral endovascular interventions can influence the incidence of cardiovascular events in the longer term, with a complex multifactorial explanation likely. Future studies should address differences in best medical treatment and surveillance to understand the underlying reasons for the apparent sex differences. If evidence shows worse outcomes for open surgery, future guidelines should include corresponding recommendations for sex-specific treatment. The results from present study could only provide one of two important answers leading to such recommendations.

## CONCLUSIONS

In the present propensity score-matched analysis of health insurance claims, we observed superior cardiovascular event-free survival, AFS, and overall survival during 5 years of follow-up after percutaneous ER for intermittent claudication, ischemic rest pain, and wound healing disorders in female patients. Future studies should address the sex disparities in the open surgical treatment of symptomatic peripheral arterial occlusive disease.

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## AUTHOR CONTRIBUTIONS

Conception and design: FH, JK, FP, CB
Analysis and interpretation: FH, JK, FP, UM, HL, LA, CB
Data collection: FH, JK, FP, AK, UM, HL, LA, NR, PG, ED, UR, CB
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Critical revision of the article: FH, JK, FP, AK, UM, HL, LA, NR, PG, ED, UR, CB
Final approval of the article: FH, JK, FP, AK, UM, HL, LA, NR, PG, ED, UR, CB
Statistical analysis: JK, FP, LA
Obtained funding: CB
Overall responsibility: CB
FH and JK contributed equally to this article and share co-first authorship.

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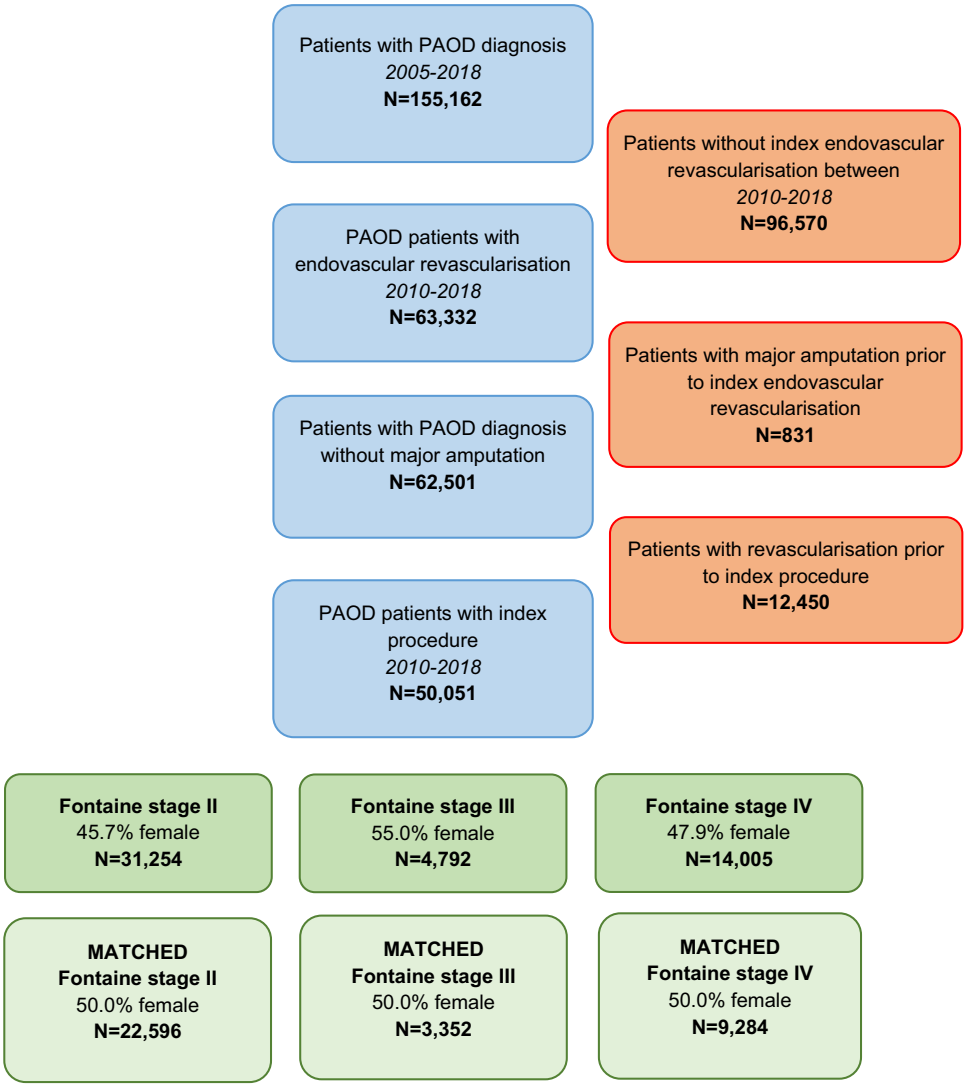


**Supplementary Fig (online only).** Flow chart of inclusion criteria for patient selection. *PAOD,* Peripheral arterial occlusive disease.

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**Supplementary Table I (online only).** International Classification of Diseases, 10th revision, operational and procedure coding, and Anatomical Therapeutic Chemical coding criteria used

| Variable | ICD-10 code, ATC code, OPS code |
|---|---|
| Fontaine stages | |
| | Before 2015: I70.21, pelvic-leg arteries with exercise induced pain, walking distance <200 m, Fontaine II; I70.22, Pelvic-leg arteries with rest pain, Fontaine III; I70.23-24, pelvic-leg arteries with ulcerations and/or gangrene, Fontaine IV |
| | 2015 onward: I70.21-22, pelvic-leg arteries with exercise induced pain, Fontaine II; I70.23, pelvic-leg arteries with rest pain, Fontaine III; I70.24-25, pelvic-leg arteries with ulcerations and/or gangrene, Fontaine IV |
| | Other: E10.50-51, type 1 diabetes mellitus with peripheral vascular complications; E10.7, type 1 diabetes mellitus with diabetic foot syndrome; E11.50-51, type 2 diabetes mellitus with peripheral vascular complications; E11.7, type 2 diabetes mellitus with diabetic foot syndrome; I73.0, other peripheral vascular diseases, Raynaud syndrome; I73.1, Other peripheral vascular diseases, thrombangiitis obliterans; I73.8, other peripheral vascular diseases; I73.9, other peripheral vascular diseases; I74.0, arterial embolism and thrombosis, aorta abdominalis; I74.1, arterial embolism and thrombosis, aorta; I74.2, arterial embolism and thrombosis, upper extremities; I74.3, arterial embolism and thrombosis, lower extremities; I74.4, arterial embolism and thrombosis, arteries of the extremities; I74.5, arterial embolism and thrombosis, aorta iliac; I74.8, arterial embolism and thrombosis, other arteries; I74.9, arterial embolism and thrombosis, other arteries; L03.01-2, L03.11, cellulitis of finger and toe, including acute lymphangitis; L98.4, chronic ulcer of skin, not elsewhere classified; R02, gangrene, not elsewhere classified |
| Stroke or transient ischemic attack | I61, I63, I64, G45 |
| Dyslipidemia | E78 |
| Coronary artery disease | I20-25 |
| Smoking | F17 |
| Myocardial infarction | I20.0, I21-I24 |
| Cancer | |
| | Metastatic cancer: C77-C80 |
| | Solid tumor without metastasis: C00-C26, C30-C34, C37-C41, C43, C45-C58, C60-C76, C97 |
| Polypharmacy | Number of different prescriptions during 1 year before index admission |
| Lipid-lowering drugs | C10 |
| Antithrombotic agents | B01 |
| Antihypertensive agents | C02, Antihypertensive drugs; C03, diuretic drugs; C07, β-blocking agents; C08, calcium channel blockers; C09, agents acting on renin-angiotensin system |
| Amputation | 5-864, Major amputation, above the ankle; 5-865, Minor amputation, below the ankle |
| Endovascular revascularization | |
| Aortoiliac | 8-836.04, 8-836.14, 8-836.24, 8-836.74, 8-836.p4, 8-836.r4, 8-836.34, 8-836.84, 8-83c.b4, 8-840.04, 8-840.14, 8-840.24, 8-840.34, 8-840.44, 8-840.54, 8-841.04, 8-841.14, 8-841.24, 8-841.34, 8-841.44, 8-841.54, 8-843.04, 8-843.14, 8-843.24, 8-843.34, 8-843.44, 8-843.54, 8-845.04, 8-845.14, 8-846.04, 8-846.14, 8-849.04, 8-849.14, 8-84a.04, 8-84a.14, 8-836.0q, 8-836.09, 8-836.1h, 8-836.19, 8-836.2h, 8-836.29, 8-836.7h, 8-836.79, 8-836.ph, 8-836.p9, 8-836.rh, 8-836.r9, 8-836.3h, 8-836.39, 8-836.8h, 8-836.89, 8-83c.b9, 8-840.0q-.5q, 8-840.09, 8-840.19, 8-840.29, 8-840.39, 8-840.49, 8-840.59, 8-841.0q-.5q, 8-841.09, 8-841.19, 8-841.29, 8-841.39, 8-841.49, 8-841.59, 8-842.0q-.5q, 8-842.09, 8-842.19, 8-842.29, 8-842.39, 8-842.49, 8-842.59, 8-843.0q-.5q, 8-843.09, 8-843.19, 8-843.29, 8-843.39, 8-843.49, 8-843.59, 8-845.0q, 8-845.1q, 8-845.09, 8-845.19, 8-846.0q, 8-846.1q, 8-846.09, 8-846.19, 8-848.0q-.5q, 8-848.09, 8-848.19, 8-848.29, 8-848.39, 8-848.49, 8-848.59, 8-849.0q, 8-849.1q, 8-849.09, 8-849.19, 8-84a.0q, 8-84a.1q, 8-84a.09, 8-84a.19, 8-84d.0q-.5q |
| Femoropopliteal | 8-836.0s, 8-836.0b, 8-836.1k, 8-836.1b, 8-836.2k, 8-836.2b, 8-836.7k, 8-836.7b, 8-836.pk, 8-836.pb, 8-836.rk, 8-836.rb, 8-836.3k, 8-836.3b, 8-836.wk, 8-836.wb, 8-836.8k, 8-836.8b, 8-83c.bb, 8-840.0s-.5s, 8-840.0b-.5b, 8-841.0s-.5s, 8-841.0b-.5b, 8-842.0s-.5s, 8-842.0b-.5b, 8-843.0s-.5s, 8-843.0b-.5b, 8-845.0s, 8-845.1s, 8-845.0b, 8-845.1b, 8-846.0s, 8-846.1s, 8-846.0b, 8-846.1b, 8-848.0s-.5s, 8-848.0b-.5b, 8-849.0s, 8-849.1s, 8-849.0b, 8-849.6b, 8-84a.0s, 8-84a.1s, 8-84a.0b, 8-84a.1b, 8-84d.0s-.5s |
| Crural | 8-836.0c, 8-836.1c, 8-836.2c, 8-836.3c, 8-836.7c, 8-836.8c, 8-836.pc, 8-836.rc, 8-836.wc, 8-83c.bc, 8-840.0c-.5c, 8-841.0c-.5c, 8-842.0c-.5c, 8-843.0c-.5c, 8-844.0c-.5c, 8-845.0c, 8-845.1c, 8-846.0c, 8-846.1c, 8-848.0c-.5c, 8-849.0c, 8-849.1c, 8-84a.0c, 8-84a.1c, 8-84d.0c-.5c |
| Open surgical revascularization | 5-380, 5-381, 5-382, 5-383, 5-384, 5-38c, 5-38d, 5-38e, 5-38f, 5-393, 5-394, 5-395, 5-396, 5-98a |

*ATC,* Anatomical Therapeutic Chemical; *ICD-10,* International Classification of Diseases, 10th revision; *OPC,* operational and procedure coding.

**Supplementary Table II (online only).** Performance of propensity score matching

| Variable | Fontaine stage II | | Fontaine stage III | | Fontaine stage IV | |
|---|---|---|---|---|---|---|
| | SMD unmatched | SMD matched | SMD unmatched | SMD matched | SMD unmatched | SMD matched |
| Age | 0.386 | 0.029 | 0.430 | 0.043 | 0.545 | 0.053 |
| Congestive heart failure | 0.074 | <0.001 | 0.015 | 0.005 | 0.024 | 0.002 |
| Cardiac arrhythmias | 0.065 | 0.002 | 0.014 | 0.004 | 0.105 | 0.003 |
| Valvular disease | 0.003 | 0.010 | 0.039 | 0.011 | 0.028 | 0.016 |
| Pulmonary circulation disorders | 0.041 | 0.010 | 0.069 | 0.022 | 0.046 | 0.018 |
| Hypertension | 0.044 | 0.010 | 0.149 | 0.014 | 0.073 | 0.001 |
| Paralysis | 0.042 | 0.008 | 0.030 | 0.012 | 0.066 | 0.005 |
| Neurodegenerative disorders | 0.025 | 0.003 | 0.011 | 0.012 | 0.022 | 0.016 |
| Chronic pulmonary disease | 0.036 | 0.006 | 0.020 | 0.006 | 0.035 | 0.008 |
| Diabetes, uncomplicated | 0.166 | 0.004 | 0.086 | 0.024 | 0.211 | 0.006 |
| Diabetes, complicated | 0.148 | 0.012 | 0.128 | 0.004 | 0.374 | 0.013 |
| Renal failure | 0.018 | 0.002 | 0.044 | 0.003 | 0.007 | 0.007 |
| Liver disease | 0.038 | 0.006 | 0.088 | 0.003 | 0.052 | 0.002 |
| Peptic ulcer disease, no bleeding | 0.019 | 0.004 | 0.001 | 0.014 | 0.009 | 0.002 |
| Lymphoma | 0.006 | 0.003 | 0.047 | 0.010 | 0.003 | 0.007 |
| Metastatic cancer | 0.011 | 0.002 | 0.016 | 0.017 | 0.016 | 0.006 |
| Solid tumor without metastasis | 0.069 | 0.013 | 0.111 | 0.006 | 0.103 | 0.008 |
| Rheumatoid arthritis/collagen vascular disease | 0.102 | 0.008 | 0.152 | 0.037 | 0.184 | 0.004 |
| Coagulopathy | 0.061 | 0.004 | 0.046 | 0.006 | 0.091 | <0.001 |
| Obesity | 0.085 | 0.006 | 0.025 | 0.002 | 0.081 | 0.006 |
| Weight loss | 0.044 | 0.001 | 0.078 | 0.015 | 0.096 | 0.005 |
| Fluid and electrolyte disorders | 0.092 | 0.015 | 0.106 | 0.004 | 0.160 | 0.012 |
| Blood loss anemia | 0.003 | 0.008 | 0.014 | 0.024 | 0.040 | 0.008 |
| Deficiency anemia | 0.032 | 0.010 | 0.052 | 0.019 | 0.077 | 0.004 |
| Drug abuse | 0.011 | <0.001 | 0.040 | 0.018 | 0.007 | 0.002 |
| Psychosis | 0.012 | 0.004 | 0.007 | 0.010 | 0.042 | <0.001 |
| Depression | 0.137 | 0.019 | 0.178 | 0.022 | 0.161 | 0.026 |
| Previous stroke or transient ischemic attack | 0.047 | 0.009 | 0.030 | 0.006 | 0.036 | 0.004 |
| Smoking | 0.103 | 0.010 | 0.176 | 0.013 | 0.115 | 0.015 |
| Previous myocardial infarction | 0.131 | 0.003 | 0.103 | 0.030 | 0.114 | 0.002 |
| Dyslipidemia | 0.079 | 0.003 | 0.111 | 0.007 | 0.162 | 0.017 |
| History of coronary artery disease | 0.265 | 0.014 | 0.253 | 0.041 | 0.292 | 0.014 |
| Lesion level | 0.133 | 0.014 | 0.160 | 0.044 | 0.241 | 0.016 |
| Antihypertensive medication before index surgery | 0.090 | 0.010 | 0.195 | 0.010 | 0.088 | 0.007 |
| Lipid lowering medication before index surgery | 0.132 | 0.002 | 0.194 | 0.011 | 0.276 | 0.022 |
| Antithrombotic medication before index surgery | 0.110 | 0.011 | 0.103 | 0.017 | 0.163 | 0.010 |
| No. of previous medications | 0.156 | 0.017 | 0.149 | 0.022 | <0.001 | 0.007 |
| No. of previous hospital admissions | 0.042 | 0.003 | 0.050 | 0.001 | 0.024 | 0.005 |
| No. of previous PAOD-related outpatient visits | 0.163 | 0.027 | 0.174 | 0.021 | 0.245 | 0.017 |
| Discharge year | 0.038 | 0.001 | 0.058 | 0.010 | 0.030 | 0.002 |

*PAOD,* Peripheral arterial occlusive disease; *SMD,* standardized mean difference.

**Supplementary Table III (online only).** Results of landmark analysis excluding patients with events during hospital stay or 30 days after discharge using Cox proportional hazards models

| Fontaine stage | HR | 95% CI |
|---|---|---|
| II | | |
| Overall mortality | 0.68 | 0.63-0.74 |
| Amputation or death | 0.69 | 0.64-0.75 |
| Cardiovascular event or death | 0.77 | 0.73-0.82 |
| III | | |
| Overall mortality | 0.77 | 0.67-0.88 |
| Amputation or death | 0.80 | 0.70-0.92 |
| Cardiovascular event or death | 0.81 | 0.73-0.91 |
| IV | | |
| Overall mortality | 0.89 | 0.84-0.95 |
| Amputation or death | 0.88 | 0.83-0.93 |
| Cardiovascular event or death | 0.91 | 0.86-0.96 |

*CI,* Confidence interval; *HR,* hazard ratio.

**Supplementary Table IV (online only).** Baseline characteristics of unmatched cohort (n = 50,051)

| | Fontaine stage II | | | Fontaine stage III | | | Fontaine stage IV | | |
|---|---|---|---|---|---|---|---|---|---|
| Variable | Men | Women | SMD | Men | Women | SMD | Men | Women | SMD |
| Patients, No. | 16,967 | 14,287 | NA | 2155 | 2637 | NA | 7292 | 6713 | NA |
| Follow-up, days | 1276.00 (634.00-1826.00) | 1273.00 (627.00-1826.00) | 0.003 | 1109.00 (487.00-1826.00) | 1064.00 (446.00-1826.00) | 0.025 | 682.00 (235.00-1385.00) | 655.00 (212.00-1360.00) | 0.032 |
| Age, years | 67.42 ± 9.76 | 71.24 (9.99) | 0.386 | 70.51 ± 11.21 | 75.31 ± 11.16 | 0.430 | 74.77 ± 10.16 | 80.26 ± 9.98 | 0.545 |
| Van Walraven score >9 | 3878 ± 22.9 | 3008 ± 21.1 | 0.044 | 808 ± 37.5 | 964 ± 36.6 | 0.019 | 4270 ± 58.6 | 3906 ± 58.2 | 0.008 |
| Congestive heart failure | 2817 (16.6) | 1992 (13.9) | 0.074 | 567 (26.3) | 677 (25.7) | 0.015 | 3191 (43.8) | 2857 (42.6) | 0.024 |
| Cardiac arrhythmias | 3072 (18.1) | 2238 (15.7) | 0.065 | 614 (28.5) | 735 (27.9) | 0.014 | 3282 (45.0) | 2675 (39.8) | 0.105 |
| Valvular disease | 1214 (7.2) | 1013 (7.1) | 0.003 | 266 (12.3) | 360 (13.7) | 0.039 | 1328 (18.2) | 1295 (19.3) | 0.028 |
| Pulmonary circulation disorders | 365 (2.2) | 399 (2.8) | 0.041 | 101 (4.7) | 165 (6.3) | 0.069 | 559 (7.7) | 600 (8.9) | 0.046 |
| Hypertension | 13,270 (78.2) | 11,427 (80.0) | 0.044 | 1715 (79.6) | 2248 (85.2) | 0.149 | 6284 (86.2) | 5947 (88.6) | 0.073 |
| Paralysis | 657 (3.9) | 444 (3.1) | 0.042 | 155 (7.2) | 170 (6.4) | 0.030 | 886 (12.2) | 676 (10.1) | 0.066 |
| Neurodegenerative disorders | 698 (4.1) | 518 (3.6) | 0.025 | 165 (7.7) | 194 (7.4) | 0.011 | 788 (10.8) | 680 (10.1) | 0.022 |
| Chronic pulmonary disease | 2155 (12.7) | 1990 (13.9) | 0.036 | 382 (17.7) | 447 (17.0) | 0.020 | 1326 (18.2) | 1131 (16.8) | 0.035 |
| Diabetes, uncomplicated | 4474 (26.4) | 2773 (19.4) | 0.166 | 641 (29.7) | 683 (25.9) | 0.086 | 3431 (47.1) | 2465 (36.7) | 0.211 |
| Diabetes, complicated | 2908 (17.1) | 1704 (11.9) | 0.148 | 490 (22.7) | 464 (17.6) | 0.128 | 4158 (57.0) | 2596 (38.7) | 0.374 |
| Renal failure | 3459 (20.4) | 2811 (19.7) | 0.018 | 706 (32.8) | 810 (30.7) | 0.044 | 3641 (49.9) | 3327 (49.6) | 0.007 |
| Liver disease | 628 (3.7) | 431 (3.0) | 0.038 | 104 (4.8) | 82 (3.1) | 0.088 | 503 (6.9) | 378 (5.6) | 0.052 |
| Peptic ulcer disease | 88 (0.5) | 95 (0.7) | 0.019 | 19 (0.9) | 23 (0.9) | 0.001 | 95 (1.3) | 81 (1.2) | 0.009 |
| Lymphoma | 63 (0.4) | 48 (0.3) | 0.006 | 11 (0.5) | 6 (0.2) | 0.047 | 57 (0.8) | 54 (0.8) | 0.003 |
| Metastatic cancer | 226 (1.3) | 172 (1.2) | 0.011 | 43 (2.0) | 47 (1.8) | 0.016 | 166 (2.3) | 137 (2.0) | 0.016 |
| Solid tumor without metastasis | 1235 (7.3) | 797 (5.6) | 0.069 | 225 (10.4) | 192 (7.3) | 0.111 | 708 (9.7) | 462 (6.9) | 0.103 |
| Rheumatoid arthritis/collagen vascular disease | 329 (1.9) | 517 (3.6) | 0.102 | 62 (2.9) | 158 (6.0) | 0.152 | 297 (4.1) | 572 (8.5) | 0.184 |
| Coagulopathy | 864 (5.1) | 548 (3.8) | 0.061 | 201 (9.3) | 212 (8.0) | 0.046 | 1161 (15.9) | 855 (12.7) | 0.091 |
| Obesity | 2168 (12.8) | 1440 (10.1) | 0.085 | 295 (13.7) | 339 (12.9) | 0.025 | 1433 (19.7) | 1110 (16.5) | 0.081 |
| Weight loss | 279 (1.6) | 322 (2.3) | 0.044 | 81 (3.8) | 142 (5.4) | 0.078 | 424 (5.8) | 555 (8.3) | 0.096 |
| Fluid and electrolyte disorders | 2516 (14.8) | 2606 (18.2) | 0.092 | 580 (26.9) | 837 (31.7) | 0.106 | 3291 (45.1) | 3565 (53.1) | 0.160 |
| Blood loss anemia | 136 (0.8) | 119 (0.8) | 0.003 | 34 (1.6) | 37 (1.4) | 0.014 | 181 (2.5) | 211 (3.1) | 0.040 |
| Deficiency anemia | 343 (2.0) | 356 (2.5) | 0.032 | 82 (3.8) | 128 (4.9) | 0.052 | 580 (8.0) | 683 (10.2) | 0.077 |
| Drug abuse | 166 (1.0) | 125 (0.9) | 0.011 | 25 (1.2) | 43 (1.6) | 0.040 | 123 (1.7) | 119 (1.8) | 0.007 |
| Psychosis | 60 (0.4) | 61 (0.4) | 0.012 | 12 (0.6) | 16 (0.6) | 0.007 | 52 (0.7) | 75 (1.1) | 0.042 |
| Depression | 806 (4.8) | 1159 (8.1) | 0.137 | 145 (6.7) | 313 (11.9) | 0.178 | 644 (8.8) | 936 (13.9) | 0.161 |
| Previous stroke or transient ischemic attack | 1159 (6.8) | 814 (5.7) | 0.047 | 218 (10.1) | 243 (9.2) | 0.030 | 998 (13.7) | 837 (12.5) | 0.036 |
| Smoking | 3845 (22.7) | 2644 (18.5) | 0.103 | 456 (21.2) | 381 (14.4) | 0.176 | 818 (11.2) | 527 (7.9) | 0.115 |
| Previous myocardial infarction | 2043 (12.0) | 1160 (8.1) | 0.131 | 306 (14.2) | 285 (10.8) | 0.103 | 1172 (16.1) | 813 (12.1) | 0.114 |
| Dyslipidemia | 9339 (55.0) | 7298 (51.1) | 0.079 | 1153 (53.5) | 1265 (48.0) | 0.111 | 3794 (52.0) | 2950 (43.9) | 0.162 |

**Supplementary Table IV (online only).** Continued.

| Variable | Fontaine stage II | | | Fontaine stage III | | | Fontaine stage IV | | |
|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | SMD | Men | Women | SMD | Men | Women | SMD |
| History of coronary artery disease | 6302 (37.1) | 3571 (25.0) | 0.265 | 925 (42.9) | 812 (30.8) | 0.253 | 3527 (48.4) | 2292 (34.1) | 0.292 |
| Aortoiliac lesion treated | 6994 (41.2) | 4969 (34.8) | 0.133 | 593 (27.5) | 548 (20.8) | 0.160 | 705 (9.7) | 633 (9.4) | 0.241 |
| Femoropopliteal lesion treated | 7676 (45.2) | 7177 (50.2) | | 810 (37.6) | 1112 (42.2) | | 1712 (23.5) | 2292 (34.1) | |
| Crural lesion treated | 2297 (13.5) | 2141 (15.0) | | 752 (34.9) | 977 (37.0) | | 4875 (66.9) | 3788 (56.4) | |
| Previous (1 year) hypertensive medication | 13,466 (79.4) | 11,840 (82.9) | 0.090 | 1731 (80.3) | 2306 (87.4) | 0.195 | 6487 (89.0) | 6146 (91.6) | 0.088 |
| Previous (1 year) lipid-lowering medication | 9683 (57.1) | 7212 (50.5) | 0.132 | 1093 (50.7) | 1084 (41.1) | 0.194 | 3476 (47.7) | 2298 (34.2) | 0.276 |
| Previous (1 year) antithrombotic medication | 7858 (46.3) | 5839 (40.9) | 0.110 | 1129 (52.4) | 1246 (47.3) | 0.103 | 4455 (61.1) | 3561 (53.0) | 0.163 |
| Previous medications, No. | 7.00 (4.00-11.00) | 8.00 (5.00-12.00) | 0.156 | 9.00 (5.00-13.00) | 10.00 (6.00-14.00) | 0.149 | 12.00 (8.00-17.00) | 12.00 (8.00-17.00) | <0.001 |
| Previous hospital admissions, No. | 2.00 (1.00-4.00) | 2.00 (1.00-4.00) | 0.042 | 3.00 (1.00-5.00) | 3.00 (1.00-5.00) | 0.050 | 4.00 (2.00-6.00) | 4.00 (2.00-6.00) | 0.024 |
| Previous outpatient visits, No. | 2.00 (1.00-11.00) | 1.00 (0.00-6.00) | 0.163 | 2.00 (0.00-12.00) | 1.00 (0.00-7.00) | 0.174 | 3.00 (0.00-15.00) | 1.00 (0.00-8.00) | 0.245 |

*NA*, Not applicable; *SMD*, standardized mean difference.
Data presented as mean ± standard deviation, median (interquartile range), or number (%), unless noted otherwise.

**Supplementary Table V (online only).** Baseline characteristics of patients excluded from propensity score matching

| Characteristic | Sex | |
|---|---|---|
| | Male | Female |
| Age, years | 70.23 ± 10.19 | 74.26 ± 11.19 |
| Patients, No. | 7962 | 5319 |
| Van Walraven score >9 | 3825 (48.0) | 2530 (47.6) |
| Congestive heart failure | 2915 (36.6) | 1864 (35.0) |
| Cardiac arrhythmias | 2700 (33.9) | 1634 (30.7) |
| Valvular disease | 1193 (15.0) | 842 (15.8) |
| Pulmonary circulation disorders | 422 (5.3) | 325 (6.1) |
| Hypertension | 7216 (90.6) | 4888 (91.9) |
| Paralysis | 654 (8.2) | 425 (8.0) |
| Neurodegenerative disorders | 628 (7.9) | 430 (8.1) |
| Chronic pulmonary disease | 1672 (21.0) | 1082 (20.3) |
| Diabetes, uncomplicated | 3492 (43.9) | 1885 (35.4) |
| Diabetes, complicated | 3683 (46.3) | 1902 (35.8) |
| Hypothyroidism | 774 (9.7) | 1365 (25.7) |
| Renal failure | 3374 (42.4) | 2273 (42.7) |
| Liver disease | 524 (6.6) | 309 (5.8) |
| Peptic ulcer disease, no bleeding | 111 (1.4) | 77 (1.4) |
| Lymphoma | 44 (0.6) | 23 (0.4) |
| Metastatic cancer | 157 (2.0) | 99 (1.9) |
| Solid tumor without metastasis | 768 (9.6) | 374 (7.0) |
| Rheumatoid arthritis/ collagen vascular disease | 236 (3.0) | 376 (7.1) |
| Coagulopathy | 1151 (14.5) | 695 (13.1) |
| Obesity | 1849 (23.2) | 1103 (20.7) |
| Weight loss | 344 (4.3) | 328 (6.2) |
| Fluid and electrolyte disorders | 3048 (38.3) | 2356 (44.3) |
| Blood loss anemia | 207 (2.6) | 221 (4.2) |
| Deficiency anemia | 593 (7.4) | 538 (10.1) |
| Alcohol abuse | 742 (9.3) | 182 (3.4) |
| Drug abuse | 153 (1.9) | 92 (1.7) |
| Psychosis | 47 (0.6) | 32 (0.6) |
| Depression | 703 (8.8) | 796 (15.0) |

Data presented as mean ± standard deviation or number (%).

# Sex Disparities in Long Term Outcomes After Open Surgery for Chronic Limb Threatening Ischaemia: A Propensity Score Matched Analysis of Health Insurance Claims

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**WHAT THIS PAPER ADDS**

This study investigates sex disparities in long term outcomes after open surgical treatment of chronic limb threatening ischaemia. A propensity score matched cohort analysis including 6 502 patients revealed that female sex was associated with improved overall survival, amputation free survival, and cardiovascular event free survival during a five year follow up. The study adds to the scarce and inconsistent data on sex dependent long term outcomes after open revascularisation in peripheral arterial occlusive disease.

**Objective:** Several studies suggest a disadvantage for women in peri-operative morbidity and mortality after open surgery in peripheral arterial occlusive disease. In addition to their heterogeneity regarding design and analysed cohorts, long term data are mostly missing. This study aimed to determine sex disparities in outcomes after open revascularisation in chronic limb threatening ischaemia (CLTI).

**Methods:** Using health insurance claims data of the second largest insurance fund in Germany, BARMER, a large cohort of patients was sampled consecutively for analysis including index open surgical revascularisations of CLTI performed between 1 January 2010, and 31 December 2018. Propensity score matching was used to adjust for confounding. Sex related differences regarding overall survival, amputation free survival (AFS), and cardiovascular event free survival (CVEFS) during the five years after surgery were determined using Kaplan—Meier time to event curves, log rank test, logistic, and Cox regression.

**Results:** Among 9 526 patients (49.5% women) in the entire cohort, 6 502 patients were matched. Before matching, women were older at presentation (78.0 *vs.* 71.8 years, $p < .001$) and suffered more often from multiple comorbidities (van Walraven score $> 9$, 55.5% *vs.* 50.6%, $p < .001$). During the hospital stay, there were 692 (7.3%) deaths, while 4 631 deaths (48.6%) occurred during the follow up. In the matched cohort, the median follow up was 746 days for women and 871 days for men. In the matched analyses, female sex was significantly associated with better overall survival (hazard ratio, HR, 0.80, log rank $p < .001$), AFS (HR 0.81, log rank $p < .0001$), and CVEFS (HR 0.84, log rank $p < .001$) five years after the index treatment.

**Conclusion:** In this largest propensity score matched analysis of health insurance claims to date from Germany, evidence was found for better long term outcomes in women after open surgical revascularisations for chronic limb threatening ischaemia. Future guidelines and studies should address the impact of sex on patient selection practice and outcomes to determine the underlying reasons for existing disparities.

**Keywords:** Bypass surgery, Gender research, Health services research, Outcomes, Peripheral artery disease
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## INTRODUCTION

To date, valid societal guidelines on peripheral arterial occlusive disease (PAOD) do not contain sex specific recommendations for diagnosis or treatment.[1–3] However, such guidelines cite studies reporting worse outcomes in women after invasive revascularisation.

There is broad evidence of sex differences in presentation and treatment of patients with PAOD. For instance, women

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are known to be older when they are selected for invasive treatment, and there is striking evidence of sex disparities in terms of optimal pharmacological treatment during long term surveillance.[4–7]

Advances in endovascular therapy of PAOD have moved vascular surgery practice away from open surgical revascularisation over the last decade. However, particularly in chronic limb threatening ischaemia (CLTI), open revascularisation still plays an important role for limb salvage. There are conflicting results concerning sex related major outcomes after open surgical revascularisations for CLTI in available studies that were mostly limited to short term results and poorly adjusted for confounding. In a recent systematic review and meta-analysis on the effect of sex on outcomes after lower extremity revascularisation, the authors found that women were at increased risk of 30 day death, 30 day amputation, cardiac events, and strokes after vascular interventions compared with men.[8] In the largest retrospective observational study to date, the authors used 2.4 million hospitalisations from New York, New Jersey, and Florida, and found that sex disparities were most pronounced after open procedures. Unfortunately, the study was limited to the hospital stay because of a lack of longitudinal follow up.[9]

Based on the hypothesis that results from previous observational studies were affected by a paucity of follow up and adjustment for confounding, the current retrospective analysis of propensity score matched health insurance claims data aimed to determine the association between female sex and long term outcomes after invasive open surgical treatment for CLTI.

## METHODS

This was a retrospective observational study of health insurance claims data. Results were reported following the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.[10]

### *BARMER cohort*

The BARMER is Germany's second largest insurance fund and enables the analysis of longitudinal data on inpatient as well as outpatient medical care of 9 million German citizens (10.8% of Germany's population). The BARMER cohort is nationally generalisable and shows an age and sex distribution similar to other western European countries. A regular random sample validation of internal and external validity is performed by the Medical Service of the Health Funds (MDK) in Germany, and various peer reviewed validation studies have been published before.[11–14]

The International Classification of Diseases in its German Modification (ICD-10-GM) was used to identify diagnoses and Operations and Procedures Codes (OPS) coding to identify procedures (Table S1). The German OPS code is adapted to the International Classification of Procedures in Medicine (ICPM). The medical prescriptions were identified using the German version of the international Anatomical Therapeutic Chemical (ATC) Classification.[15] Characteristic features of the German healthcare system are reported elsewhere.[15]

### *Study population*

This study was a retrospective analysis of longitudinal inpatient and outpatient data. Patients were eligible for inclusion if they were aged ≥40 years and had an index hospital stay for an open surgical revascularisation between 1 January 2010, and 31 December 2018. Index stay is defined as the first revascularisation in hospital for a PAOD related procedure with a lookback period of five years. Data were truncated at five years after inclusion to enable complete follow up until death or the end of the study. Only patients with symptomatic PAOD in the Fontaine stages III or IV were included.

CLTI patients were identified using ICD-10-GM codes of primary or secondary diagnosis during inpatient stay. The primary diagnosis for inclusion was ischaemic rest pain (I70.22 until 2014 and I70.23 since 2015) and ischaemic wound healing disorders (ulcer, gangrene, I70.23–24 until 2014 and I70.24–25 since 2015) with or without diabetic foot syndrome (E10.50–51, E10.7, E11.50–51, E11.7) (Table S1).

In cases where PAOD was coded as the secondary diagnosis, the patient was eligible for inclusion if the concurrent primary diagnosis was diabetes with peripheral vascular complications. This ensured the inclusion of patients with diabetic foot syndrome with absence of primary CLTI diagnosis.

Considered open surgical revascularisation procedures included endarterectomy with or without patch plasty or bypass surgery of the aorto-iliac, femoropopliteal, and crural arteries. Patients with a hybrid procedure, previous revascularisation, or major amputation prior to their index stay were excluded.

### *Study variables*

The primary study endpoints were overall survival and the composite endpoints amputation free survival (AFS) (freedom from incident major amputation or all cause death), and cardiovascular event free survival (CVEFS, freedom from myocardial infarction, stroke, or all cause death).

For the baseline characteristics, a selection of the 30 Elixhauser comorbidity groups was used, categorised by ICD-10-GM codes[16,17] during five years before the first PAOD diagnosis (lookback). In 1998, Elixhauser *et al.*[17] introduced a systematic classification to identify relevant comorbidities among primary or secondary diagnoses at the time of discharge. The linear van Walraven score is a weighted sum score based on the Elixhauser groups and ranges from −19 to +89 based on the Elixhauser groups, and has been validated.[18] Accordingly, the van Walraven comorbidity score can be used to compare the impact of different comorbidities or their combination (case mix) on in hospital survival. The lookback period was one year for medication.

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**Table 1. Baseline characteristics of the entire propensity score matched cohort comprising 6 502 matched patients treated by open surgery for chronic limb threatening ischaemia in this retrospective analysis of health insurance claims between 2010 and 2018**

| | Men ($n$ = 3 251) | Women ($n$ = 3 251) | SMD |
|---|---|---|---|
| Age − y | 74.32 ± 9.84 | 74.96 ± 10.60 | 0.065 |
| *Lesion treated* | | | 0.007 |
| Aorto-iliac | 58 (1.8) | 60 (1.8) | |
| Femoropopliteal | 2 065 (63.5) | 2 055 (63.2) | |
| Crural | 1 128 (34.7) | 1 136 (34.9) | |
| *Comorbidities* | | | |
| van Walraven score >9 | 1 669 (51.3) | 1 688 (51.9) | 0.012 |
| Congestive heart failure | 1 163 (35.8) | 1 186 (36.5) | 0.015 |
| Cardiac dysrhythmias | 1 188 (36.5) | 1 209 (37.2) | 0.013 |
| Hypertension | 2 680 (82.4) | 2 729 (83.9) | 0.040 |
| Chronic pulmonary disease | 704 (21.7) | 700 (21.5) | 0.003 |
| Uncomplicated diabetes | 959 (29.5) | 946 (29.1) | 0.009 |
| Complicated diabetes | 866 (26.6) | 838 (25.8) | 0.020 |
| Renal failure | 1 145 (35.2) | 1 161 (35.7) | 0.010 |
| Liver disease | 185 (5.7) | 180 (5.5) | 0.007 |
| Obesity | 447 (13.7) | 447 (13.7) | <0.001 |
| Fluid and electrolyte disorders | 1 616 (49.7) | 1 620 (49.8) | 0.002 |
| Prior stroke or TIA | 380 (11.7) | 393 (12.1) | 0.012 |
| History of coronary artery disease | 1 293 (39.8) | 1 282 (39.4) | 0.007 |
| Prior myocardial infarction | 483 (14.9) | 467 (14.4) | 0.014 |
| Dyslipidaemia | 1 514 (46.6) | 1 488 (45.8) | 0.016 |
| *Pre-admission medication* | | | |
| Antihypertensives before admission | 2 742 (84.3) | 2 766 (85.1) | 0.021 |
| Lipid lowering drugs before admission | 1 354 (41.6) | 1 315 (40.4) | 0.024 |
| Antithrombotic drugs before admission | 1 675 (51.5) | 1 664 (51.2) | 0.007 |

Data are presented as $n$ (%) or mean ± standard deviation. SMD = standardised mean difference; TIA = transient ischaemic attack.

### Declaration of Helsinki

The study complied with the Declaration of Helsinki. All analyses were based on a factual anonymised administrative database so that neither locally appointed ethics committee approval nor informed consent was applicable.

### Statistical analysis

For the baseline characteristics, continuous variables were described as means with standard deviation (SD) for normally distributed variables and median with interquartile range (IQR) for non-normally distributed variables. Discrete variables are shown as percentages. For each variable, a comparison of prevalence between the two groups was assessed by standardised mean differences (Table S2), where values above 0.1 indicate a meaningful difference.

Propensity score matching was performed as an adjustment of baseline differences between men and women using the variables age, discharge year, number of prior hospital admissions, and PAOD related outpatient admissions, number of different prescriptions in the prior year, prescription for antithrombotics, antihypertensives, lipid lowering drugs in the prior year, the Elixhauser comorbidities (excluding peripheral vascular disease, hypothyroidism, AIDS/HIV, and alcohol abuse), prior stroke or transient ischaemic attack, dyslipidaemia, history of coronary artery disease, smoking, prior myocardial infarction, the level of lesion treated (aorto-iliac, femoropopliteal or crural), and whether the procedure included a revision of a former procedure site or a bypass procedure as covariates. The scores were calculated and matched using nearest neighbour matching, and strictly chosen within the range of 0.1 standard deviations of the distance measure. The performance and quality of the matching were assessed using standardised mean differences, where values above 0.1 indicate a meaningful difference (Table S3).

The long term outcomes were landmark analyses excluding patients that died during the hospital stay or within 30 days after discharge. Outcomes of interest were overall survival and the composite endpoints amputation free survival (major amputation or all cause mortality) and cardiovascular event free survival (myocardial infarction, stroke or transient ischaemic attack, and all cause mortality). They were estimated using Cox proportional hazards models and expressed as hazard ratios (HR) with 95% confidence intervals (CI). Individuals were considered right censored after five years to compute robust five year rates. To plot survival functions and to test for differences between women and men, the Kaplan—Meier estimator with 95% CI and log rank test was used.

For short term outcomes, patients were analysed using logistic regression for the combined endpoint of in hospital death and death within 30 days after discharge and the singular endpoint in hospital death. In hospital death was defined if the patient died during the index hospital stay (as

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**Table 2. Results of the logistic and Cox regression using a propensity score matched cohort comprising 6 502 matched patients treated by open surgery for chronic limb threatening ischaemia in this retrospective analysis of health insurance claims between 2010 and 2018. Odds ratios and hazard ratios for female *vs.* male patients regarding the corresponding endpoint**

| Endpoint (women *vs.* men) | Odds ratio | Hazard ratio | 95% CI |
|---|---|---|---|
| Short term mortality during the hospital stay | 1.17 | N/A | 0.95–1.43 |
| Short term mortality during 30 days after index treatment | 1.06 | N/A | 0.90–1.25 |
| Long term overall survival | N/A | 0.80 | 0.73–0.86 |
| Long term amputation free survival | N/A | 0.81 | 0.75–0.88 |
| Long term cardiovascular event free survival | N/A | 0.84 | 0.78–0.90 |

N/A = not applicable; CI = confidence interval.

reported by the hospital to the insurance fund). The short term outcome was expressed as odds ratios (OR) with 95% CI.

To account for potential remaining confounding after matching, short and long term analyses were additionally adjusted for age, number of prior hospital admissions, and PAOD related outpatient admissions, number of different prescriptions in the prior year, lipid lowering drug prescriptions in the prior year, the Elixhauser comorbidities (excluding valvular disease, peripheral vascular disease, hypothyroidism, AIDS/HIV, solid tumour without metastasis, obesity, deficiency anaemia, alcohol abuse, drug abuse, and depression), dyslipidaemia, coronary artery disease, smoking, prior myocardial infarction, and whether the procedure included revision of a former procedure site or a bypass procedure. The choice of covariates was based on backward selection.

As sensitivity analyses, Cox proportional hazards regressions were conducted excluding patients with bypass procedures (only endarterectomy) or co-payment exempt (as proxy variable for low socioeconomic status) as well as separate models for Fontaine stages III and IV, and an unadjusted model. For comparison, adjusted and unadjusted Cox proportional hazards regressions were performed on the unmatched cohort (Table S4). Patients with missing data (0.53%) were excluded from the study, with complete case deletion.

The statistical analysis was performed using SAS 9.4 (SAS Institute, NC, USA) and R version 3.3.3 (The R Foundation for Statistical Computing, Vienna, Austria).

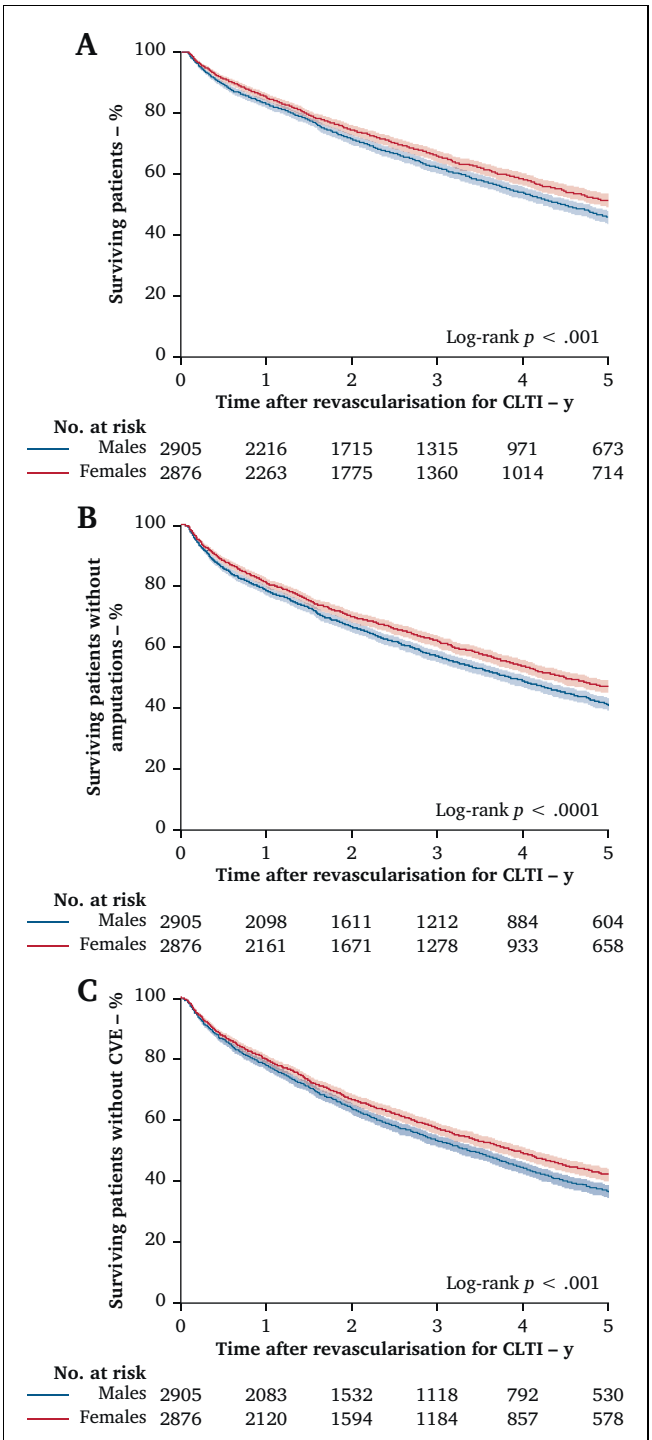


**Figure 1.** Propensity score matched cumulative Kaplan–Meier estimates by sex and corresponding *p* values (log rank) for (A) overall survival, (B) amputation free survival, and (C) cardiovascular event (CVE) free survival. A propensity score matched cohort of patients undergoing open surgical revascularisations for chronic limb threatening ischaemia (CLTI) between 2010 and 2018 was analysed in this retrospective observational study of health insurance claims in Germany.

## RESULTS

A total of 9 526 patients (49.5% women) was included in the current study, and 6 502 patients (68.2% of the entire cohort) were matched using the nearest neighbour propensity score. The median follow up times were 871 days for men and 746 days for women. Among the entire unmatched cohort, 692 in hospital deaths (7.3%) occurred, and 4 631 deaths occurred during follow up (48.6%).

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In the unmatched cohort, women were older at the time of presentation (78.0 *vs.* 71.8 years, $p < .001$) and more often suffered from multiple comorbidities (van Walraven score > 9, 55.5% *vs.* 50.6%, $p < .001$), especially pronounced for congestive heart failure (39.1% *vs.* 35.8%, $p = .001$), cardiac dysrhythmias (39.4% *vs.* 35.9%, $p = .001$), renal failure (38.1% *vs.* 33.5%, $p < .001$), and fluid and electrolyte disorders (56.0% *vs.* 44.4%, $p < .001$), while male patients suffered more often from uncomplicated (31.0% *vs.* 26.8%, $p < .001$) and complicated diabetes (30.1% *vs.* 22.5%, $p < .001$) (Table S2).

The baseline characteristics of the matched cohort are presented in Table 1.

### *Short and long term outcomes (matched cohort)*

The results of the multivariable logistic and Cox regression are presented in Table 2. During the five year follow up, female sex was associated with better overall survival (HR 0.80, 95% CI 0.73—0.86), AFS (HR 0.81, 95% CI 0.75—0.88), and CVEFS (HR 0.84, 95% CI 0.78—0.90).

The results of the Kaplan—Meier survival analysis using propensity score matched cohorts are presented in Fig. 1. Significantly better overall survival ($p < .001$), AFS ($p < .0001$), and CVEFS ($p < .001$) were observed in women.

### *Sensitivity analysis*

The results of sensitivity analyses were in accordance with those of the main analyses (Table S4). The variation of HRs between the different models was 0.12 (0.75—0.87) for overall survival, 0.07 (0.79—0.86) for AFS, and 0.09 (0.79—0.88) for CVEFS (Table S4).

## DISCUSSION

In this largest propensity score matched analysis of health insurance claims from Germany to date, women experienced a significantly better overall survival, AFS, and CVEFS at five years after the open surgical treatment of chronic limb threatening ischaemia when compared with their male counterparts.

The aspect of patient sex and its possible impact on outcomes is attracting increased attention as there is broad evidence for female patient disadvantage in cardiovascular disease.[4,5,7,19,20] Women suffering from PAOD tend to present at a greater age and with more severe symptoms when compared with men, while there is evidence for lower rates of prior outpatient treatment.[5–7] In a recently published VASCUNET report including 1 164 497 hospitalisations (40% women) for symptomatic PAOD in 11 countries, the authors revealed that women were approximately three years older and underwent treatment at a more advanced disease stage. The proportion of intermittent claudication was +15% higher in male patients while the proportion of octogenarians was +21% higher in female patients pointing out a rigorous selection of female patients.[21]

The current study indicates a non-significant trend towards worse short term outcomes in women compared with men, in line with results of previous studies that were mostly limited to in hospital or 30 day follow up.[9,22–25] Interestingly, beyond the 30 day duration, the current study found better outcomes in women than most of the previous observational studies.[8] In accordance, Budtz-Lilly *et al.* also presented better long term cardiovascular outcomes for women in long term data after open revascularisation in PAOD by performing a retrospective analysis using the Danish Vascular Registry including 11 234 patients.[26] While most of the previous studies used unmatched analyses, relevant confounding should be considered. Emphasising this methodological argument, the unmatched cohorts in the current study differed widely in terms of various relevant comorbidities and risk factors. In complex observational study designs the challenge of residual confounding becomes increasingly important and there is evidence that marginal differences in selection of the target population, matching and adjustment, and definition of variables probably cause marked differences in results.[27,28]

Although randomised studies are usually not suited to illuminating underlying causalities for existing sex disparities, it appears interesting that female patients remain under represented in trials while they represent half of the cohorts of real world studies.[29] In a secondary propensity score matched analysis of the Bypass versus Angioplasty in Severe Ischaemia of the Leg (BASIL-1) data on 452 patients, women had similar short term but better long term outcomes after revascularisation, although they were older at randomisation.[30] The current study confirms these interesting findings. This observation might support a possible impact of devices and techniques insufficiently evaluated in female patients in PAOD treatment. Against this backdrop, it is unclear whether the consideration of dichotomised sex (female *vs.* male) is applicable to approximate to the complex aspect of gender including more sophisticated constructs (e.g. social, cultural, economic, genetic, and other factors).

As the burden of PAOD, and consequently the number of PAOD procedures performed, is increasing, this study underlines the need for further investigation and focus on the influence of patient sex in PAOD and for future societal guidelines to take sex disparities regarding presentation and treatment into account. To what degree possible sex differences in disease awareness, later onset and clinical symptoms, social welfare, patient compliance, and phenotypes play a substantial role should be addressed in future studies. Both prospective cohort studies and registries may possibly help to improve the knowledge base.

Besides several strengths of the present study, there are also limitations. Firstly, there is an ongoing discussion concerning the scientific value of routinely collected administrative data.[31] The present authors believe that the validation of health insurance claims data in Germany is, to some degree, better than in selected registries because of the regular and independent random sample and risk based validation of data performed by a service provider in Germany.[32] In addition, there are numerous peer reviewed

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validation studies of this data source, proving good validity of outcomes with major health impact (e.g. mortality, myocardial infarction, stroke, amputation).[32] Possible selection bias, especially when using only one of many insurance providers, cannot be completely ruled out; however, there is evidence that the BARMER cohort is only marginally affected and rather comparable to the wider German population. This includes not just age and gender, but also educational and socioeconomic factors.[33] Secondly, the long term outcomes are influenced by several factors and there is, as yet no accepted method to completely neutralise residual confounding in non-randomised study design. A rigorous design was applied in the present study with very restricted inclusion criteria, stratification, and propensity score matching to address confounding in a sophisticated manner. Furthermore, all sensitivity analyses were confirmative.

Another important aspect attracting increased attention from the scientific community concerns the generalisability of data from national registries to the global treatment reality. The recent VASCUNET report on PAOD treatment revealed that wide variations exist with regard to patient selection and treatment modalities.[21] Furthermore, there is broad evidence for significant differences in risk factors and healthcare spending between populations in Western European, US, and Asian countries that should be considered when generalising results.[34]

### *Conclusion*

In this large scale propensity score matched analysis of health insurance claims from Germany, evidence was found for better long term outcomes in female patients after open surgical revascularisations for chronic limb threatening ischaemia. Future guidelines and studies should address the impact of sex on patient selection practice and outcomes to determine underlying reasons for existing disparities.

## ACKNOWLEDGEMENTS

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## CONFLICT OF INTEREST

None.

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## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2020.11.006.

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# Editor's Choice – Optimal Pharmacological Treatment of Symptomatic Peripheral Arterial Occlusive Disease and Evidence of Female Patient Disadvantage: An Analysis of Health Insurance Claims Data

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**WHAT THIS PAPER ADDS**

In 2018, women are still disadvantaged in terms of optimal pharmacological treatment for peripheral arterial occlusive disease after hospital discharge. Although presenting at older age and with more severe symptoms, women have a lower prescription prevalence of optimal pharmacological treatment, particularly with respect to lipid lowering drugs. The sex prescription gap did not narrow over time, despite an overall upward trend in prescription prevalence for both women and men.

**Objective:** Optimal pharmacological treatment (OPT) for peripheral arterial occlusive disease (PAOD) includes prescription of lipid lowering drugs, antithrombotics, and antihypertensives to symptomatic patients affected by intermittent claudication or chronic limb threatening ischaemia. This study sought to determine sex disparities and time trends in prescription of OPT in this population (clinicaltrials.gov NCT03909022).

**Methods:** Using data from the second largest insurance fund in Germany, BARMER, data on patients with an index admission for symptomatic PAOD between 1 January 2010 and 30 June 2018 with follow up until the end of 2018 were analysed. Sex disparities in post-discharge prescription status six months after index admission were tested and adjusted for patient and healthcare variables using bivariable tests and logistic regression analysis. Time trends in the prescription prevalence of OPT were analysed and tested.

**Results:** There were 83 867 patients (mean age 71.9 years and 45.8% women) eligible for inclusion in the study. When compared with men, women had lower rates of prior outpatient care for PAOD (39.8% *vs.* 47.0%), were admitted more often with ischaemic rest pain (13.9% *vs.* 10.4%) and were older (74 *vs.* 70 y). After discharge, women had a lower rate of prescriptions for lipid lowering drugs (52.4% *vs.* 59.9%), while they received antihypertensive drugs more often (86.7% *vs.* 84.1%). We found evidence for a lower prescription prevalence of OPT in females (37.0% *vs.* 42.7%). Differences in patient and healthcare variables (e.g. demographics, comorbidities, prior treatment) between women and men explained 56% of this gap. The sex prescription gap did not narrow over time despite an overall upward trend in prescription prevalence for both women and men.

**Conclusion:** Although presenting older and with more severe symptoms at the index admission for PAOD, women have a lower prescription prevalence of OPT compared with men, particularly with respect to lipid lowering drugs.

**Keywords:** Chronic limb threatening ischaemia, Intermittent claudication, Optimal medical therapy, Peripheral arterial occlusive disease, Sex disparities

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## INTRODUCTION

More than 200 million patients are known to be affected by peripheral arterial occlusive disease (PAOD) worldwide.[1] The widespread adoption and further development of innovative endovascular techniques to treat symptomatic PAOD are associated with increasing numbers of revascularisations in Western European countries.[1,2] Meanwhile, improvement in optimal medical treatment recommended

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by societal practice guidelines[3–7] led to decreasing overall mortality in ageing populations and ameliorated the long term results following invasive treatment of vascular diseases such as carotid artery stenosis[8–10] or abdominal aortic aneurysm.[11–13]

Recently, sex disparities in vascular medicine regained the attention of the scientific community and there are results from prior studies suggesting that the sexes are not treated equally. Females tend to be older and suffer from different or even atypical symptoms at the time of presentation compared with their male counterparts.[14–17]

The longterm cardiovascular outcome of patients with intermittent claudication or chronic limb threatening ischaemia depends on consistent optimal pharmacological treatment (OPT). This includes pharmaceuticals such as lipid lowering drugs, angiotensin converting enzyme inhibitors (ACEIs), or angiotensin receptor blockers (ARBs), and antiplatelets as first-line treatment.[3,4,18,19] To improve walking distance after claudication, cilostazol and statins are recommended. Furthermore, valid guidelines recommend non-pharmacological risk factor management including smoking cessation, healthy diet, weight loss, and regular physical exercise.[20] A concise overview of the current guidelines is provided in the Supplementary material (Table S4).

This study aimed to determine the OPT sex differences in patients with symptomatic PAOD using data on a population based cohort from a large health insurance provider in Germany. It was hypothesised that provision of OPT is worse in female patients compared with their male counterparts.

## METHODS

### *BARMER cohort*

The health insurance claims data of Germany's second largest insurance provider, BARMER, include information on outpatient and inpatient medical care provided to approximately 9.1 million German citizens (10.8% of Germany's population). The patient characteristics in the BARMER cohort are similar to those of populations in Western European countries, and the cohort has been widely used for research projects before.[2,21–23] The German adaptation of the International Classification of Diseases (ICD-10-GM) was used to identify diagnoses and Operations and Procedures Codes (OPS) to identify procedures. The German OPS code is adapted to the International Classification of Procedures in Medicine (ICPM). To identify medical prescriptions, the German version of the international Anatomical Therapeutic Chemical (ATC) Classification was used.

### *Study sample*

This study was a retrospective analysis of inpatient and outpatient data. Patients aged $\geq$ 40 years with an index stay for symptomatic PAOD between 1 January 2010 and 30 June 2018 were eligible for inclusion in the study. Index stay denotes the first in-hospital admission within five years. To assess post-discharge prescription status adequately, patients who were referred to a hospice or died during hospital stay or up to six months after discharge were excluded (follow up data until 31 December 2018) to prevent immortal time bias (landmark analysis).[24] Only patients with full observation time (insured continuously five years prior to index stay and alive six months after index stay) were included.

Symptomatic PAOD patients were identified using ICD-10-GM codes of primary or secondary diagnosis during in hospital stay (Table S1).

If PAOD was coded as secondary diagnosis only, inclusion additionally required a primary diagnosis of diabetes with peripheral vascular complications to include patients with diabetic foot syndrome who have not been coded with chronic limb threatening ischaemia (Table S1).[25] The ICD codes were grouped according to Fontaine stage II (intermittent claudication), Fontaine stage III (ischaemic rest pain), and Fontaine stage IV (ischaemic ulcers or gangrene) representing different degrees of PAOD severity.[26]

### *Study variables*

The primary outcome of this study was the evidence of provision of OPT within six months after hospital discharge, consisting of at least a lipid lowering drug, an antithrombotic agent, and an antihypertensive drug (Table S3). Additionally, prescription prevalence was measured for the more refined subgroups statins, antiplatelets, vitamin K antagonists, novel oral anticoagulant drugs, aspirin, clopidogrel, cilostazol, diuretics, betablockers, calcium channel blockers, and ACEIs/ARBs. For each of the medication groups, it was assessed whether at least one prescription in each category (within six months) was filled by the patient at the pharmacy from the first day until six months after hospital discharge.

Covariates were sex, calendar time (discharge year), age in 10 year age groups, polypharmacy (0–4, 5–10, 11+ prescriptions up to one year before index stay), prior outpatient diagnosis of PAOD, inpatient diagnosis by Fontaine stage (II, III, and IV), invasive revascularisation or amputation (peripheral vascular intervention, open surgical repair, any minor or major amputation combined), and total length of hospital stay in days. In addition, based on the WHO ICD-10-GM classification, the following comorbidities were included: coronary artery disease, dyslipidaemia, congestive heart failure, cardiac dysrhythmia, diabetes (complicated), depression, hypothyroidism, renal failure, stroke/transient ischaemic attack (TIA), myocardial infarction, smoking, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, valvular disease, alcohol abuse, liver disease, hypertension, tumour/metastatic cancer.

These comorbidities were obtained from current and previous in hospital diagnoses using the WHO ICD-10-GM and coded according to the 30 item classification developed by Elixhauser *et al.*, validated for this data set previously.[23,27] Coronary artery disease, stroke/TIA, myocardial infarction, dyslipidaemia and smoking were grouped and

**Table 1. Baseline characteristics of the study sample**

| Characteristics | Males ($n$ = 45 436) | Females ($n$ = 38 431) | Difference in % | Standardised difference |
|---|---|---|---|---|
| *Age − years* | | | | |
| Mean age ± standard deviation | 69.8 ± 10.2 | 74.3 ± 11.0 | −6.6* | 0.43 |
| Age group 40–49 | 1 213 (2.7) | 778 (2.0) | 0.6 | −0.04 |
| Age group 50–59 | 7 335 (16.1) | 3 556 (9.3) | 6.9† | −0.21 |
| Age group 60–69 | 13 589 (29.9) | 8 215 (21.4) | 8.5† | −0.20 |
| Age group 70–79 | 15 801 (34.8) | 13 345 (34.7) | 0.1 | 0.00 |
| Age group 80–89 | 6 862 (15.1) | 10 142 (26.4) | −11.3* | 0.28 |
| Age group 90+ | 636 (1.4) | 2 395 (6.2) | −4.8* | 0.25 |
| *Symptoms* | | | | |
| Intermittent claudication (Fontaine II) | 25 275 (55.6) | 20 049 (52.2) | 3.5† | −0.07 |
| Ischaemic rest pain (Fontaine III) | 4 716 (10.4) | 5 326 (13.9) | −3.5* | 0.11 |
| Ischaemic wound healing disorders (Fontaine IV) | 15 445 (34.0) | 13 056 (34.0) | 0.0 | 0.00 |
| *Invasive procedure* | | | | |
| None | 9 213 (20.3) | 7 939 (20.7) | −0.4 | 0.01 |
| PVI | 22 351 (49.2) | 20 304 (52.8) | −3.6* | 0.07 |
| OSR | 11 489 (25.3) | 8 870 (23.1) | 2.2† | −0.05 |
| Amputation only | 2 383 (5.2) | 1 318 (3.4) | 1.8 | −0.09 |
| *Length of hospital stay − days* | | | | |
| 1–3 | 14 251 (31.4) | 11 323 (29.5) | 1.9 | −0.04 |
| 4–7 | 9 441 (20.8) | 8 730 (22.7) | −1.9 | 0.05 |
| 8+ | 21 744 (47.9) | 18 378 (47.8) | 0.0 | 0.00 |
| Prior outpatient diagnosis PAOD | 21 366 (47.0) | 15 296 (39.8) | 7.2† | −0.15 |
| *Polypharmacy − prescriptions* | | | | |
| 0–4 | 12 508 (27.5) | 8 354 (21.7) | 5.8† | −0.13 |
| 5–10 | 12 662 (27.9) | 10 759 (28.0) | −0.1 | 0.00 |
| 11+ | 20 266 (44.6) | 19 318 (50.3) | −5.7* | 0.11 |
| Hypertension | 36 781 (81.0) | 31 974 (83.2) | −2.2* | 0.06 |
| Coronary artery disease | 18 441 (40.6) | 11 202 (29.1) | 11.4† | −0.25 |
| Congestive heart failure | 11 912 (26.2) | 9 715 (25.3) | 0.9 | −0.02 |
| Cardiac dysrhythmias | 12 507 (27.5) | 9 808 (25.5) | 2.0† | −0.05 |
| Dyslipidaemia | 23 795 (52.4) | 17 870 (46.5) | 5.9† | −0.09 |
| Diabetes, complicated | 14 554 (32.0) | 8 853 (23.0) | 9.0† | −0.20 |
| Hypothyroidism | 3 552 (7.8) | 8 395 (21.8) | −14.0* | 0.40 |
| Renal failure | 13 343 (29.4) | 11 365 (29.6) | −0.2 | 0.00 |
| Depression | 2 894 (6.4) | 4 459 (11.6) | −5.2* | 0.18 |
| Stroke/TIA | 4 136 (9.1) | 3 472 (9.0) | 0.1 | 0.00 |
| Myocardial infarction | 5 586 (13.0) | 3 599 (9.9) | 3.1† | −0.10 |
| Smoking | 8 636 (19.0) | 5 762 (15.0) | 4.0† | −0.11 |
| Rheumatoid arthritis/collagen vascular diseases | 1 206 (2.7) | 2 046 (5.3) | −2.7* | 0.14 |
| Coagulopathy | 4 164 (9.2) | 2 886 (7.5) | 1.7 | −0.06 |
| Obesity | 7 637 (16.8) | 5 395 (14.0) | 2.8† | −0.08 |
| Valvular disease | 4 853 (10.7) | 4 418 (11.5) | −0.8 | 0.03 |
| Alcohol abuse | 3 564 (7.8) | 1 275 (3.3) | 4.5† | −0.20 |
| Liver disease | 2 377 (5.2) | 1 637 (4.3) | 1.0 | −0.05 |
| Tumour/metastatic cancer | 3 910 (8.6) | 2 502 (6.5) | 2.1† | −0.08 |

Data are presented as $n$ (%) unless stated otherwise. Differences > 2% and standardised differences > 0.1 were interpreted as clinically relevant. OSR = open surgical revascularisation; PAOD = peripheral arterial occlusive disease; PVI = peripheral vascular intervention; TIA = transient ischaemic attack.

* Larger values for females.

† Larger values for males.

measured in line with earlier studies using the BARMER cohort[25,28] (Table S2). Relevant covariates were selected for inclusion in regression analyses using the Least Absolute Shrinkage and Selection Operator (LASSO) method and based on clinical relevance from previous studies (Table S8).[29]

The lookback period was five years for collecting information on prior outpatient diagnosis and comorbidities, and one year for assessing polypharmacy.

### Statistical analysis

Descriptive characteristics of PAOD patients were compared between males and females using mean (±standard deviation) for continuous variables and percentages and standardised differences for categorical variables.[30] For binary outcomes, generalised linear models with logit link were used. To adjust for confounding on the sex prescription gap, the probability to receive OPT was modelled

through a logistic regression model. Sex was entered into the model as an independent variable along with all other confounders. Using the coefficient of sex and the intercept of the regression model, the adjusted probability was predicted for OPT for males and females and the gap was calculated. To ensure that the intercept of the regression model represented an average patient, effect coding for all variables in the model was applied (e.g. for hypertension: −1 = no hypertension, 1 = hypertension). Multivariable regression results were reported as odds ratios (OR) with 95% confidence intervals (CI) (Table 2). Trends in prescription prevalence were inspected visually and using the Cochrane–Armitage test. Missing information with respect to sex, age, or follow up was handled by case exclusion before analysing the data (about 0.49% of all cases). All analyses were performed with software SAS version 9.04 (SAS Institute, NC, USA). Results were reported following the reporting of studies conducted using the observational routinely collected health data (RECORD) statement,[31] the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement,[32] good practice of secondary data analysis,[33] and following international recommendations on medical device evaluation studies.[34] More details about the broader study of which this analysis is part and the German healthcare system are available in a corresponding study protocol (clinicaltrials.gov NCT03909022).[35]

### Declaration of Helsinki

The study complied with the Declaration of Helsinki. All analyses were based on a pseudonymised administrative database so that neither locally appointed ethics committee approval nor informed consent were applicable.

## RESULTS

In total, 83 867 patients (mean age 71.9 y and 45.8% women) were identified with an index hospitalisation for symptomatic PAOD (54.0% for intermittent claudication) between 1 January 2010 and 30 June 2018 (Fig. S1).

### Baseline characteristics

The baseline characteristics of the study cohort by sex are shown in Table 1. When compared with men, women were older, more often presented with ischaemic rest pain, and were more often treated endovascularly with peripheral vascular interventions. Male patients more often presented with intermittent claudication (IC) and were more often amputated without invasive revascularisation during the same hospital stay.

During the prior outpatient care, women were less often diagnosed with PAOD (39.8% *vs.* 47.0%), and they were more likely to receive ≥ 11 different medication prescriptions as a sign of clinically relevant polypharmacy (50.3% *vs.* 44.6%).

**Table 2. Sex prescription gap in observed unadjusted and adjusted prescription prevalence including odds ratios and 95% confidence intervals of secondary prevention within six months after hospital admission for symptomatic peripheral arterial occlusive disease between males and females, the impact of adjustment for confounding or suppression on this gap**

| | Prevalence | | Difference between males and females | | | |
|---|---|---|---|---|---|---|
| | Males − % | Females − % | I. Gap Unadjusted | II. Gap Adjusted‡ | Adjusted OR (95% CI)‡ | Change in gap (II.-I.)/I. − %§ |
| Optimal pharmacological treatment | 42.7 | 37.0 | −5.7† | −2.5† | 0.89 (0.86–0.92) | −56 |
| Lipid lowering drugs | 59.9 | 52.4 | −7.4† | −3.3† | 0.87 (0.85–0.90) | −55 |
| Statins | 56.2 | 49.8 | −6.5† | −2.8† | 0.89 (0.87–0.92) | −57 |
| Antithrombotics | 73.8 | 73.5 | −0.3 | −0.5 | 0.97 (0.94–1.00) | |
| Antiplatelets | 59.9 | 60.3 | 0.4 | 0.3 | 1.01 (0.98–1.04) | |
| VKA | 12.4 | 10.0 | −2.4† | −1.7 | 0.78 (0.74–0.82) | −31 |
| NOAC | 7.0 | 8.2 | 1.2 | 0.6 | 1.13 (1.06–1.20) | |
| Aspirin | 36.1 | 35.4 | −0.7 | −1.0 | 0.96 (0.93–0.99) | |
| Clopidogrel | 38.2 | 39.6 | 1.4 | 1.2 | 1.06 (1.03–1.10) | |
| Cilostazol | 2.7 | 2.5 | −0.2 | −0.1 | 0.91 (0.83–1.00) | |
| Antihypertensives | 84.1 | 86.7 | 2.6* | 1.8 | 1.10 (1.05–1.16) | −33 |
| Diuretics | 39.4 | 42.8 | 3.3* | 2.3* | 1.10 (1.06–1.14) | −31 |
| Betablockers | 53.4 | 55.1 | 1.7 | 4.1* | 1.18 (1.14–1.22) | 148 |
| Calcium channel blockers | 27.5 | 30.4 | 2.9* | 0.6 | 1.07 (1.03–1.11) | −78 |
| ACEI/ARBs | 68.1 | 66.3 | −1.8 | −3.0† | 0.87 (0.84–0.90) | 64 |

Differences > 2% were treated as clinically meaningful. ACEI = angiotensin converting-enzyme inhibitor; ARBs = angiotensin II receptor blocker; OR = odds ratio; CI = confidence interval; NOAC = novel oral anticoagulant drug; PAOD = peripheral arterial occlusive disease; VKA = vitamin K antagonist.

* Larger values for females.

† Larger values for males.

‡ Adjusted for discharge year, length of in hospital stay, age, polypharmacy, inpatient diagnosis, invasive procedure, prior outpatient diagnosis PAOD, coronary artery disease, dyslipidaemia, congestive heart failure, cardiac dysrhythmias, diabetes (complicated), depression, hypothyroidism, renal failure, stroke/transient ischaemic attack, myocardial infarction, smoking, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, valvular disease, alcohol abuse, liver disease, cancer, hypertension.

§ Positive % = gap widening after adjustment; negative % = gap narrowing after adjustment.

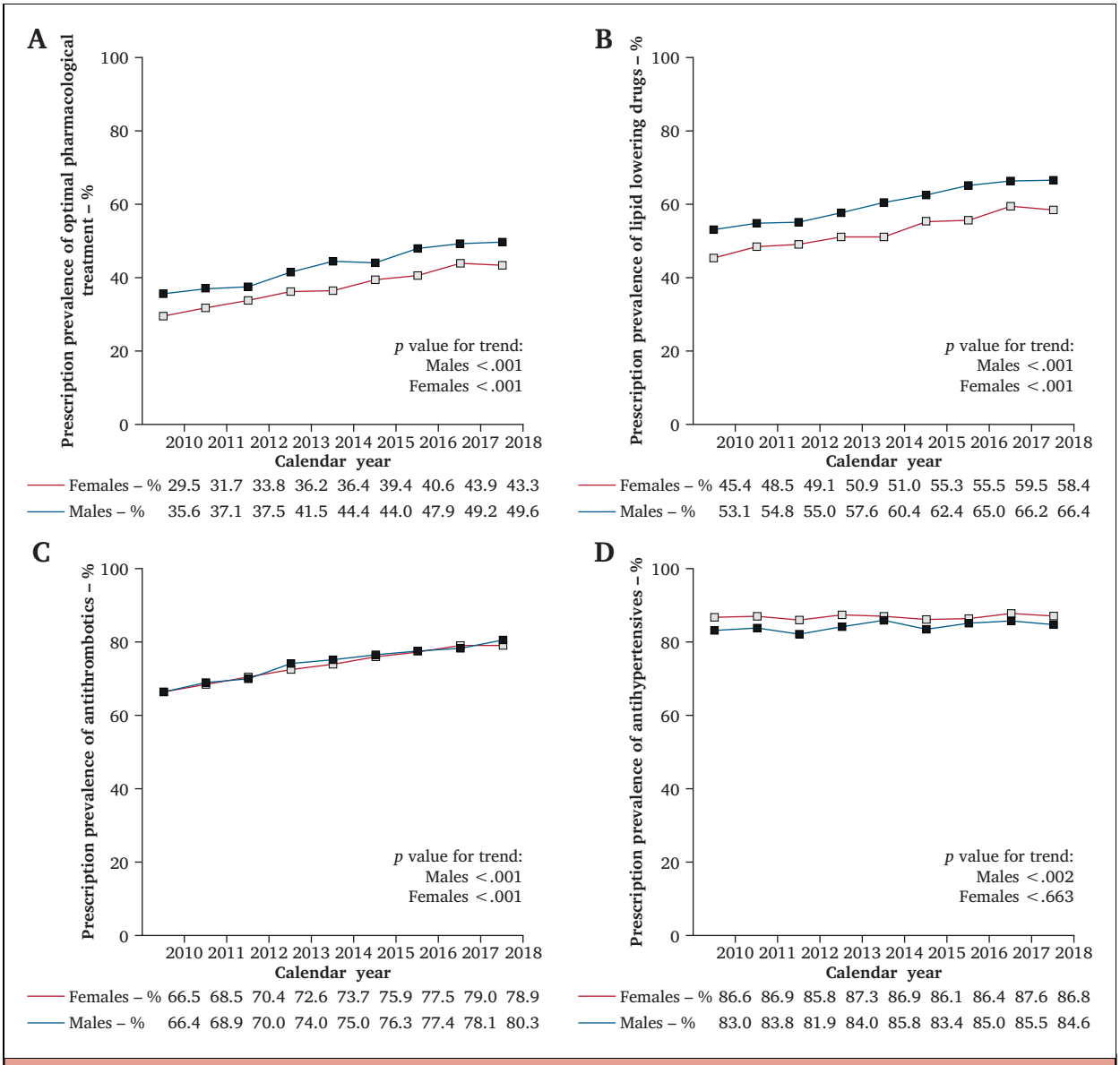


**Figure 1.** Unadjusted sex differences in time trends in prescription prevalence of optimal pharmacological treatment (OPT) (A) and its components: lipid lowering drugs (B), antithrombotics (C), and antihypertensives (D) within two quarters after hospital admission for symptomatic peripheral arterial occlusive disease (PAOD), 1 January 2010 until 30 June 2018.

When analysed separately by PAOD disease severity, sex differences in baseline characteristics were larger in the chronic limb threatening ischaemia subsample than in the intermittent claudication subsample (Table S7).

### *Prescription prevalence by sex*

Differences in the prescription prevalence of OPT and the impact of adjusting variables are shown in Table 2. When compared with men, women were less often treated with OPT (37.0% *vs.* 42.7%, OR 0.89, 95% CI 0.86—0.92). While women less often received lipid lowering drugs (52.4% *vs.* 59.9%, OR 0.87, 95% CI 0.85—0.90), they were more often treated with antihypertensives (86.7% *vs.* 84.1%, OR 1.10, 95% CI 1.05—1.16). There were no sex differences with respect to prescription of antithrombotics (73.5% *vs.* 73.8%, OR 0.97, 95% CI 0.94—1.00).

### *Time trends of OPT prescription rates*

During the study period, the overall prescription prevalence increased significantly for lipid lowering drugs, and antithrombotic drugs but not significantly for antihypertensive drugs (Fig. 1). The sex prescription gap remained largely stable over time in all medication groups (Fig. 1).

### *Impact of baseline characteristics on sex prescription gap*

The impact of different baseline characteristics on the observed unadjusted sex prescription gap for OPT is shown in Table 2. Adjusting the prescription prevalence for differences in baseline characteristics reduced the observed unadjusted sex prescription gap for OPT (−56% gap narrowing), lipid lowering drugs (−55% gap narrowing), statins (−57% gap narrowing), vitamin K anticoagulants (−31% gap narrowing), antihypertensives (−33% gap narrowing), and

calcium channel blockers (−78% gap narrowing). Respectively, the sex prescription gap increased for betablockers (+148% gap widening) and ACEI/ARBs (+64% gap widening) after adjustment. Thereby, sex differences in adjusted prescription prevalence varied between −3.3% for lipid lowering drugs (OR 0.87, 95% CI 0.85−0.90) and +4.1% (OR 1.18, 95% CI 1.14−1.22) for betablockers.

## DISCUSSION

According to valid guidelines regarding symptomatic PAOD of the lower limbs, OPT consists at least of pharmaceuticals such as lipid lowering drugs, ACEI or ARB, and antiplatelets as first line treatment. In this large scale longitudinal cohort study, evidence was found of lower prescription rates for OPT in women, especially lipid lowering drugs, when compared with men. In addition, women who presented with more severe symptoms and more advanced age at their index stay were less often diagnosed with PAOD in their prior outpatient course. Although there was an increasing trend in overall OPT prescription rates over time, only about half of the cohort received OPT or lipid lowering drugs after in hospital treatment of symptomatic PAOD. Unfortunately, this study was not able to identify the underlying reasons for the lack of guideline adherence.[36,37]

Societal practice guidelines recommend lipid lowering drugs, antiplatelets, and ACEIs or ARBs as first line OPT in patients with symptomatic PAOD to help to prevent limb related or cardiovascular events.[3,4] Interestingly, adherence to the guideline recommendations varies considerably in the literature, and OPT prescription rates are infrequently reported and rarely distinguished by sex (Tables S5 and S6). The OPT sex differences could be almost fully explained by differences in lipid lowering drug prescription rates. Statin prescription rates of 56.2% and 49.8% were documented in men and women (gap 6.5%), similar to recent results from German survey data (58.6% and 51.4%, gap 7.2%) and Swedish registry data (57.4% and 48.9%, gap 8.5%).[38−41] Internationally, the sex gap ranges from 3% in Canada[42] and 6% in the USA[43] up to 15% in Italy,[44] with overall prescription rates ranging from 11% in Japan[36] to 86% in the USA.[37]

However, it appears challenging to interpret these remarkable disparities. A recent review identified the following factors as the main driving forces of international variations: differences in reimbursement policies and national priority settings, medicine pricing, patient co-payment, access to specialists, and variations in clinical practice and prescribing patterns.[45] In Germany, patients receive their individual prescriptions from their primary care physician after being discharged from the hospital. This is different from the situation in the USA and other countries, in which the hospital physician would provide the prescription to the patient. Hence, the observed sex prescription gap could be partially accounted for by a potential lack of knowledge about peripheral vascular prevention among general practitioners.

The higher proportion of cardiac comorbidities in men may lead to a greater awareness and willingness of physicians in outpatient care to prescribe lipid lowering drugs as patients with coronary diseases are, in general, more intensively treated.[46] Another possible explanation might be the significantly higher proportion of polypharmacy in women. If a woman with PAOD already received more than 11 different prescriptions, it seems conceivable that the primary care physician would more likely argue against another prescription including statins. Yet, in the present sample, polypharmacy lowers the risk of not receiving OPT by 27% (95% CI 0.70−0.75, Fig. S2). This confirms earlier findings that new users were more likely adhere to statin therapy if they had more medications at baseline.[47] Interestingly, despite their higher degree of polypharmacy, women are generally less likely to adhere to statins.[48]

There are prior publications reporting sex disparities in clinical symptoms at initial presentation. Female patients tend to present later and in a more urgent stage with ischaemic rest pain, while their male counterparts are revascularised electively for intermittent claudication.[15,16] The significantly lower rate of prior outpatient PAOD diagnoses in women in the current study confirms earlier disease recognition, prevention, and management in males as compared with females as reported in the literature.[49]

An overall positive time trend establishes that guideline recommendations led to improving prescription rates over time. Nevertheless, based on the present study results, every year approximately 53 000 patients with symptomatic PAOD would not receive OPT during the six months after admission. Mean costs of 6076 euros per hospitalisation in 2016[23] are contrasted with annual costs of statin therapy of $<$ 100 euros per patient.[50] It seems worthwhile evaluating awareness campaigns and actions to improve the situation for all PAOD patients, including early ankle brachial index (ABI) based screening of high risk profile females combined with promotion of lifestyle measures, including smoking cessation, exercise therapy, and weight loss.[49]

This study has several strengths, but it also has limitations. Firstly, the merely observational design of this retrospective cohort study does not allow any causative conclusion to be drawn, and the large sample size makes it likely to measure significant differences. The current study could not rule out that the observed disparities are explained by individual contraindications or other clinical reasons. Therefore, it is up to the vascular community to ponder between statistically significant results and clinical relevance. However, by involving experienced health service researchers and biostatisticians, the aim was to limit the chance of false positive results.[30,51−53]

Secondly, the current study is limited by the merely dichotomic approach to characterise sex. Recent sex research introduced various additional aspects such as genetic, social, or identity determinism that cannot be embraced by these study data. The impact of sex on prescription prevalence was modelled in a pooled model, assuming that the effect of all confounders on this relation is similar for males and females. Sensitivity analyses where separate models for males and females were computed

confirmed the validity of this assumption. It must be highlighted that the current study only illuminated pharmacological treatment as an important pillar of best medical treatment in patients with symptomatic PAOD. However, there are additional aspects such as smoking cessation and healthy diet not covered by the BARMER data. Furthermore, the complex issue of how to handle patients who died early remains challenging in retrospective observational studies. It was decided to use a landmark approach by excluding patients who died up to six months after discharge. However, this might affect results when looking for a sex related disadvantage in care as those who died may have received an even lower standard of care.

Lastly, the current study is primarily covering patients fulfilling their prescription in a pharmacy after being discharged from the hospital, but there may be patients with or without OPT not validly covered. It could neither be ensured that the patients are actually taking the pills after fulfilling the prescription nor could the hypothetical chance be eliminated that they receive their medication using a private prescription or directly if they are authorised accordingly (over the counter medication). Yet, the central estimates here are in line with survey results on medication use[40] and studies on primary non-adherence report proportions markedly lower than 10%.[54–56] Thus, the sex differences uncovered in this study at least partly also reflect differences in prescriptions in line with prior evidence on less intensive treatment of women among providers, particularly with respect to statins.[48] Unfortunately, the complex aspect of patient compliance was not within the scope of the current study. A follow up study will address adherence to pharmacological prescriptions and possible contraindications as explanatory factors for the remarkably low prevalence of OPT.

## CONCLUSIONS

This study revealed evidence of significant sex disparities in OPT in people with symptomatic PAOD. The results suggest a prescription behaviour that relies to a large extent on patient variables such as comorbidities, which conflicts with current guidelines. Lower rates of pre-admission care, the higher degree of polypharmacy, and a more common treatment with endovascular therapy despite presenting with more severe disease signals broader disadvantages in optimal care of female patients.

## CONFLICTS OF INTEREST

None.

## FUNDING

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## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2020.05.001.

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COUP D'OEIL

# Endovascular Management of Tibioperoneal Trunk Pseudoaneurysm with Arteriovenous Fistula

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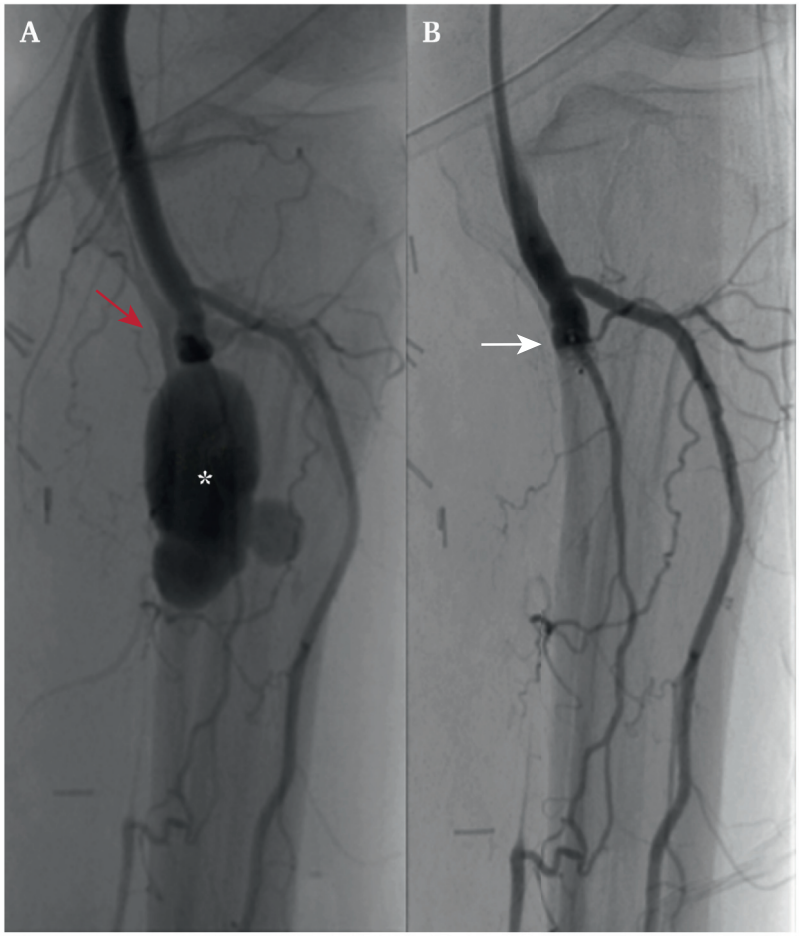


A 49 year old man presented with pain and swelling of the left leg. Two years previously he had had a gunshot injury to the left lower leg. Angiography (A) revealed a 52 mm tibioperoneal trunk pseudoaneurysm (asterisk) with arteriovenous fistula (red arrow). Owing to the occlusion of the posterior tibial and peroneal arteries, an 8 × 20 mm vascular plug (AGA Medical Corporation, Plymouth, MA, USA) was placed in the tibioperoneal trunk (B, white arrow) excluding the pseudoaneurysm while preserving the collateral circulation and anterior tibial artery which continued into the foot. Six months after the procedure, the patient was asymptomatic.

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Journal of the American Heart Association

ORIGINAL RESEARCH

# Long-Term Effectiveness and Safety of Initiating Statin Therapy After Index Revascularization In Patients With Peripheral Arterial Occlusive Disease

Frederik Peters, MSc, PhD; Jenny Kuchenbecker, MSc; Thea Kreutzburg, MSc; Ursula Marschall, MD; E. Sebastian Debus, MD; Christian-Alexander Behrendt, MD

**BACKGROUND:** An increasing number of patients with a peripheral arterial occlusive disease were put on statins during the past years. This study assessed whether statin therapy was effective and safe for these new users.

**METHODS AND RESULTS:** Using health insurance claims data from Germany's second-largest insurance fund, BARMER, we identified patients with peripheral arterial occlusive disease who had index revascularization between 2008 and 2018 without prior statin therapy. We compared patients with and without statin therapy in addition to antithrombotics during the first quarter after discharge (new users versus nonusers). Outcomes were all-cause mortality, cardiovascular events, and incident major amputation for effectiveness and incident diabetes mellitus and incident myopathy for safety. Propensity score matching was used to balance the study groups. All analyses were stratified into patients with chronic limb-threatening ischemia and intermittent claudication. A total of 22 208 patients (mean age 71.1 years and 50.3% women) were included in the study. In 10 922 matched patients, statin initiation was associated with lower all-cause mortality (chronic limb-threatening ischemia: hazard ratio [HR], 0.75 [95% CI, 0.68–0.84]; intermittent claudication: HR, 0.80 [95% CI, 0.70–0.92]), lower risk of major amputation in patients with chronic limb-threatening ischemia (HR, 0.73; 95% CI, 0.58–0.93) and lower risk of cardiovascular events (hazard ratio, 0.80; 95% CI, 0.70–0.92) in patients with intermittent claudication during 5 years of follow-up. Safety outcomes did not differ among the study groups.

**CONCLUSIONS:** Initiating statin therapy in patients with peripheral arterial occlusive disease after index revascularization is efficient and safe with an effect size comparable to earlier studies. Awareness campaigns for evidence-based optimal pharmacological treatment among patients are recommended.

**Key Words:** chronic limb-threatening ischemia ■ intermittent claudication ■ peripheral arterial occlusive disease ■ statin-induced myopathy ■ statin therapy

During the past decades, various pharmacological therapies for vascular diseases became available, effectively preventing cardiovascular events.[1] Valid guidelines consistently emphasize the importance of the prescription of statins in patients with peripheral arterial occlusive disease (PAOD) irrespective of their concomitant risk profile as a cornerstone of secondary prevention.[2–7] Patients with PAOD are particularly dependent on optimal pharmacological treatment because of considerably elevated risks of cardiovascular events, acute limb ischemia, and amputation markedly impairing quality of life.[8–10] Yet, this subgroup exhibits particularly low utilization rates of statins as compared with patients with coronary artery disease or a history of stroke.[11,12]

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## CLINICAL PERSPECTIVE

### What is New?

- This is the first study assessing long-term benefits and harms of initiating statin therapy after lower limb revascularization for symptomatic peripheral arterial occlusive disease in a real-world setting.
- The proportion of patients initiating statin therapy doubled throughout the study period but is still substantially below societal guideline recommendations.
- Initiating statin therapy is effective and safe in patients with intermittent claudication or chronic limb-threatening ischemia.

### What Are the Clinical Implications?

- Awareness campaigns emphasizing the importance of prescribing statins in the follow-up of patients should involve general practitioners and other medical specialist disciplines.
- The surveillance of patients after invasive revascularizations should comprise regular interviews for optimal pharmacological treatment and patient compliance.
- Health insurance claims can be used to automatically identify patients with potential for improvement in secondary prevention.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **ATC** | Anatomical Therapeutic Chemical |
| **CLTI** | chronic limb-threatening ischemia |
| **IC** | intermittent claudication |
| **ICD-10-GM** | International Classification of Diseases, Tenth Revision, German Modification |
| **PAOD** | peripheral arterial occlusive disease |

The underutilization of statin therapy has been predominantly ascribed to the lack of awareness about risks and therapy options among providers and patients[12,13] and concerns about adverse reactions such as myopathy and onset of diabetes mellitus.[14–16] Given the solid evidence of the benefits of statin therapy and, at the same time, the sharp increase in hospitalizations and costs related to PAOD, experts urge providers to push efficient secondary prevention more insistently.[17]

Recent observational studies confirmed that statins are effective and safe in both low- and high-risk patients with PAOD[18,19] and offer additional benefits at high-intensity doses.[18,20] Although these studies differed in study design and sample composition, they arrived at similar conclusions comparable to findings from randomized controlled trials.

Fueled by intensified guideline recommendations, statin utilization rates increased throughout the past decade among patients with PAOD.[21] In the current study, we determine the success of the expansion of statins in PAOD treatment and the impact on major outcomes in the longer term. This may contribute to the understanding of how effects measures in randomized controlled trials translate to the heterogenous real-world population and to what extent the benefit of the drug diminishes as prescription rates increase. This concept was recently discussed for other domains of health care.[22]

Our study employed a large nationwide database for quantifying the long-term effectiveness and safety of initiating statin therapy in symptomatic patients with PAOD after index revascularization. We aimed to quantify to what degree the initiation of statin therapy prolongs survival, reduces the risk for major amputation and cardiovascular events, and potentially increases the risk of the onset of diabetes mellitus or myopathy.

## METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. Our study complies with the Declaration of Helsinki 2013. Several review boards determined that using factual anonymized data from claims or national statistics retrospectively is not considered human subject research because deidentified data sets were used. All analyses were in accordance with the European Union's General Data Privacy Regulation, taking into account the theoretical concept of k-anonymity. Thus, patient informed consent was not obtained for this retrospective secondary data analysis. Our study is part of a larger project on outcomes of patients with PAOD after revascularization. Further details regarding this project can be found in the published study protocol (clinicaltrials.gov NCT03909022).[23]

### Sample and Database

The longitudinal data of Germany's second-largest insurance fund, BARMER, includes the outpatient and inpatient medical care provided to ≈9.4 million German citizens (13.2% of Germany's population) involving >21 million hospitalizations between January 1, 2008, and December 31, 2018. The BARMER cohort is similar to Western European countries and has been widely used for research projects.[24,25] A regular random sample validation of internal and

external validity is performed by the Medical Service of the Health Funds in Germany, and various peer-reviewed validation studies have been previously published.[26,27]

The diagnoses and comorbidities routinely collected in health insurance claims data follow the commonly accepted international standard for reporting diseases and health conditions using World Health Organization *International Classification of Diseases, Tenth Revision, German Modification* (*ICD-10-GM*), operations and procedures codes, and the German version of the international Anatomical Therapeutic Chemical (ATC) classification.

In our analyses, we created separate cohorts for Fontaine stage II labeling intermittent claudication (IC) and Fontaine stages III to IV labeling chronic limb-threatening ischemia (CLTI) (for detailed coding see Table S1). We included patients with a primary diagnosis of IC (I70.22 until 2014 and I70.21-22 since 2015) and CLTI (I70.22-24 until 2014 and I70.23-25 since 2015) or IC and CLTI as a secondary diagnosis in combination with a primary diagnosis of diabetic foot syndrome (E10.50-51, E10.7, E11.50-51, E11.7), other peripheral vascular diseases (I73), arterial embolism and thrombosis (I74), cellulitis of the finger and toe including acute lymphangitis (L03.01-02, L03.11), or chronic ulcer of skin and gangrene (L98.4, R02) using the *ICD-10-GM*.

The index admission for symptomatic PAOD (denoted as index stay) was identified between January 1, 2008, and December 31, 2018, with follow-up until December 31, 2018. We used 3-year lookback in the BARMER data set[26] to create relevant comorbidities (available data going back to 2005) and to ensure index admission for symptomatic PAOD.

Statin-naive patients (statins: ATC coding C10AA, C10BA, or C10BX) without statin utilization for at least 3 years before index stay were selected for inclusion in our study. We further included only patients with at least 1 prescription for an antithrombotic agent (eg, acetylsalicylic acid, clopidogrel, or oral anticoagulation) during the first quarter after discharge to prevent selection bias caused by prevalent users.[5]

The following patients were excluded: patients aged <40 years, patients with prior major amputation or recorded myopathy (outpatient or inpatient), patients discharged without revascularization (amputation only or best medical treatment only) and death, patients with major amputation, and patients with cardiovascular events (myocardial infarction, stroke or transient ischemic attack) during the first quarter after discharge. Further, we excluded patients treated with other lipid-lowering drugs than statins or statin combinations during the first quarter after discharge to ensure that all patients were eligible for statin prescription. Few cases with missing information on age, sex, or follow-up (≈0.5%) were removed using complete case deletion.

## Study Variables

We identified new users as patients filling at least 1 prescription for statins during the first quarter after index stay. Patients not filling a statin prescription during the quarter after index stay were denoted as nonusers.

The primary outcome was all-cause mortality during follow-up. In German claims data, the information about the death of the insured person is complete and validated.[27]

Secondary outcomes were incident major amputation and cardiovascular events (myocardial infarction, stroke, or transient ischemic attack), obtained from primary and secondary inpatient diagnoses.

Safety outcomes were incident diabetes mellitus and incident myopathy. Specifically, incidence was defined as first diagnosis after discharge from index stay. For assessing the risk of developing diabetes mellitus, we further excluded patients with diabetes mellitus during the 3 years before the index stay. For measuring incident outcomes, we evaluated both outpatient and inpatient diagnoses and, in the case of diabetes mellitus, also the prescription of oral and parenteral antidiabetic agents.[28] For detecting myopathy, we used the broader list of conditions previously used for the identification of statin-associated myopathy in German claims data.[29]

All outcomes were recorded at 3 months after discharge from index stay until the first event or end of study time. Follow-up times were censored after 5 years to compute robust 5-year event probabilities.

## Statistical Analysis

We summarized baseline characteristics of the patients with means and SDs for normally distributed variables, medians and interquartile ranges for non-normally distributed variables, or percentages and standardized differences for discrete variables. Cochrane Armitage trend test was used to test the change in the proportion of statin therapy over the calendar year. To balance study groups, nearest neighbor propensity score matching was applied using the following variables: discharge year; age; sex; van Walraven score: category 0 (–19 to –1 points), category 1 (0 points), category 2 (1–9 points), and category 3 (10 points and more); congestive heart failure, cardiac arrhythmias; chronic pulmonary disease; renal failure; depression; prior stroke or transient ischemic attack; smoking; obesity; prior myocardial infarction; dyslipidemia; coronary artery disease; diabetes mellitus (complicated and uncomplicated); cancer; hypertension; prior outpatient

diagnosis of PAOD; number of different prescriptions; number of previous inpatient admissions; number of prior PAOD outpatient visits; invasive procedures (peripheral vascular intervention, peripheral vascular intervention, or open-surgical revascularization); and hospital length of stay. The linear van Walraven sum score and most of the comorbidities are based on the list of Elixhauser categories, also used in various other claims data analyses.[30] We evaluated the validity of these comorbidities over time thoroughly in an earlier study.[25]

Incident diabetes mellitus was assessed in a reduced cohort additionally excluding patients with any inpatient or outpatient diagnosis of diabetes mellitus or prescription for antidiabetic agents during the 3 years before the index stay. Since this exclusion affected the balance of the study groups, we performed a second propensity score matching for this cohort (without diabetes mellitus as a matching variable).

Outcomes were estimated using Kaplan-Meier curves (with log-rank test) and Cox proportional hazards models. Using hazard ratios (HRs), we computed the 5-year probability of each outcome with 95% CIs for each study group.

For sensitivity analyses, we estimated Cox proportional hazards models in the unmatched data using the matching variables as covariates. We estimated models adjusting for co-medication during the 3 months after discharge (angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors [ATC code C09A-D], calcium channel blockers [ATC code C08], β-blockers [ATC code C07], and oral anticoagulation [ATC code B01AA, B01AE, or B01AF]), and models stratified by sex, models stratified by age [age <75 years and ≥75 years], models stratified by calendar time (2008–2012 and 2013–2018), and models stratified by statin intensity (low-to-moderate and high).

The data processing was performed with software SAS version 9.04 (SAS Institute Inc) and R software version 3.3.3 (package survival and MatchIt,[31] The R Foundation for Statistical Computing). We reported results using the Reporting of Studies Conducted Using Observational Routinely Collected Health Data statement, the Strengthening the Reporting of Observational Studies in Epidemiology statement,[32] and following international recommendations on medical device evaluation studies.[33]

# RESULTS

## Unmatched Study Sample

A total of 22 208 symptomatic patients with PAOD (22.2% with CLTI, 50.3% women; Table S2) were hospitalized during the study period from January 1, 2008, to December 31, 2018, undergoing invasive revascularization (Figure 1 and Table 1). The average age was 71.1±11.6 years (median follow-up, 1277 days; interquartile range, 616–1827). In our study sample, the annual proportion of new users after discharge increased between 2008 and 2018 from 17% to 34% in patients with CLTI ($P$<0.001) and from 22% to 43% in patients with IC ($P$<0.001) (Figure S1).

In the CLTI group, when compared with nonusers, new users were younger (71.6 versus 76.1 years), less often women (51.0% versus 55.9%), and more often smokers (18.9% versus 12.4%) (Table 1). Moreover, new users experienced fewer comorbidities, with a van Walraven score of >9 points in 29.5% versus 43.0% when compared with nonusers. Dyslipidemia was diagnosed more often in new users than in nonusers (40.5% versus 14.4%). New users were treated less frequently and less intensely before index admission with respect to the number of different prescriptions, prior PAOD outpatient diagnosis, previous inpatient admissions, and prior PAOD outpatient visits.

In the IC group, when compared with nonusers, new users were younger (66.4 versus 69.0 years) and more often smokers (25.0% versus 21.1%), but there were no sizable differences with respect to sex. New users experienced fewer comorbidities, with a van Walraven score of >9 points in 10.7% versus 17.6% when compared with nonusers. Dyslipidemia was diagnosed in 45.4% of the new users and 14.8% of the nonusers. New users were treated less frequently and less intensely before index admission with respect to the number of different prescriptions, prior PAOD outpatient diagnosis, previous inpatient admissions, and prior PAOD outpatient visits.

The proportion of patients undergoing open surgical revascularization (bypass, endarterectomy) when compared with endovascular revascularization was less prevalent in new users than in nonusers for IC (20.7% versus 27.2%).

## Matched Study Sample

Using the propensity score, we matched 10 922 patients with PAOD: 4 224 (38.7%) patients with CLTI and 6 698 patients with IC (Figure 1 and Table S3). Demographics and comorbidities of the matched study sample are presented in Table 2. In total, 89.2% new users could be matched to nonusers and no clinically relevant standardized differences among the study groups remained after matching.

## Prescription Prevalence for Statins and Antithrombotic Agents

Among 18 095 patients with CLTI and 30 424 patients with IC, 43.4% in the CLTI group and 54% in the IC group received both antithrombotics and statins after

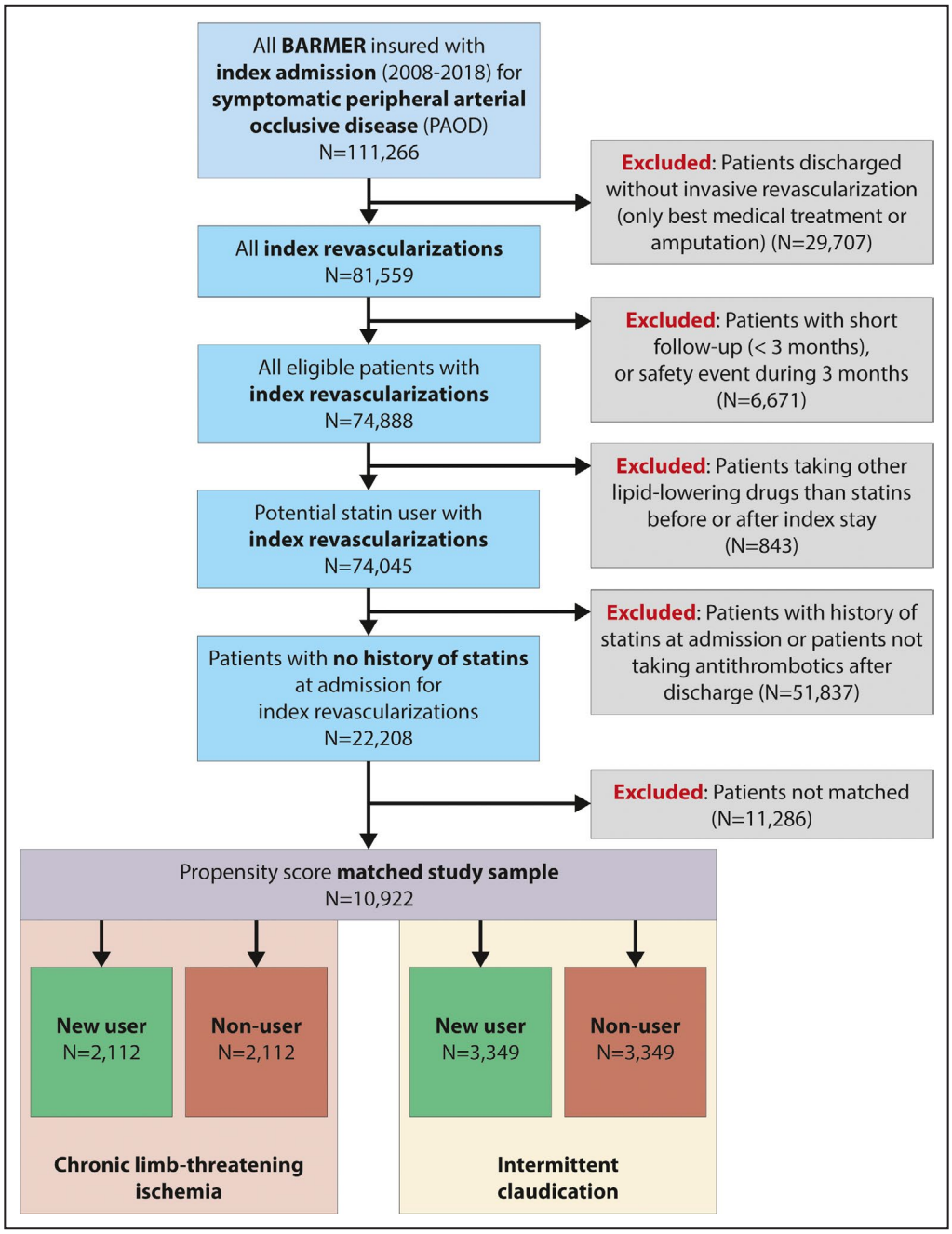


**Figure 1.** **Study flow chart.**

index stay, which was 36.4% in CLTI and 39% in IC before admission (Figure 2). Neither receiving statins before or after index stay (nonusers, red flows in Figure 2) was the case in 37.3% (18.5% with and 20.8% without antithrombotics before) of patients with CLTI and 28% (9.9% with and 18.1% without antithrombotics before) in patients with IC. Initiating statin therapy after index stay (new users, green flows in Figure 2) was the case in 13.1% (4.1% with and 9% without antithrombotics before) of patients with CLTI and 13.9% (3.4% with and 10.5% without antithrombotics before) of patients with IC.

## Independent Predictors of Receiving Statins in the Matched Study Sample

The most important predictors of initiating statin therapy in the CLTI group were dyslipidemia (odds ratio [OR], 4.50; 95% CI, 4.01–5.06), discharge year (OR, 1.10; 95% CI, 1.08–1.12), age (OR, 0.89; 95% CI, 0.87–0.92), number of different prescriptions (OR, 0.86; 95% CI, 0.82–0.89), and prior myocardial infarction (OR, 1.60; 95% CI, 1.22–2.10) (Figure S2). In the IC group, the most important predictors of initiating statin therapy were dyslipidemia (OR, 5.19; 95% CI, 4.73–5.68), discharge

**Table 1. Baseline Characteristics of the Unmatched Study Cohort (N=22 208)**

| Variable | New Users, CLTI n=2367 | Nonusers, CLTI n=7096 | Standardized Differences* | New Users, IC n=4227 | Nonusers, IC n=8518 | Standardized Differences* |
|---|---|---|---|---|---|---|
| Age, mean (SD), y | 71.64 (11.73) | 76.09 (11.52) | 0.382 | 66.44 (10.27) | 69.00 (10.70) | 0.245 |
| Women, n (%) | 1208 (51.0) | 3969 (55.9) | 0.098 | 1981 (46.9) | 4008 (47.1) | 0.004 |
| Van Walraven score >9, n (%) | 698 (29.5) | 3052 (43.0) | 0.284 | 454 (10.7) | 1503 (17.6) | 0.199 |
| Congestive heart failure, n (%) | 445 (18.8) | 1970 (27.8) | 0.213 | 275 ( 6.5) | 841 (9.9) | 0.123 |
| Cardiac arrhythmias, n (%) | 519 (21.9) | 2414 (34.0) | 0.272 | 373 ( 8.8) | 1288 (15.1) | 0.195 |
| Chronic pulmonary disease, n (%) | 302 (12.8) | 1130 (15.9) | 0.09 | 481 (11.4) | 1154 (13.5) | 0.066 |
| Renal failure, n (%) | 593 (25.1) | 2336 (32.9) | 0.174 | 511 (12.1) | 1235 (14.5) | 0.071 |
| Depression, n (%) | 176 (7.4) | 591 (8.3) | 0.033 | 196 (4.6) | 449 (5.3) | 0.029 |
| Prior stroke or TIA, n (%) | 99 (4.2) | 420 (5.9) | 0.079 | 72 (1.7) | 205 (2.4) | 0.05 |
| Smoking, n (%) | 448 (18.9) | 882 (12.4) | 0.179 | 1057 (25.0) | 1794 (21.1) | 0.094 |
| Obesity, n (%) | 206 (8.7) | 674 (9.5) | 0.028 | 304 (7.2) | 712 (8.4) | 0.044 |
| Prior myocardial infarction, n (%) | 127 (5.4) | 293 (4.1) | 0.058 | 101 (2.4) | 196 (2.3) | 0.006 |
| Dyslipidemia, n (%) | 959 (40.5) | 1023 (14.4) | 0.611 | 1919 (45.4) | 1261 (14.8) | 0.707 |
| Coronary artery disease, n (%) | 437 (18.5) | 1439 (20.3) | 0.046 | 434 (10.3) | 1132 (13.3) | 0.094 |
| Diabetes mellitus, any, n (%) | 821 (34.7) | 2658 (37.5) | 0.058 | 692 (16.4) | 1787 (21.0) | 0.118 |
| Cancer, any, n (%) | 120 ( 5.1) | 464 (6.5) | 0.063 | 166 (3.9) | 514 (6.0) | 0.097 |
| Hypertension, n (%) | 1717 (72.5) | 5413 (76.3) | 0.086 | 2771 (65.6) | 5820 (68.3) | 0.059 |
| Prior outpatient diagnosis PAOD, n (%) | 651 (27.5) | 2288 (32.2) | 0.104 | 1049 (24.8) | 2816 (33.1) | 0.183 |
| No. of different prescriptions, median (IQR) | 11.00 (5.00–17.00) | 14.00 (9.00–21.00) | 0.396 | 8.00 (5.00–13.00) | 10.00 (6.00–16.00) | 0.304 |
| No. of previous inpatient admissions, total (including index), median (IQR) | 2.00 (1.00–3.00) | 2.00 (1.00–4.00) | 0.237 | 1.00 (1.00–2.00) | 2.00 (1.00–3.00) | 0.207 |
| No. of prior PAOD outpatient visits, median (IQR) | 1.00 (0.00–3.00) | 1.00 (0.00–5.00) | 0.145 | 1.00 (0.00–2.00) | 1.00 (0.00–4.00) | 0.213 |
| Invasive procedure: OSR, n (%) | 914 (38.6) | 2714 (38.2) | 0.008 | 876 (20.7) | 2317 (27.2) | 0.152 |
| Hospital length of stay, days, median (IQR) | 12.00 (7.00–21.00) | 12.00 (7.00–22.00) | 0.009 | 4.00 (3.00–8.00) | 4.00 (3.00–9.00) | 0.082 |

CLTI indicates chronic limb-threatening ischemia; IC, intermittent claudication; IQR, interquartile range; OSR, open surgical revascularization; PAOD, peripheral arterial occlusive disease; and TIA, transient ischemic attack.

*Values >0.1 were deemed to indicate meaningful differences.

year (OR, 1.10; 95% CI, 1.08–1.11), age (OR, 0.92; 95% CI, 0.90–0.94), number of different prescriptions (OR, 0.88; 95% CI, 0.85–0.91), and open surgical repair at index stay (OR, 0.68; 95% CI, 0.61–0.77) (Figure S3).

## Long-Term Effectiveness Outcomes in the Matched Study Sample

Compared with nonusers, both in the CLTI and the IC groups, new users had a significant lower probability for all-cause mortality (for CLTI: HR, 0.75 [95% CI, 0.68–0.84]; for IC: HR, 0.80 [95% CI, 0.70–0.92]) (Table 3). Further, statin initiation was associated with a lower risk of major amputation (HR, 0.73; 95% CI, 0.58–0.93) in CLTI and a lower risk for cardiovascular events (HR, 0.80; 95% CI, 0.70–0.92) in IC. In absolute terms, statin initiation was associated with 8.8% lower probability of dying in the CLTI group (37.3% versus 46.1%) and 3.4% lower probability of dying in the IC group (15.5% versus 18.9%). The survival benefit of new users compared with nonusers increased over time in CLTI and was stable in IC (Figure 3). The probability for major amputation was 2.9% lower in the CLTI group (8.4% versus 11.3%) and for cardiovascular events was 3.3% lower in the IC group (15.2% versus 18.5%). The amputation benefit in CLTI increased over time (Figure S4), while the benefit in respect to cardiovascular events in IC was stable (Figure 3).

## Long-Term Safety Outcomes in the Reduced Matched Study Sample

We did not detect significant differences in the probability for incident diabetes mellitus (in the reduced sample) or myopathy between the study groups (Table 3 and Figure S4).

## Sensitivity Analyses

The results for effectiveness outcomes and safety outcomes were largely similar when fitting the Cox models directly to the unmatched data (Figure S5).

**Table 2. Baseline Characteristics of the Matched Study Cohort (N=10 922)**

| Variable | New Users, CLTI n=2112 | Nonusers, CLTI n=2112 | Standardized Differences* | New Users, IC n=3349 | Nonusers, IC n=3349 | Standardized Differences* |
|---|---|---|---|---|---|---|
| Age, mean (SD), y | 72.52 (11.64) | 72.67 (12.05) | 0.012 | 67.10 (10.31) | 67.34 (10.47) | 0.023 |
| Women, n (%) | 1100 (52.1) | 1106 (52.4) | 0.006 | 1564 (46.7) | 1589 (47.4) | 0.015 |
| Van Walraven score >9, n (%) | 673 (31.9) | 723 (34.2) | 0.05 | 411 (12.3) | 438 (13.1) | 0.024 |
| Congestive heart failure, n (%) | 422 (20.0) | 444 (21.0) | 0.026 | 251 (7.5) | 263 (7.9) | 0.013 |
| Cardiac arrhythmias, n (%) | 494 (23.4) | 555 (26.3) | 0.067 | 334 (10.0) | 369 (11.0) | 0.034 |
| Chronic pulmonary disease, n (%) | 279 (13.2) | 280 (13.3) | 0.001 | 403 (12.0) | 405 (12.1) | 0.002 |
| Renal failure, n (%) | 562 (26.6) | 602 (28.5) | 0.042 | 417 (12.5) | 428 (12.8) | 0.01 |
| Depression, n (%) | 161 (7.6) | 170 (8.0) | 0.016 | 161 (4.8) | 157 (4.7) | 0.006 |
| Prior stroke or TIA, n (%) | 96 (4.5) | 111 (5.3) | 0.033 | 62 (1.9) | 69 (2.1) | 0.015 |
| Smoking, n (%) | 362 (17.1) | 354 (16.8) | 0.01 | 794 (23.7) | 804 (24.0) | 0.007 |
| Obesity, n (%) | 192 (9.1) | 189 (8.9) | 0.005 | 249 (7.4) | 263 (7.9) | 0.016 |
| Prior myocardial infarction, n (%) | 111 (5.3) | 116 (5.5) | 0.01 | 76 (2.3) | 79 (2.4) | 0.006 |
| Dyslipidemia, n (%) | 705 (33.4) | 714 (33.8) | 0.009 | 1041 (31.1) | 1046 (31.2) | 0.003 |
| Coronary artery disease, n (%) | 387 (18.3) | 425 (20.1) | 0.046 | 369 (11.0) | 393 (11.7) | 0.023 |
| Diabetes mellitus, any, n (%) | 741 (35.1) | 771 (36.5) | 0.03 | 591 (17.6) | 586 (17.5) | 0.004 |
| Cancer, any, n (%) | 114 (5.4) | 120 (5.7) | 0.012 | 138 (4.1) | 149 (4.4) | 0.016 |
| Hypertension, n (%) | 1539 (72.9) | 1567 (74.2) | 0.03 | 2182 (65.2) | 2227 (66.5) | 0.028 |
| Prior outpatient diagnosis PAOD, n (%) | 604 (28.6) | 626 (29.6) | 0.023 | 900 (26.9) | 976 (29.1) | 0.051 |
| No. of different prescriptions, median (IQR) | 11.00 (6.00–18.00) | 12.00 (7.00–18.00) | 0.043 | 9.00 (5.00–14.00) | 9.00 (5.00–14.00) | 0.038 |
| No. of previous inpatient admissions, total (including index), median (IQR) | 2.00 (1.00–3.00) | 2.00 (1.00–3.00) | 0.033 | 1.00 (1.00–2.00) | 1.00 (1.00–2.00) | 0.027 |
| No. of prior PAOD outpatient visits, median (IQR) | 1.00 (0.00–3.00) | 1.00 (0.00–4.00) | 0.022 | 1.00 (0.00–3.00) | 1.00 (0.00–3.00) | 0.054 |
| Invasive procedure: OSR, n (%) | 816 (38.6) | 779 (36.9) | 0.036 | 747 (22.3) | 783 (23.4) | 0.026 |
| Hospital length of stay, days, median (IQR) | 12.00 (7.00–22.00) | 12.00 (7.00–22.00) | 0.008 | 4.00 (3.00–8.00) | 4.00 (3.00–8.00) | 0.007 |

CLTI indicates chronic limb-threatening ischemia; IC, intermittent claudication; IQR, interquartile range; OSR, open surgical revascularization; PAOD, peripheral arterial occlusive disease; and TIA, transient ischemic attack.

*Values >0.1 were deemed to indicate meaningful differences.

Without adjustment for confounding, statin users had even more favorable effectiveness outcomes, but safety outcomes were hardly affected. The effect of statins was robust to the inclusion of other important medication groups, ie, angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors, calcium channel blockers, β-blockers, or oral anticoagulation (Figure S6). The effect of statins did not significantly differ between men and women, except for amputation in patients with CLTI (HR in women: 0.54 [95% CI, 0.29–0.76]; HR in men: 1.10 [95% CI, 0.85–1.42]) (Figure S7). Stratifying the analysis by age revealed that older patients (≥75 years) benefit most from initiating statins for survival and diabetes mellitus in patients with IC (Figure S8). Further, there were no sizeable differences when stratifying by discharge years (Figure S9). The same was true for statin intensity (patients taking high-intensity statins: n=415, 6.2%), where the CIs for low-to-moderate intensity and high-intensity statins overlapped for all outcomes (Figure S10). We found a significant association between high-intensity statin use and myopathy in patients with IC. No differences were detected when stratifying by procedure type at index stay (Figure S11).

## DISCUSSION

This is the first real-world study assessing the effectiveness and safety of initiating statin therapy in symptomatic patients with PAOD after revascularization in a large nationwide cohort. Compared with nonusers, new users of statin therapy had a considerably lower relative and absolute probability of all-cause mortality in both CLTI and IC, major amputation in CLTI, and cardiovascular events in IC. At the same time, the

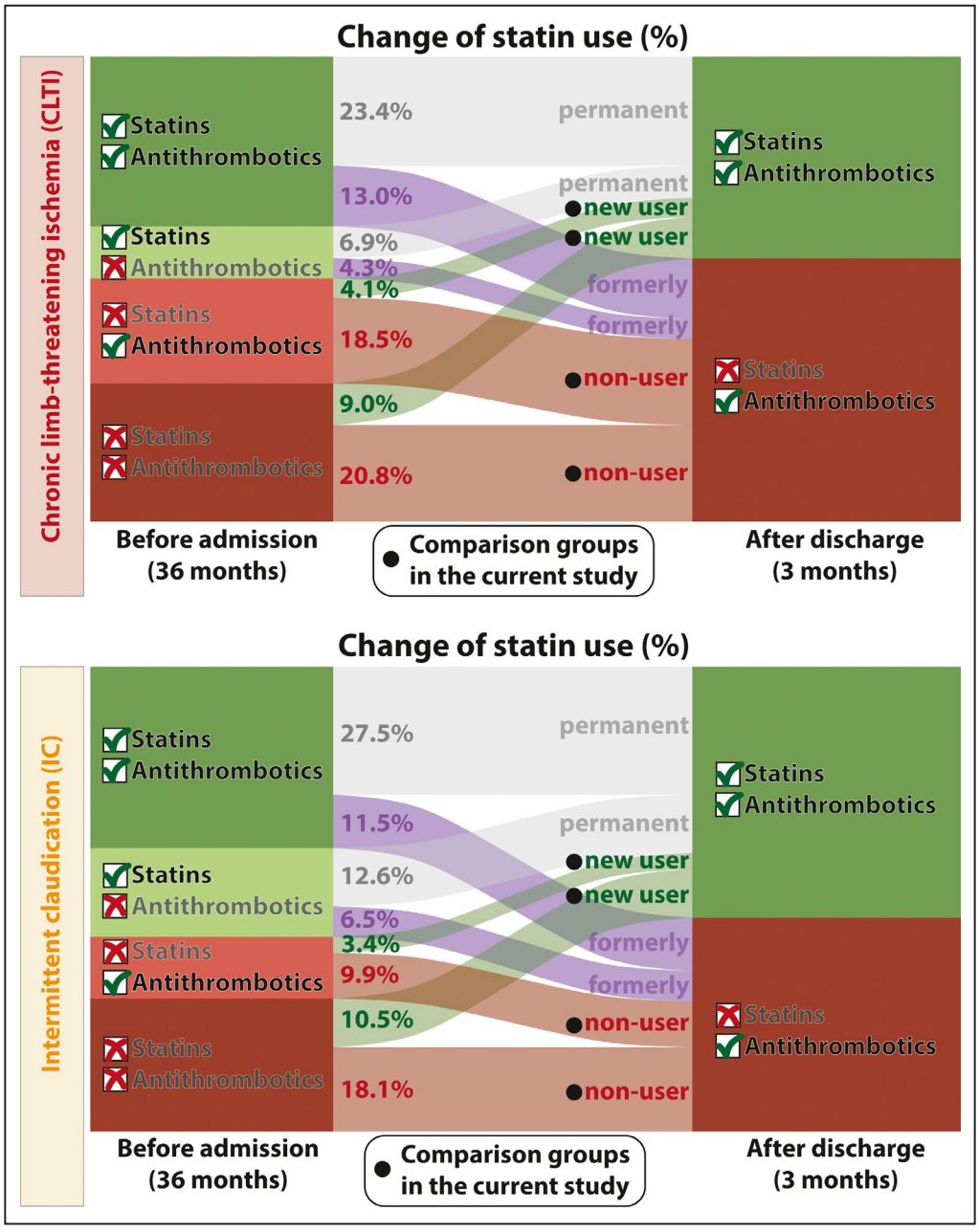


**Figure 2. Alluvial diagram illustrating the proportion of new users and nonusers (n=9 463 patients with chronic limb-threatening ischemia [CLTI] and n=12 745 patients with intermittent claudication [IC]) among all statin users meeting the inclusion criteria of the study also showing formerly and permanent use (n=18 095 patients with CLTI and n=30 424 patients with IC).**
Shown is the frequency of statin therapy and prescription of antithrombotics during the 3 years before and 3 months after index revascularization for symptomatic peripheral arterial occlusive disease.

incidence of diabetes mellitus and myopathy was not associated with new statin prescription. As same as that documented in primary prevention,[34] we found no evidence for the assumption that new patient groups benefit less from statins, emphasizing the importance of quality improvement and awareness campaigns to further promote their prescription.

Valid guidelines call for more evidence on the comparative effectiveness of pharmacological therapy along the full spectrum of clinical reality.[35] Yet, existing real-world evidence stems from smaller randomized controlled trials with short follow-up or observational studies based on smaller registries, single centers, geographic regions, or predominantly male patients. The particular merit of routinely collected data from health insurance claims is the large sample size, long follow-up, and high variety and completeness of information available to adjust for confounding allowing

**Table 3. Probability of Experiencing the Outcomes of Interest Within 5 Years After Index Revascularization in New Users Versus Nonusers of Statin Therapy**

| Strata | Outcomes of Interest | Probability for New Users (95% CI) | Probability for Nonusers (95% CI) | HR (95% CI) | No. | Events |
|---|---|---|---|---|---|---|
| CLTI | All-cause mortality | 37.3 (34.8–39.7) | 46.1 (43.5–48.6) | 0.75 (0.68–0.84) | 4224 | 1315 |
| CLTI | Major amputation | 8.4 (6.9–9.9) | 11.3 (9.5–13.1) | 0.73 (0.58–0.93) | 4224 | 278 |
| CLTI | Myocardial infarction/stroke/TIA | 23.3 (21.0–25.6) | 25.7 (23.2–28.1) | 0.89 (0.77–1.04) | 4224 | 658 |
| CLTI | Diabetes mellitus | 20.3 (17.1–23.3) | 20.8 (17.5–23.9) | 0.97 (0.77–1.23) | 2232 | 284 |
| CLTI | Myopathy | 4.6 (3.4–5.8) | 4.0 (2.9–5.2) | 1.15 (0.79–1.67) | 4224 | 109 |
| IC | All-cause mortality | 15.5 (14.0–17.0) | 18.9 (17.3–20.5) | 0.80 (0.70–0.92) | 6698 | 805 |
| IC | Major amputation | 1.5 (1.0–2.0) | 1.6 (1.1–2.1) | 0.93 (0.58–1.49) | 6698 | 70 |
| IC | Myocardial infarction/stroke/TIA | 15.2 (13.7–16.6) | 18.5 (16.9–20.1) | 0.80 (0.70–0.92) | 6698 | 788 |
| IC | Diabetes mellitus | 15.0 (13.2–16.7) | 15.2 (13.3–16.9) | 0.99 (0.83–1.18) | 4678 | 490 |
| IC | Myopathy | 6.5 (5.5–7.5) | 5.4 (4.5–6.4) | 1.21 (0.96–1.52) | 6698 | 287 |

CLTI indicates chronic limb-threatening ischemia; HR, hazard ratio; IC, intermittent claudication; and TIA, transient ischemic attack. All estimates are based on Cox proportional hazards models using the matched data.

study of the full heterogeneity of patients in daily care. Especially, rare and potentially late outcomes, such as major amputations and the incidence of myopathy and diabetes mellitus, could be analyzed with sufficient statistical power.[36,37] We included these safety outcomes, while prior studies focused mostly on effectiveness. Yet, our study present the central findings both for absolute and relative risk differentials. Furthermore, we used both inpatient and outpatient data, and, for the detection of incident diabetes mellitus, corresponding prescriptions. The long lookback and follow-up periods made it possible to minimize the risk of not detecting a large portion of adverse reactions.

Among patients not on statin therapy before index stay, the proportion of statin therapy after index stay doubled during the study period. Yet, still less than half of the patients received statins in 2018, with particularly low rates among patients with CLTI. These interesting and striking results are in line with a previous study concerning sex disparities in optimal pharmacological treatment of symptomatic patients with PAOD in Germany, where only 55% of the patients received a lipid-lowering drug. Notably, there was also preliminary evidence that patient characteristics (eg, age, sex, and comorbidities) were more influential than healthcare variables such as the type of revascularization procedure.[38] Because of the nonrandomized observational study design, all results should be considered as merely hypothesis generating. Hence, it appears challenging to explain the low utilization of statins before as well as after revascularization. Unwarranted variation in best medical treatment can be attributable to a lack of high-level evidence or insufficient application of existing evidence. In terms of statins, similar to antithrombotics, there is good evidence available from many international guidelines.[2,6,7] The relationship between patients, inpatient physicians, and general practitioners is likely affected by a multifactorial system of influencing factors. It seems reasonable to address this healthcare issue with awareness campaigns and actions to improve both prescription prevalence and patient compliance.

Our results confirm findings from a large Swedish cohort study reporting higher statin utilization in patients with IC than in patients with CLTI.[39] Stavroulakis et al[40] presumed that the insufficient use in patients with CLTI might be caused by the paucity of evidence on the benefits of statins with regard to limb outcomes. At the same time, the evidence is accumulating that the walking distance in patients with IC could be positively influenced.[41]

Internationally, large variations in statin utilization rates have been documented, pointing at the role of national healthcare systems (prescription patterns and regulations). For example, only 21% of patients with CLTI in Japan with below-the-knee lesions received statins,[42] while 83% received statins in the US Veterans Affairs Health System.[18] Prescription rates probably differ between reimbursement systems. In Germany, during the study period, medications were solely prescribed within the outpatient sector while hospital physicians communicate their recommendations in the medical report at discharge. Despite continuous efforts in raising awareness for this issue,[17] missed opportunities caused by low undertreatment of patients with PAOD remain.[11]

Recently, Arya et al[18] reported a reduction in all-cause mortality and amputation-free survival of ≈20% for low-to-moderate statins compared with antiplatelets only, which is in line with our findings. Interestingly, our sensitivity analyses suggest that in patients with CLTI, women seem to benefit to a larger extent from

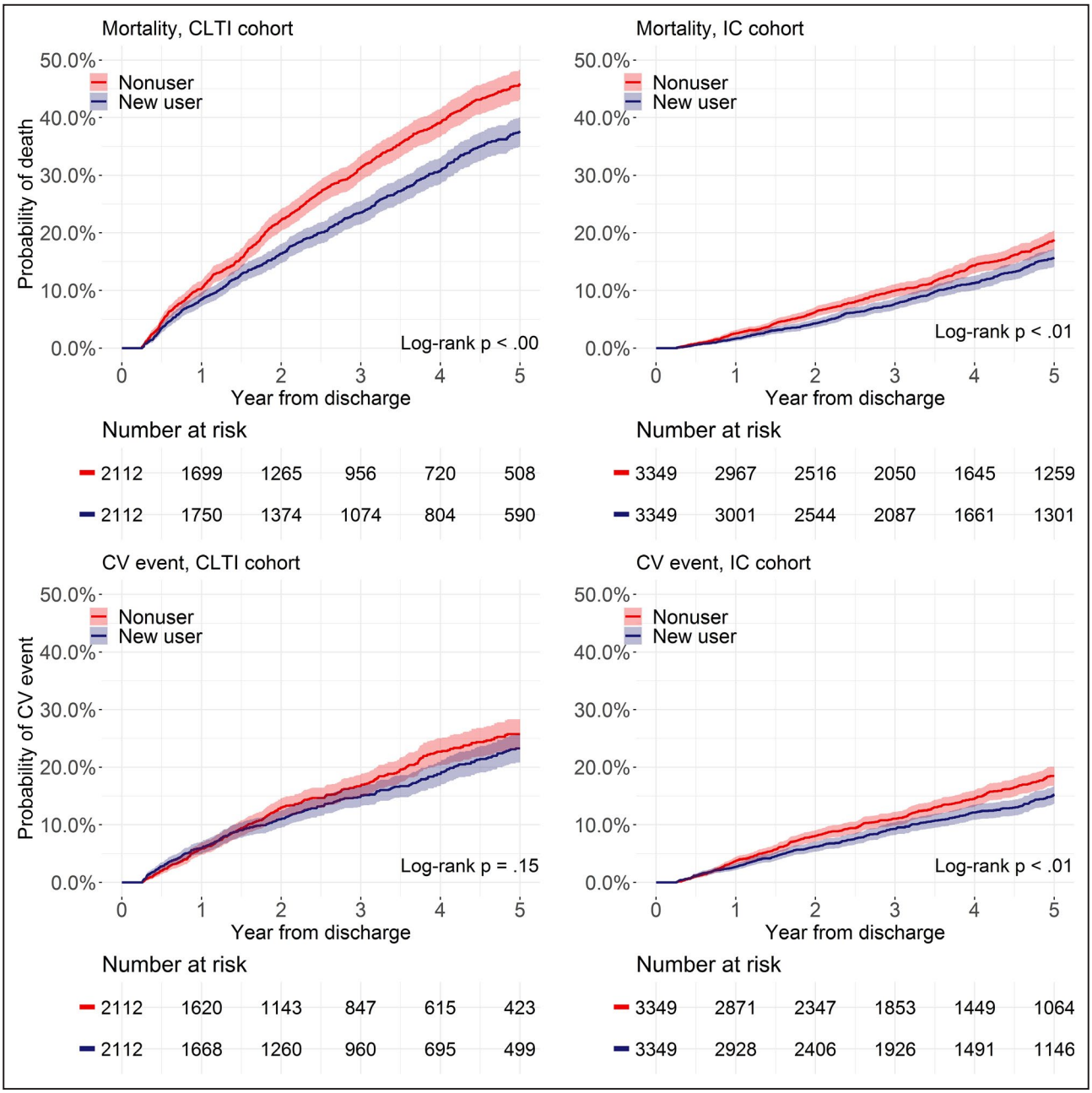


**Figure 3. Kaplan-Meier curve of 5-year all-cause mortality (upper panel) and 5-year probability for cardiovascular event (myocardial infarction, stroke, or transient ischemic attack; lower panel) in propensity score–matched cohorts including 95% Wald CI and log-rank test (*P* value).**
CLTI indicates chronic limb-threatening ischemia; and IC, intermittent claudication.

statin initiation when compared with men concerning amputation risk. Women were diagnosed more often with asymptomatic or even atypical disease symptoms without appropriate and timely treatment.[43] Thus, they might be more dependent on adequate secondary prevention for preventing severe limb outcomes when compared with their male counterparts.

Statins significantly reduced the risk for major cardiovascular events in most prior studies ranging from reductions in event rates between 10% and 62% (Table S4). Confirming prior reports, our results for the subgroup of patients with IC are situated in the lower end of this range, while the effects were nonsignificant in patients with CLTI. Reports from Swedish patients with PAOD who underwent revascularization also documented more pronounced effects in the IC group than in the CLTI group.[39]

Although many potential adverse reactions have been presumed in the literature, we focused on the established safety outcomes of incident myopathy

and diabetes mellitus.[37] Our study results are in line with prior evidence on the safety of statin therapy in patients with PAOD.[19] Collins et al[37] estimated a minor incident diabetes mellitus risk of ≈1% for a more general population. Moreover, recent guidelines state that the frequency of statin-induced diabetes mellitus strongly depends on the study sample.[44] For example, we even documented a tendency for lowered diabetes mellitus risk for statin initiation among patients with IC aged ≥75 years. This seems to contradict prior evidence, and future studies may focus on the role of age as a modifier in the relationship between diabetes mellitus and statins. Also based on German claims data, Ihle et al[29] reported ≈2% of statin-induced myopathy while Collins et al[37] presumed 0.05%. In our study, the increase in risk ranged in between these estimates with 1.1% in patients with IC and 0.6% in patients with CLTI, and both values being nonsignificant in the final analysis. Interestingly, we detected a significant association between statins and myopathy only for high-intensity statin users in patients with IC in our sensitivity analysis (HR, 2.00; 95% CI, 1.17–3.41). This might be a plausible finding and proof of a dose relationship, as statin toxicity indeed increases with statin dose.[45]

## Study Limitations

This is a retrospective propensity score–matched health insurance claims data analysis, so there is no possibility to randomize patients and observe them prospectively. Consequently, the results of this study should be viewed as hypothesis generating and not hypothesis testing. Our propensity score analysis can prevent bias but not fully exclude all sources of bias and residual confounding, eg, that caused by confounding by indication, as compared with randomization. The study groups differed with respect to some of the measured covariates, so that differences in unobserved characteristics that likely confounded our results cannot be ruled out. Yet, as is the case for randomized controlled trials, the quality of observational studies is crucial for assessing the validity of their outcomes. This study applied a rigorous study design with fixed lookback and follow-up, approved methods, transparent reporting of intermediate steps, and extensive sensitivity analyses. We believe that the risk for distortion caused by residual confounding is low in our study since results are broadly in line with findings from randomized controlled trials and prior observational studies (Table S4). Our sample covered only patients insured at one of many different health insurance funds in Germany. Although slightly different from the population composition in Germany,[46] our population-based sample is comparable to current European populations. We, therefore, believe that our results exhibit a larger degree of external validity than veteran data, more narrowly defined subgroups in trials or data from small regional registries or single-center studies. We were not able to address all contraindications, statin intolerance, or other adverse reactions. However, the prevalence of intolerance is unlikely to be larger than a few percent, as previous studies in patients with PAOD have demonstrated. It is therefore unlikely a potential explanation for the low utilization of statin therapy.[5]

The inexistent association of statin use and diabetes mellitus or myopathy risk in our study sample might be caused by insufficiently differentiating by statin type. Since statins differ, inter alia, in derivation and metabolism, varying strengths and limitations of each drug are possible in heterogeneous study populations.[47] To ensure that every patient receives the safest and most effective statin, further investigations stratified by the drug, regarding risk factors in distinct patient groups, are necessary to increase adherence and avert discontinuation.

# CONCLUSIONS

We documented increased long-term survival and freedom from amputation and cardiovascular events for initiating statin therapy after revascularization. At the same time, safety concerns about the onset of diabetes mellitus and myopathy could not be confirmed. Our findings indicate that new users of statin therapy benefit as much as common users, emphasizing the importance of quality improvement and awareness campaigns to improve prescription rates.

## ARTICLE INFORMATION

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## Disclosures

None.

## Supplementary Material

**Tables S1–S4**
**Figures S1–S11**
**References 48-71**

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# Supplementary Material

# Long-term efficacy and safety of initiating statin therapy after index revascularization in patients with peripheral arterial occlusive disease

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# Supplemental Material

*Table S1: International classification of diseases (ICD) 10th revision, operational and procedure coding (OPS), and anatomical-therapeutical-chemical (ATC) classification used for this study. TIA: Transient ischemic attack*

| Variable | ICD code (or OPS or ATC if indicated) |
|---|---|
| Symptomatic peripheral arterial occlusive disease | **<2015**:<br>I70.21 Pelvic-leg arteries with exercise induced pain, walking distance < 200m, **Fontaine stage II**<br>I70.22 Pelvic-leg arteries with rest pain, **Fontaine stage III**<br>I70.23-24 Pelvic-leg arteries with ulcerations and/or gangrene, **Fontaine stage IV**<br>**≥ 2015**:<br>I70.21-22 Pelvic-leg arteries with exercise induced pain, **Fontaine stage II**<br>I70.23 Pelvic-leg arteries with rest pain, **Fontaine stage III**<br>I70.24-25 Pelvic-leg arteries with ulcerations and/or gangrene, **Fontaine stage IV**<br>**Others**:<br>E10.50-51 Type 1 diabetes mellitus with peripheral vascular complications<br>E10.7 Type 1 diabetes mellitus with diabetic foot syndrome<br>E11.50-51 Type 2 diabetes mellitus with peripheral vascular complications<br>E11.7 Type 2 diabetes mellitus with diabetic foot syndrome<br>I73.0 Other peripheral vascular diseases, Raynaud syndrome<br>I73.1 Other peripheral vascular diseases, Thrombangiitis obliterans<br>I73.8 Other peripheral vascular diseases<br>I73.9 Other peripheral vascular diseases<br>I74.0 Arterial embolism and thrombosis, aorta abdominalis<br>I74.1 Arterial embolism and thrombosis, aorta<br>I74.2 Arterial embolism and thrombosis, upper extremities<br>I74.3 Arterial embolism and thrombosis, lower extremities<br>I74.4 Arterial embolism and thrombosis, arteries of the extremities<br>I74.5 Arterial embolism and thrombosis, aorta iliacal<br>I74.8 Arterial embolism and thrombosis, other arteries<br>I74.9 Arterial embolism and thrombosis, other arteries<br>L03.01-2, L03.11 Cellulitis of finger and toe including acute lymphangitis<br>L98.4 Chronic ulcer of skin, not elsewhere classified<br>R02 Gangrene, not elsewhere classified |
| **Medications** | |
| Lipid lowering drugs | ATC C10 |
| Statins | C10AA, C10BA, C10BX |
| Antithrombotics | B01 |
| Antidiabetics | A10 |
| **Angiotensin II receptor blockers or angiotensin-converting-enzyme inhibitors** | C09A-D |
| **Calcium channel blockers** | C08 |
| **Beta-blockers** | C07 |
| **Oral anticoagulation** | B01AA, B01AE, B01AF |
| **Covariates** | |
| Stroke or TIA | I61, I63, I64, G45 |
| Dyslipidemia | E78 |
| Coronary artery disease | I20-25 |
| Smoking | F17 |
| Myocardial infarction | I20.0, I21-I24 |
| Cancer | Metastatic cancer: C77–C80 and solid tumor without metastasis: C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C97 |
| Polypharmacy | Number of different prescriptions during year prior to index admission |
| Procedure | Amputation, peripheral vascular intervention, open surgical revascularization |
| Amputation | OPS 5-864 Major amputation, above the ankle<br>5-865 Minor amputation, below the ankle |
| Peripheral vascular intervention | 8-836, 8-840, 8-841, 8-842, 8-843, 8-844, 8-845, 8-846, 8-847, 8-848, 8-849, 8-83c, 8-84a |
| Open surgical revascularization | 5-380, 5-381, 5-382, 5-383, 5-384, 5-38a.4, 5-38a.c, 5-38c, 5-38d, 5-38e, 5-38f, 5-393, 5-394, 5-395, 5-396, 5-98a |
| **Outcomes** | |
| Major amputation | OPS 5-864 |
| Cardiovascular event | I20.0, I21-I24 Myocardial infarction, I61, I63, I64, G45 stroke/TIA |
| Incident diabetes | E10, E11, E12, E13, E14 or ATC A10 |
| Incident myopathy | G72.0, G72.8, G72.9, M60.8, M60.9, M79.1 |

*Table S2: Baseline characteristics of the unmatched study cohort excluding patients with prior diagnosis of diabetes and myopathy (N=13,561). (SD: Standard deviation; IQR: Interquartile range; PAOD: Peripheral arterial occlusive disease; TIA: Transient ischemic attack; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; OSR: Open surgical revascularization; Std. Diffs: Standardized differences (values above 0.1 deemed to indicate meaningful differences)*

| Variable | New user, CLTI N=1293 | Nonuser, CLTI N=3645 | Std. Diffs. | New user, IC N=3031 | Nonuser, IC N=5592 | Std. Diffs. |
|---|---|---|---|---|---|---|
| Age, years, mean (SD) | 71.15 (12.23) | 75.59 (12.19) | 0.364 | 65.82 (10.32) | 68.23 (10.91) | 0.227 |
| Female sex, n (%) | 703 (54.4) | 2208 (60.6) | 0.126 | 1457 (48.1) | 2788 (49.9) | 0.036 |
| Van Walraven Score >9, n (%) | 328 (25.4) | 1427 (39.1) | 0.298 | 276 ( 9.1) | 859 (15.4) | 0.192 |
| Congestive heart failure, n (%) | 191 (14.8) | 840 (23.0) | 0.212 | 157 ( 5.2) | 454 ( 8.1) | 0.118 |
| Cardiac arrhythmias, n (%) | 247 (19.1) | 1099 (30.2) | 0.259 | 226 ( 7.5) | 746 (13.3) | 0.194 |
| Chronic pulmonary disease, n (%) | 167 (12.9) | 635 (17.4) | 0.126 | 341 (11.3) | 769 (13.8) | 0.076 |
| Renal failure, n (%) | 256 (19.8) | 967 (26.5) | 0.16 | 289 ( 9.5) | 653 (11.7) | 0.07 |
| Depression, n (%) | 96 ( 7.4) | 283 ( 7.8) | 0.013 | 139 ( 4.6) | 293 ( 5.2) | 0.03 |
| Prior stroke or TIA, n (%) | 46 ( 3.6) | 194 ( 5.3) | 0.086 | 47 ( 1.6) | 117 ( 2.1) | 0.041 |
| Smoking, n (%) | 301 (23.3) | 576 (15.8) | 0.189 | 817 (27.0) | 1287 (23.0) | 0.091 |
| Obesity, n (%) | 53 ( 4.1) | 218 ( 6.0) | 0.086 | 163 ( 5.4) | 327 ( 5.8) | 0.02 |
| Prior myocardial infarction, n (%) | 59 ( 4.6) | 113 ( 3.1) | 0.076 | 63 ( 2.1) | 117 ( 2.1) | 0.001 |
| Dyslipidemia, n (%) | 517 (40.0) | 462 (12.7) | 0.652 | 1343 (44.3) | 760 (13.6) | 0.72 |
| Coronary artery disease, n (%) | 191 (14.8) | 611 (16.8) | 0.055 | 255 ( 8.4) | 640 (11.4) | 0.102 |
| Diabetes, any, n (%) | 27 ( 2.1) | 100 ( 2.7) | 0.043 | 30 ( 1.0) | 60 ( 1.1) | 0.008 |
| Cancer, any, n (%) | 65 ( 5.0) | 245 ( 6.7) | 0.072 | 120 ( 4.0) | 328 ( 5.9) | 0.088 |
| Hypertension, n (%) | 879 (68.0) | 2614 (71.7) | 0.081 | 1878 (62.0) | 3585 (64.1) | 0.045 |
| Prior outpatient diagnosis PAOD, n (%) | 261 (20.2) | 907 (24.9) | 0.113 | 624 (20.6) | 1663 (29.7) | 0.212 |
| No of different prescriptions, median (IQR) | 9.00 (5.00, 15.00) | 12.00 (7.00, 19.00) | 0.386 | 7.00 (4.00, 12.00) | 9.00 (5.00, 15.00) | 0.275 |
| No of previous inpatient admissions, total (incl. index), median (IQR) | 1.00 (1.00, 3.00) | 2.00 (1.00, 4.00) | 0.25 | 1.00 (1.00, 2.00) | 1.00 (1.00, 3.00) | 0.216 |
| No of prior PAOD outpatient visits, median (IQR) | 0.00 (0.00, 2.00) | 1.00 (0.00, 2.00) | 0.129 | 1.00 (0.00, 2.00) | 1.00 (0.00, 3.00) | 0.237 |
| Invasive procedure: OSR, n (%) | 558 (43.2) | 1579 (43.3) | 0.003 | 628 (20.7) | 1579 (28.2) | 0.176 |
| Hospital length of stay, days, median (IQR) | 11.00 (6.00, 19.00) | 12.00 (7.00, 20.00) | 0.056 | 4.00 (3.00, 7.00) | 4.00 (3.00, 8.00) | 0.08 |

*Table S3: Baseline characteristics of the matched study cohort excluding patients with prior diagnosis of diabetes or myopathy (N=6910). (SD: Standard deviation; IQR: Interquartile range; PAOD: Peripheral arterial occlusive disease; TIA: Transient ischemic attack; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; OSR: Open surgical revascularization; Std. Diffs: Standardized differences (values above 0.1 deemed to indicate meaningful differences)*

| Variable | New user, CLTI N=1116 | Nonuser, CLTI N=1116 | Std. Diffs. | New user, IC N=2339 | Nonuser, IC N=2339 | Std. Diffs. |
|---|---|---|---|---|---|---|
| Age, years, mean (SD) | 71.97 (12.24) | 72.12 (12.65) | 0.012 | 66.33 (10.38) | 66.88 (10.72) | 0.052 |
| Female sex, n (%) | 616 (55.2) | 621 (55.6) | 0.009 | 1120 (47.9) | 1157 (49.5) | 0.032 |
| Discharge year, mean (SD) | 303 (27.2) | 312 (28.0) | 0.018 | 246 (10.5) | 279 (11.9) | 0.045 |
| Van Walraven Score >9, n (%) | 174 (15.6) | 167 (15.0) | 0.017 | 139 ( 5.9) | 154 ( 6.6) | 0.026 |
| Congestive heart failure, n (%) | 230 (20.6) | 241 (21.6) | 0.024 | 205 ( 8.8) | 213 ( 9.1) | 0.012 |
| Cardiac arrhythmias, n (%) | 154 (13.8) | 170 (15.2) | 0.041 | 279 (11.9) | 286 (12.2) | 0.009 |
| Chronic pulmonary disease, n (%) | 233 (20.9) | 226 (20.3) | 0.016 | 231 ( 9.9) | 266 (11.4) | 0.049 |
| Renal failure, n (%) | 87 ( 7.8) | 81 ( 7.3) | 0.02 | 110 ( 4.7) | 139 ( 5.9) | 0.055 |
| Depression, n (%) | 44 ( 3.9) | 51 ( 4.6) | 0.031 | 40 ( 1.7) | 39 ( 1.7) | 0.003 |
| Prior stroke or TIA, n (%) | 238 (21.3) | 236 (21.1) | 0.004 | 613 (26.2) | 617 (26.4) | 0.004 |
| Smoking, n (%) | 50 ( 4.5) | 66 ( 5.9) | 0.065 | 129 ( 5.5) | 134 ( 5.7) | 0.009 |
| Obesity, n (%) | 43 ( 3.9) | 52 ( 4.7) | 0.04 | 48 ( 2.1) | 48 ( 2.1) | <0.001 |
| Prior myocardial infarction, n (%) | 341 (30.6) | 344 (30.8) | 0.006 | 651 (27.8) | 656 (28.0) | 0.005 |
| Dyslipidemia, n (%) | 160 (14.3) | 176 (15.8) | 0.04 | 217 ( 9.3) | 222 ( 9.5) | 0.007 |
| Coronary artery disease, n (%) | 24 ( 2.2) | 29 ( 2.6) | 0.029 | 26 ( 1.1) | 17 ( 0.7) | 0.04 |
| Diabetes, any, n (%) | 59 ( 5.3) | 68 ( 6.1) | 0.035 | 98 ( 4.2) | 106 ( 4.5) | 0.017 |
| Cancer, any, n (%) | 753 (67.5) | 766 (68.6) | 0.025 | 1440 (61.6) | 1488 (63.6) | 0.042 |
| Hypertension, n (%) | 235 (21.1) | 230 (20.6) | 0.011 | 531 (22.7) | 539 (23.0) | 0.008 |
| Prior outpatient diagnosis PAOD, n (%) | 10.00 (5.00, 16.00) | 10.00 (5.00, 16.00) | 0.059 | 8.00 (4.00, 12.00) | 8.00 (5.00, 13.00) | 0.051 |
| No of different prescriptions, median (IQR) | 2.00 (1.00, 3.00) | 2.00 (1.00, 3.00) | 0.014 | 1.00 (1.00, 2.00) | 1.00 (1.00, 2.00) | 0.045 |
| No of previous inpatient admissions, total (incl. Index), median (IQR) | 0.00 (0.00, 2.00) | 0.00 (0.00, 2.00) | 0.009 | 1.00 (0.00, 2.00) | 1.00 (0.00, 2.00) | 0.014 |
| No of prior PAOD outpatient visits, median (IQR) | 485 (43.5) | 477 (42.7) | 0.014 | 525 (22.4) | 561 (24.0) | 0.036 |
| Invasive procedure: OSR, n (%) | 11.00 (6.00, 19.00) | 11.00 (6.00, 19.00) | 0.018 | 4.00 (3.00, 8.00) | 4.00 (3.00, 8.00) | 0.017 |
| Hospital length of stay, days, median (IQR) | 1164.00 (582.50, 1827.00) | 1034.50 (486.25, 1827.00) | 0.12 | 1418.00 (741.50, 1827.00) | 1393.00 (726.50, 1827.00) | 0.015 |

*Table S4: Main studies (References main text: 18-21, 34, 39, 40, 42) on effectiveness and safety of statins in patients. PAOD: Peripheral arterial occlusive disease; IC: Intermittent claudication; CLTI: Critical limb threatening ischemia; AFS: Amputation-free survival; HR: Hazard ratio; OR: Odds ratio; RR: Risk ratio; IRR: Incidence Rate ratio; RCT: Randomized controlled trial; obs: Observational study; meta: Meta-analysis; HI: High-intensity; DM: Diabetes mellitus; N/A: Not applicable; n.s.: Not significant*

| Author | Year | Type | Country | N | Exposure | Age, mean years | Female | Patients with PAOD | IC | CLTI | Follow-up, years | Prevalence statins | HR, Survival | HR, Major vascular event | HR, AFS | HR, Myopathy | HR, Diabetes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Kokkinidis | 2020 | meta | INTL | 26,985 | statins | 68.5-77 | 0%-54.8% | yes | 0% | 100% | - | 50% | 0.62 | 0.50 | n.s. | - | - |
| Armitage | 2019 | meta | UK | 186,854 | statins | 63.0 | 28% | unknown | - | - | median 4.9 | N/A | 0.88 (IRR) | 0.79 (IRR) | - | - | - |
| Parmar | 2019 | obs | US | 488 | statins | - | 44% | yes | 20% | 67% | - | 41% | - | - | 0.30 | - | - |
| Reynolds | 2019 | obs | US | 11,059 | statins | 68.6 | 40% | yes | 69% | 31% | median 4.2 | 60% | 0.80 IC/0.81 CLTI | - | - | - | - |
| Arya | 2018 | obs | US | 155,647 | statins | 67.0 | 2% | yes | - | - | median 5.9 | 72% | 0.83 | - | 0.81 | - | - |
| Ramos | 2018 | obs | ES | 46,864 | statins | 77.0 | 63% | unknown | - | - | median 5.6 | 16% | n.s./0.84 (DM) | - | - | n.s./n.s. | n.s./n.s. |
| Foley | 2017 | obs | US | 909 | HI statin | 68.0 | 40% | yes | 46% | 54% | median 1.4 | 83% | 0.53 | 0.58 | n.s. | - | - |
| Hsu | 2017 | obs | TW | 69,332 | statins | 63.0 | 51% | yes | - | - | mean 5.7 | 16% | 0.72 | - | 0.75 | - | - |
| Matsubara | 2017 | obs | JP | 114 | statins | 72.1 | 31% | yes | 0% | 100% | - | 23% | - | 0.38 | - | - | - |
| Rodriguez | 2017 | obs | US | 509,766 | HI statin | 68.5 | 2% | yes | - | - | mean 1.3 | 82% | 0.91 | - | - | - | - |
| Stavroulakis | 2017 | obs | DE | 1,200 | statins | 74.5 | 34% | yes | 0% | 100% | - | 57% | 0.40 | 0.41 | n.s. | - | - |
| Proietti | 2016 | obs | INTL | 328 | statins | 72.9 | 34% | yes | - | - | max 1 | 39% | 0.64 | - | - | - | - |
| Ramos | 2016 | obs | ES | 5,480 | statins | 67.0 | 44% | yes | 0% | 0% | median 3.6 | 28% | 0.81 | 0.80 | - | n.s. | n.s. |
| Sigvant | 2016 | obs | SE | 18,742 | statins | 74.3 | 49% | yes | 37% | 63% | - | 60% | - | 0.7 IC /0.76 CLTI | - | - | - |
| Suckow | 2015 | obs | US | 2,067 | statins | 67.0 | 29% | yes | 33% | 67% | complete 1 | 74% | 0.70 | - | - | - | - |
| Antoniou | 2014 | meta | INTL | 19,368 | statins | - | - | yes | - | - | - | 52% | 0.60 | n.s. | - | - | - |
| De Martino | 2014 | obs | US | 14,489 | statins | 70.0 | 34% | yes | - | - | - | 78% | 0.70 (OR) | - | - | - | - |
| Dosluoglu | 2014 | obs | US | 717 | statins | 68 | 0% | yes | 34% | 66% | mean 4.2 | 55% | 0.74 | - | - | - | - |
| Faglia | 2014 | obs | IT | 553 | statins | 71.7 | 30% | yes | 0% | 100% | mean 2.2 | 45% | n.s. | - | - | - | - |
| Kumbhani | 2014 | obs | INTL | 5,861 | statins | 69.0 | 27% | yes | 43% | 57% | complete 4 | 62% | n.s. | 0.85 | 0.57 | - | - |
| Westin | 2014 | obs | US | 380 | statins | 68.5 | 44% | yes | 0% | 100% | median 1.1 | 65% | 0.49 | 0.53 | 0.59 | - | - |
| Sohn | 2013 | obs | US | 83,953 | statins | 52.0 | - | yes | - | - | mean 4.9 | - | - | - | 0.57 | - | - |
| Taylor | 2013 | meta | INTL | 48,060 | statins | - | - | unknown | - | - | - | N/A | 0.86 | 0.75 | - | n.s. | n.s. |
| Tomoi | 2013 | obs | JP | 812 | statins | 71.6 | 31% | yes | 0% | 100% | mean 1.6 | 21% | n.s. | - | n.s. | - | - |
| Aiello | 2012 | obs | US | 646 | statins | 77.0 | 48% | yes | 0% | 100% | mean 0.8 | 49% | 0.49 (OR) | - | - | - | - |
| Dosluoglu | 2012 | obs | US | 433 | statins | 71.1 | 0% | yes | 0% | 100% | mean 2.3 | 27% | 0.60 | - | 0.70 | - | - |
| Ridker | 2012 | RCT | US | 17,603 | rosuvastatin | 66.0 | 37% | unknown | - | - | median 2 | N/A | n.s. | 0.67 | - | - | n.s. |
| Mills | 2011 | meta | INTL | 41,778 | HI statin | 55.5 | 24% | unknown | - | - | mean 2.5 | N/A | n.s. | 0.90 | - | 2.86 (RR) | - |
| Dosluoglu | 2010 | obs | US | 746 | statins | 69.3 | 1% | yes | 27% | 73% | mean 2.2 | 58% | 1.40 (nonuse) | - | - | - | - |
| Schanzer | 2008 | obs | INTL | 1,404 | statins | 68.5 | 39% | yes | 0% | 100% | max 1 | 45% | 0.67 | - | - | - | - |
| Aung | 2007 | meta | INTL | 10,049 | lipid lowering | - | - | yes | - | - | - | N/A | n.s. | n.s. | - | - | - |
| Collins | 2002 | RCT | INTL | 20,536 | simvastatin | - | 25% | unknown | - | - | mean 5 | N/A | 0.87 (IRR) | 0.76 (IRR) | - | - | - |
| **our study** | **2020** | **obs** | **DE** | **22,208** | **statins** | **71.1** | **50%** | **yes** | **0.57** | **0.43** | **median 3.5** | **50%** | **0.75 IC /0.80 CLTI** | **0.80 IC /n.s. CLTI** | **n.s. IC /0.73 CLTI** | **n.s.** | **n.s.** |

Figure S1: Time trend in the proportion of unmatched patients initiating statin therapy after index stay (N=22,208) among all statin-naïve patients and Cochrane-Armitage trend test (p-value). CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; PAOD: Peripheral arterial occlusive disease.

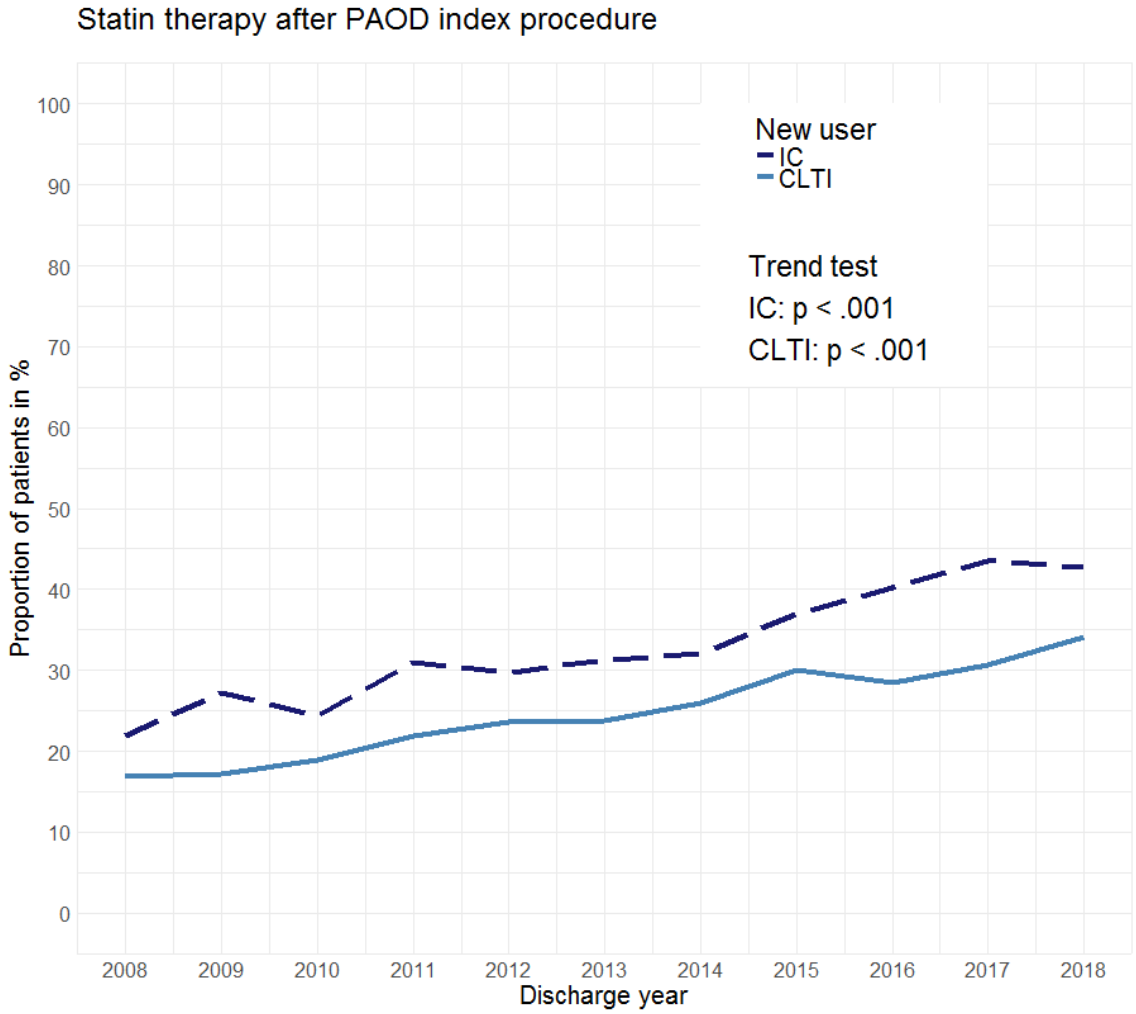
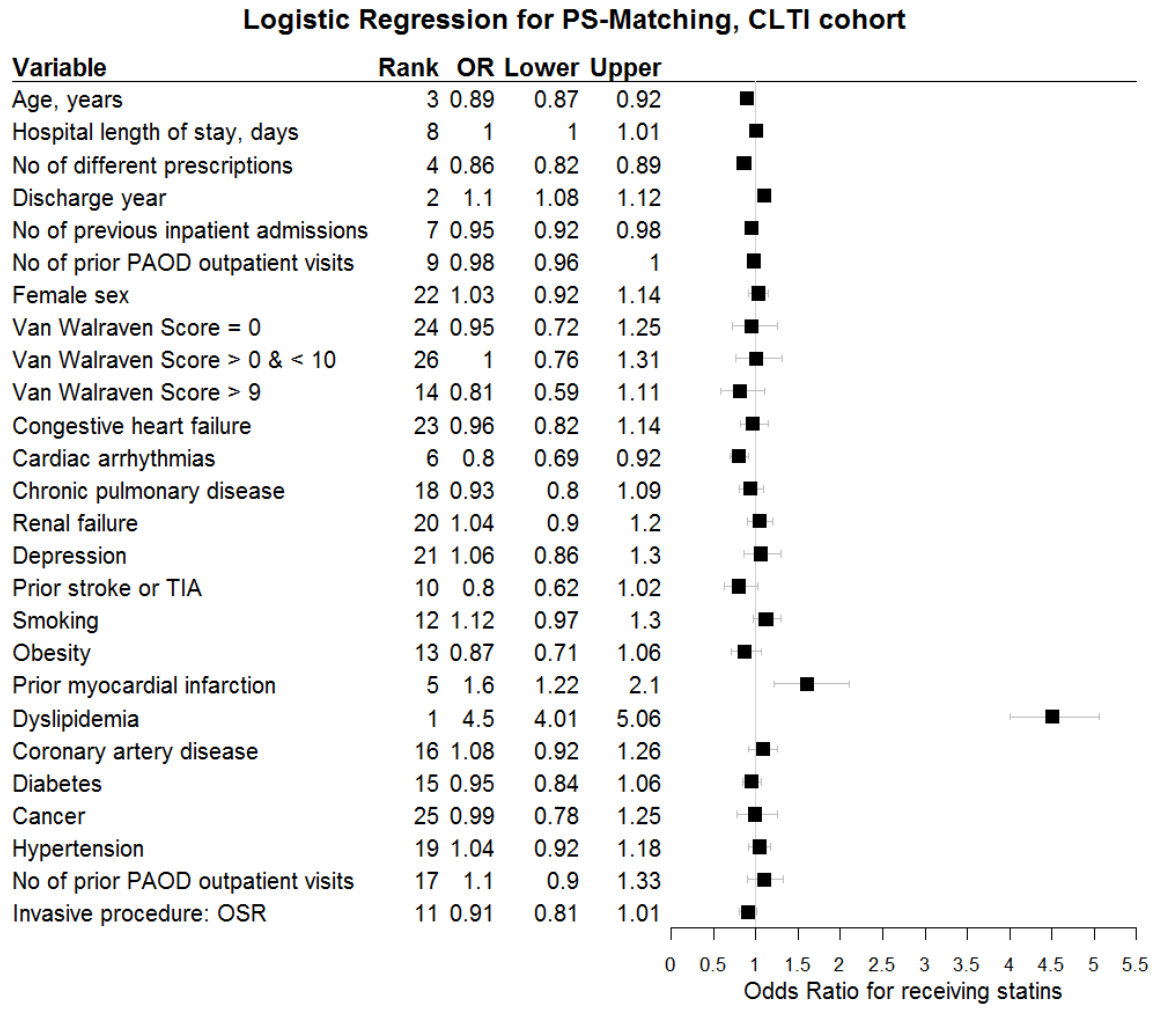


*Figure S2: Odds ratios of the probability to be a new user vs. nonuser after index discharge used in the propensity score matched patients with CLTI (N=4,224); full matching (upper panel) and restricted diabetes matching (lower panel); CLTI: Chronic limb-threatening ischemia; OR: Odds Ratio; PS: Propensity Score; Rank based on variable importance according to recursive partitioning; PAOD: Peripheral arterial occlusive disease; OSR: Open surgical revascularization; TIA: Transient ischemic attack.*



**Logistic Regression for PS-Matching, CLTI cohort, Diabetes matching**

| Variable | Rank | OR | Lower | Upper |
|---|---|---|---|---|
| Age, years | 3 | 0.91 | 0.88 | 0.95 |
| Hospital length of stay, days | 15 | 1 | 1 | 1.01 |
| No of different prescriptions | 4 | 0.87 | 0.82 | 0.92 |
| Discharge year | 2 | 1.11 | 1.08 | 1.14 |
| No of previous inpatient admissions | 6 | 0.95 | 0.91 | 0.99 |
| No of prior PAOD outpatient visits | 24 | 1 | 0.97 | 1.04 |
| Female sex | 20 | 0.98 | 0.84 | 1.13 |
| Van Walraven Score = 0 | 14 | 1.23 | 0.83 | 1.86 |
| Van Walraven Score > 0 & < 10 | 16 | 1.14 | 0.76 | 1.72 |
| Van Walraven Score > 9 | 17 | 0.9 | 0.57 | 1.43 |
| Congestive heart failure | 21 | 0.96 | 0.76 | 1.23 |
| Cardiac arrhythmias | 10 | 0.84 | 0.68 | 1.03 |
| Chronic pulmonary disease | 11 | 0.85 | 0.68 | 1.05 |
| Renal failure | 25 | 1.01 | 0.82 | 1.25 |
| Depression | 7 | 1.34 | 1.01 | 1.78 |
| Prior stroke or TIA | 12 | 0.77 | 0.52 | 1.11 |
| Smoking | 8 | 1.21 | 1 | 1.45 |
| Obesity | 9 | 0.73 | 0.5 | 1.04 |
| Prior myocardial infarction | 5 | 1.83 | 1.2 | 2.76 |
| Dyslipidemia | 1 | 4.92 | 4.19 | 5.79 |
| Coronary artery disease | 19 | 0.96 | 0.75 | 1.21 |
| Cancer | 22 | 1.04 | 0.75 | 1.43 |
| Hypertension | 18 | 1.04 | 0.88 | 1.22 |
| No of prior PAOD outpatient visits | 13 | 0.84 | 0.62 | 1.13 |
| Invasive procedure: OSR | 23 | 0.99 | 0.84 | 1.15 |

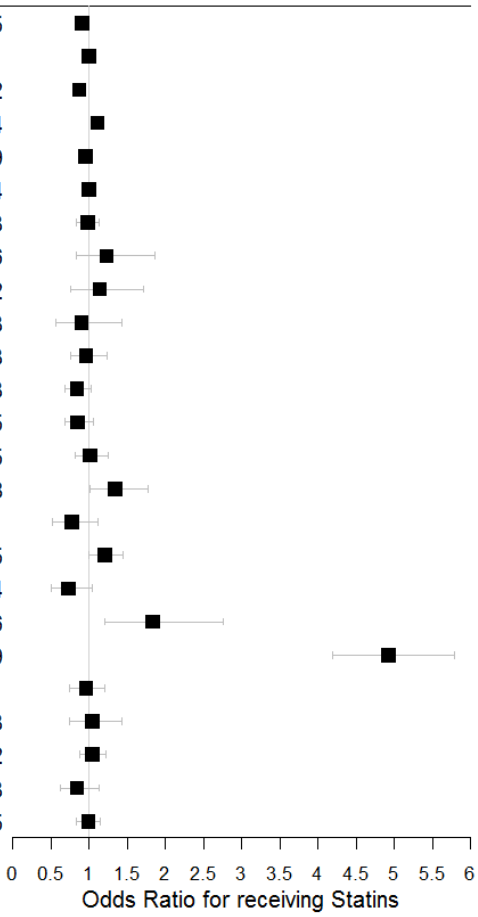



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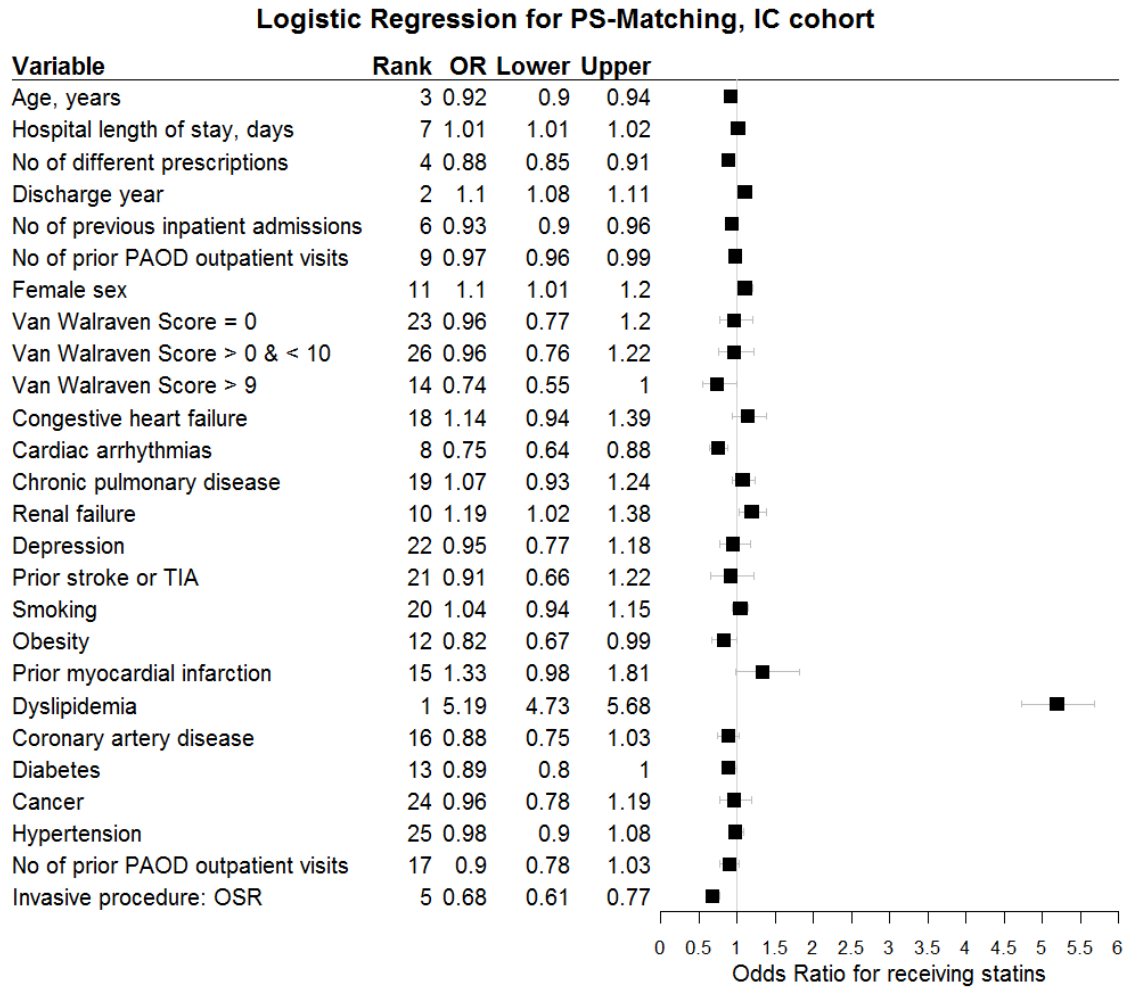
*Figure S3: Odds ratios of the probability to be a new user vs. nonuser after index discharge used in the propensity score matched patients IC (N=6698); full matching (upper panel) and restricted diabetes matching (lower panel); IC: Intermittent claudication; OR: Odds Ratio; PS: Propensity Score; Rank based on variable importance according to recursive partitioning; PAOD: Peripheral arterial occlusive disease; OSR: Open surgical revascularization; TIA: Transient ischemic attack.*



**Logistic Regression for PS-Matching, IC cohort, Diabetes matching**

| Variable | Rank | OR | Lower | Upper |
|---|---|---|---|---|
| Age, years | 4 | 0.93 | 0.9 | 0.95 |
| Hospital length of stay, days | 7 | 1.02 | 1.01 | 1.03 |
| No of different prescriptions | 5 | 0.9 | 0.86 | 0.94 |
| Discharge year | 2 | 1.11 | 1.09 | 1.13 |
| No of previous inpatient admissions | 6 | 0.92 | 0.88 | 0.96 |
| No of prior PAOD outpatient visits | 9 | 0.97 | 0.95 | 0.99 |
| Female sex | 22 | 1.03 | 0.93 | 1.15 |
| Van Walraven Score = 0 | 14 | 0.77 | 0.58 | 1.01 |
| Van Walraven Score > 0 & < 10 | 13 | 0.73 | 0.55 | 0.98 |
| Van Walraven Score > 9 | 10 | 0.59 | 0.4 | 0.85 |
| Congestive heart failure | 18 | 1.16 | 0.9 | 1.49 |
| Cardiac arrhythmias | 8 | 0.72 | 0.59 | 0.89 |
| Chronic pulmonary disease | 20 | 1.08 | 0.91 | 1.29 |
| Renal failure | 16 | 1.18 | 0.97 | 1.43 |
| Depression | 21 | 0.89 | 0.68 | 1.16 |
| Prior stroke or TIA | 23 | 0.91 | 0.61 | 1.33 |
| Smoking | 17 | 1.09 | 0.97 | 1.22 |
| Obesity | 12 | 0.71 | 0.54 | 0.93 |
| Prior myocardial infarction | 19 | 1.23 | 0.82 | 1.82 |
| Dyslipidemia | 1 | 5.41 | 4.84 | 6.06 |
| Coronary artery disease | 15 | 0.83 | 0.68 | 1.01 |
| Cancer | 24 | 0.99 | 0.76 | 1.29 |
| Hypertension | 25 | 1 | 0.9 | 1.12 |
| No of prior PAOD outpatient visits | 11 | 0.81 | 0.68 | 0.96 |
| Invasive procedure: OSR | 3 | 0.63 | 0.55 | 0.73 |

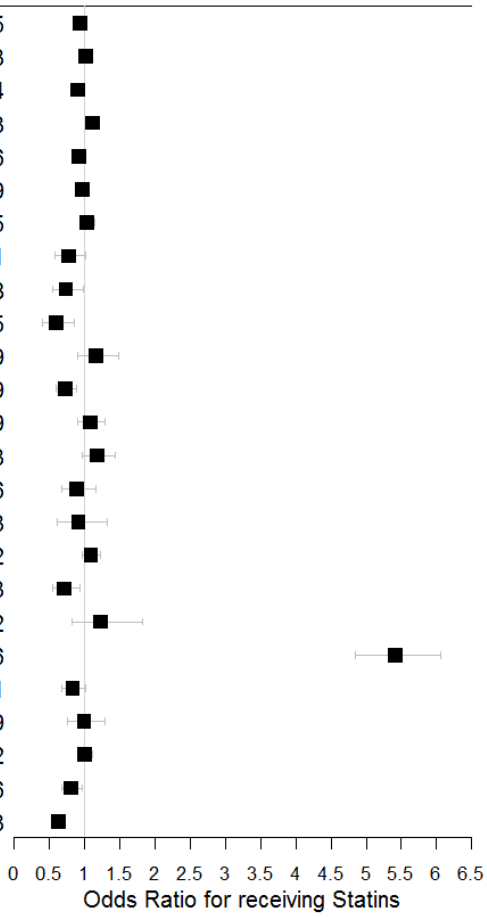



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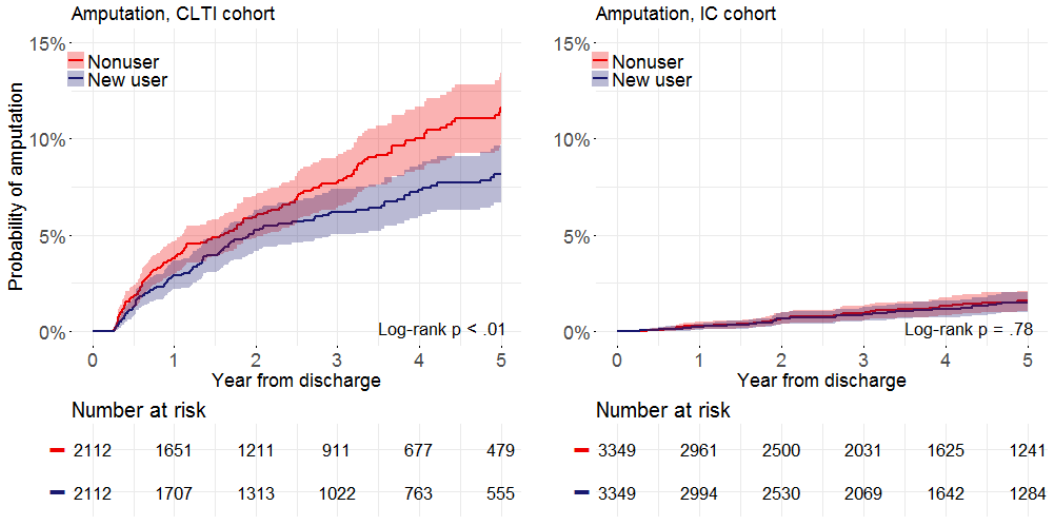
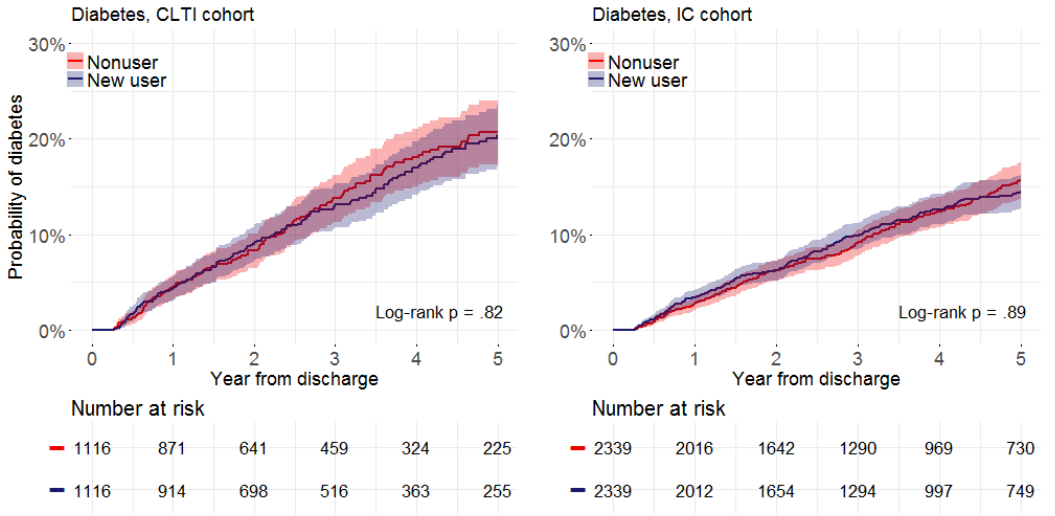
*Figure S4: Kaplan Maier curve of 5-year probability of major amputation (upper panel), incident diabetes (center panel), and incident myopathy (lower panel) in propensity score (PS) matched cohorts including 95% Wald confidence interval and log rank test (p-value). CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication*



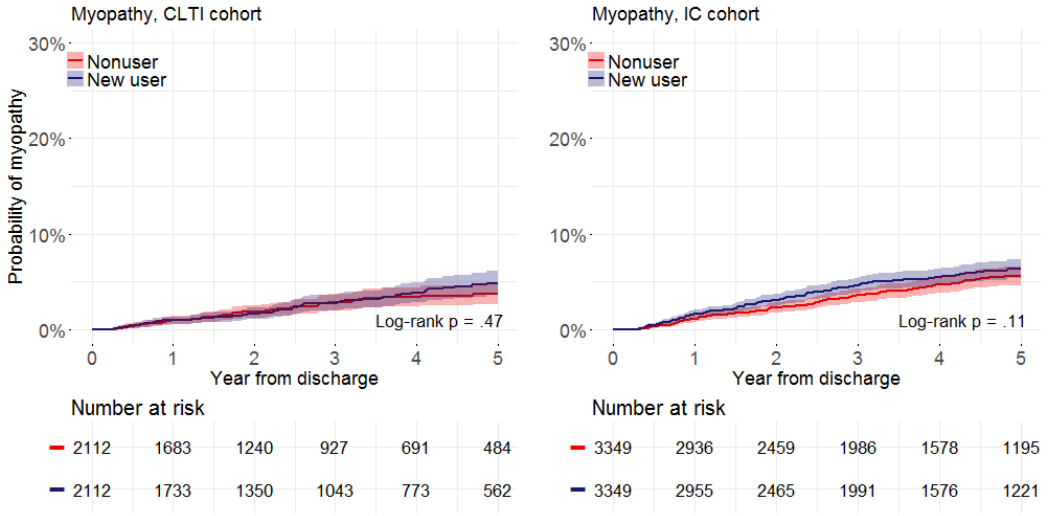



*Figure S5: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; effect of statins only (empty model) vs. full adjustment (full model); HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular*

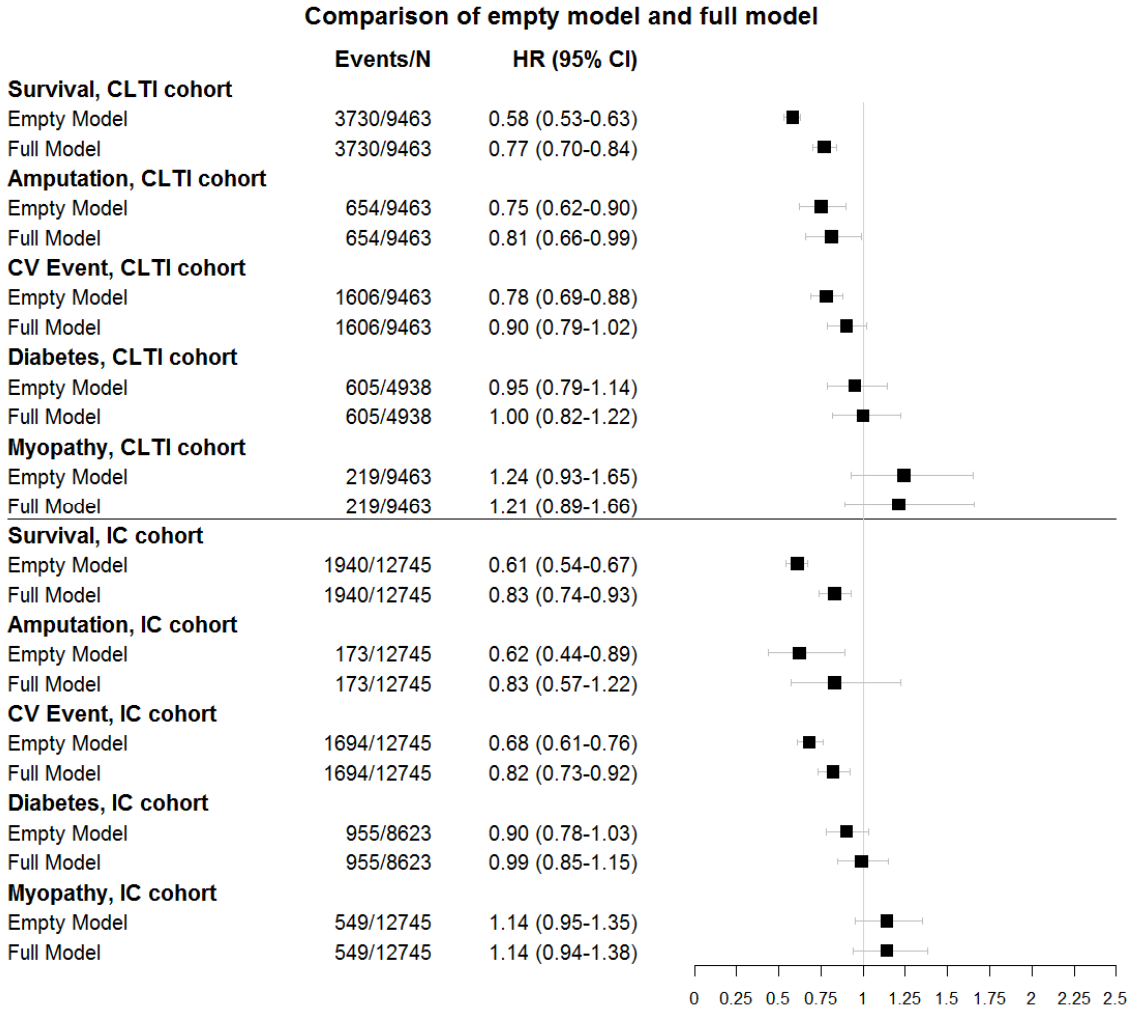


*Figure S6: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; full adjustment (full model) vs. additionally adjusting for comedications; HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular*

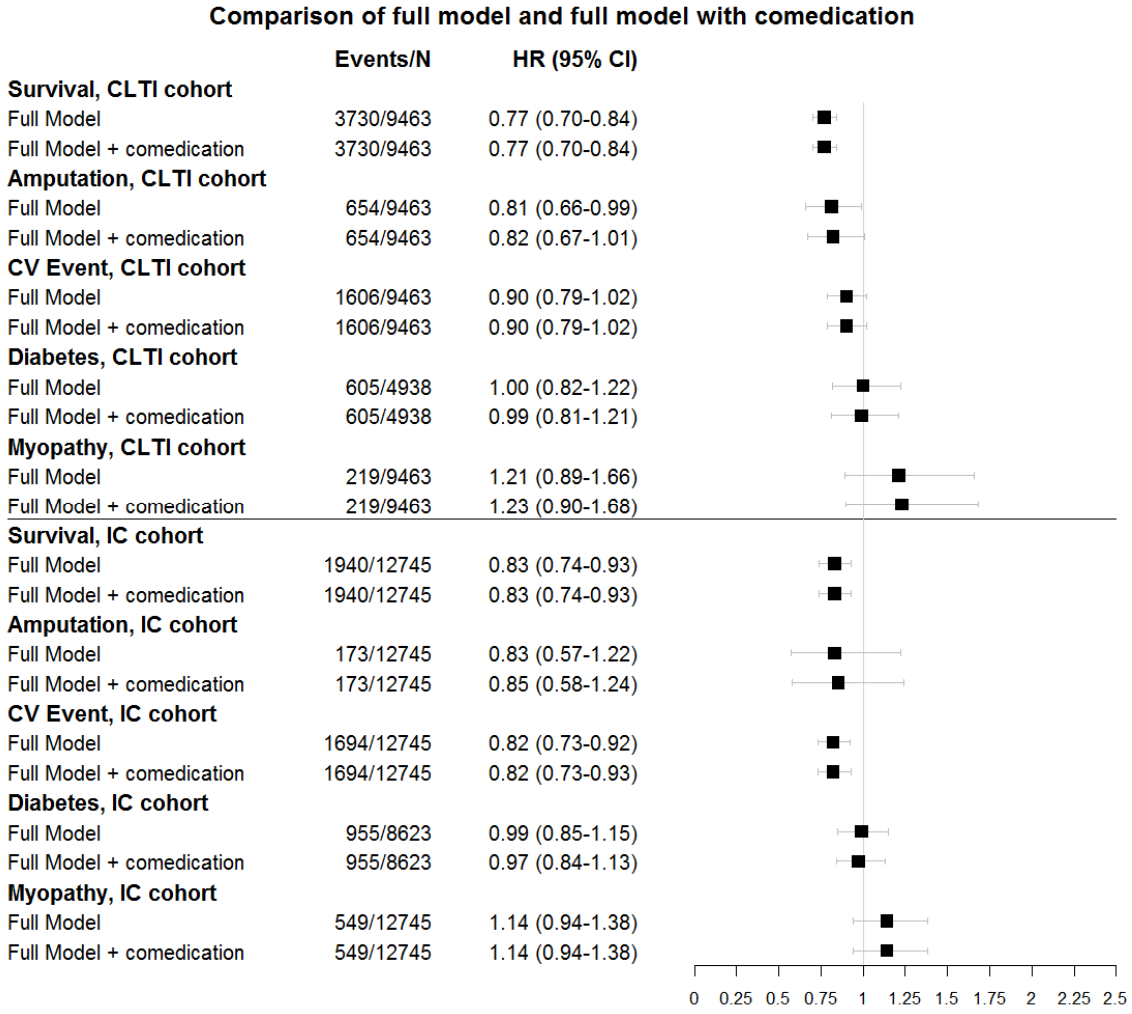


*Figure S7: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; females vs. males; HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular*

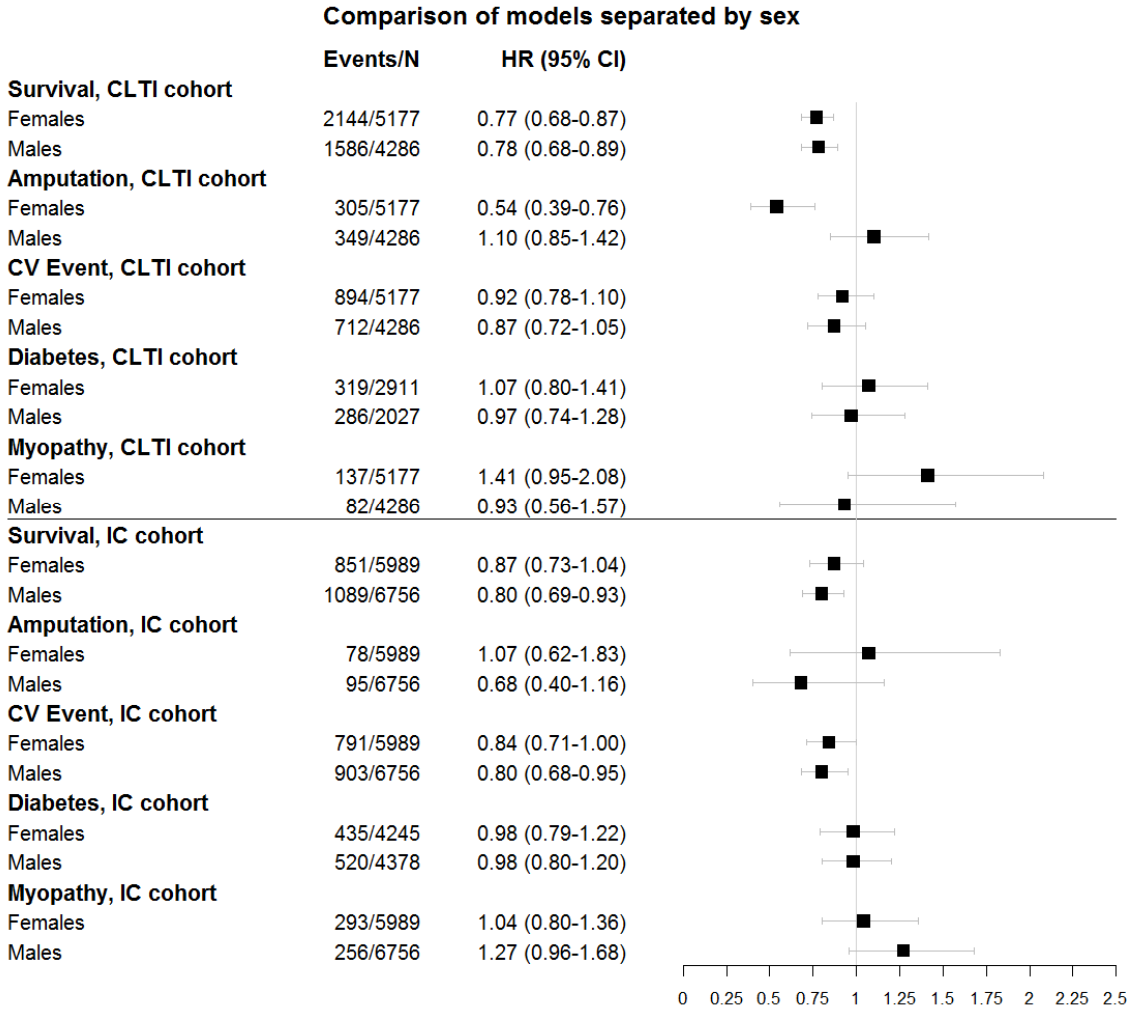


*Figure S8: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; younger patients (ages 74 and below) vs. older patients (ages 75 and above); HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular*

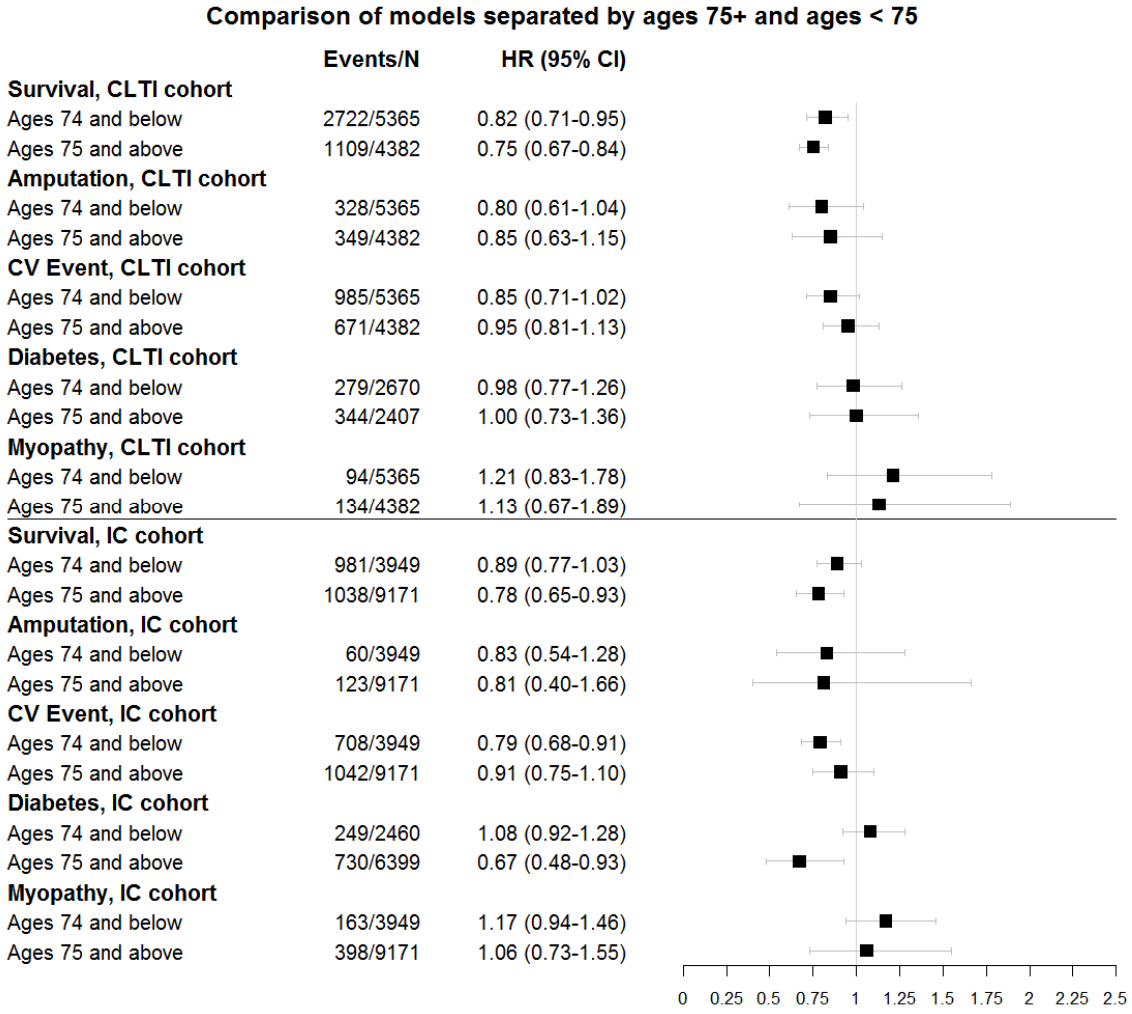


*Figure S9: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; Discharge year 2009-2012 vs. 2013-2018; HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular*

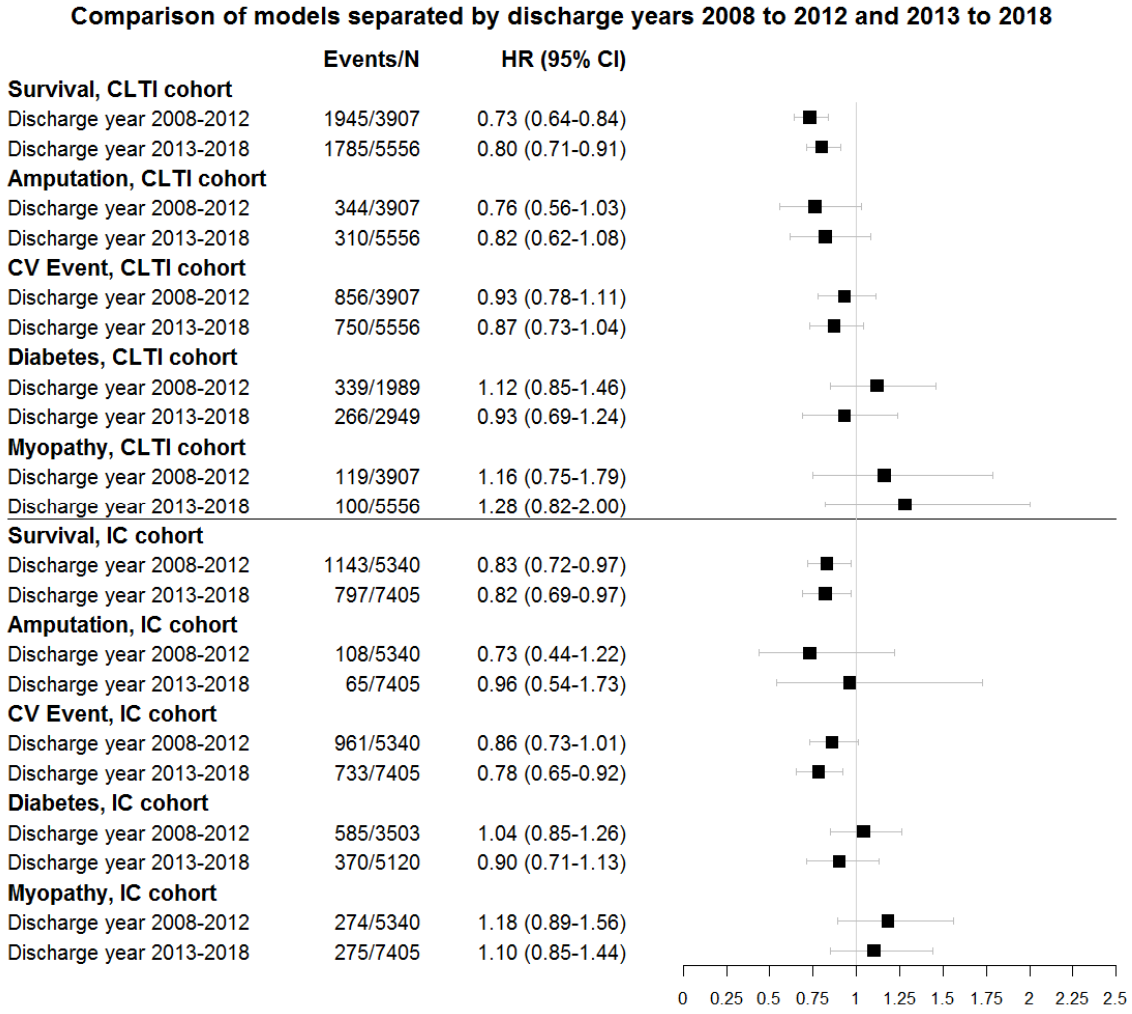
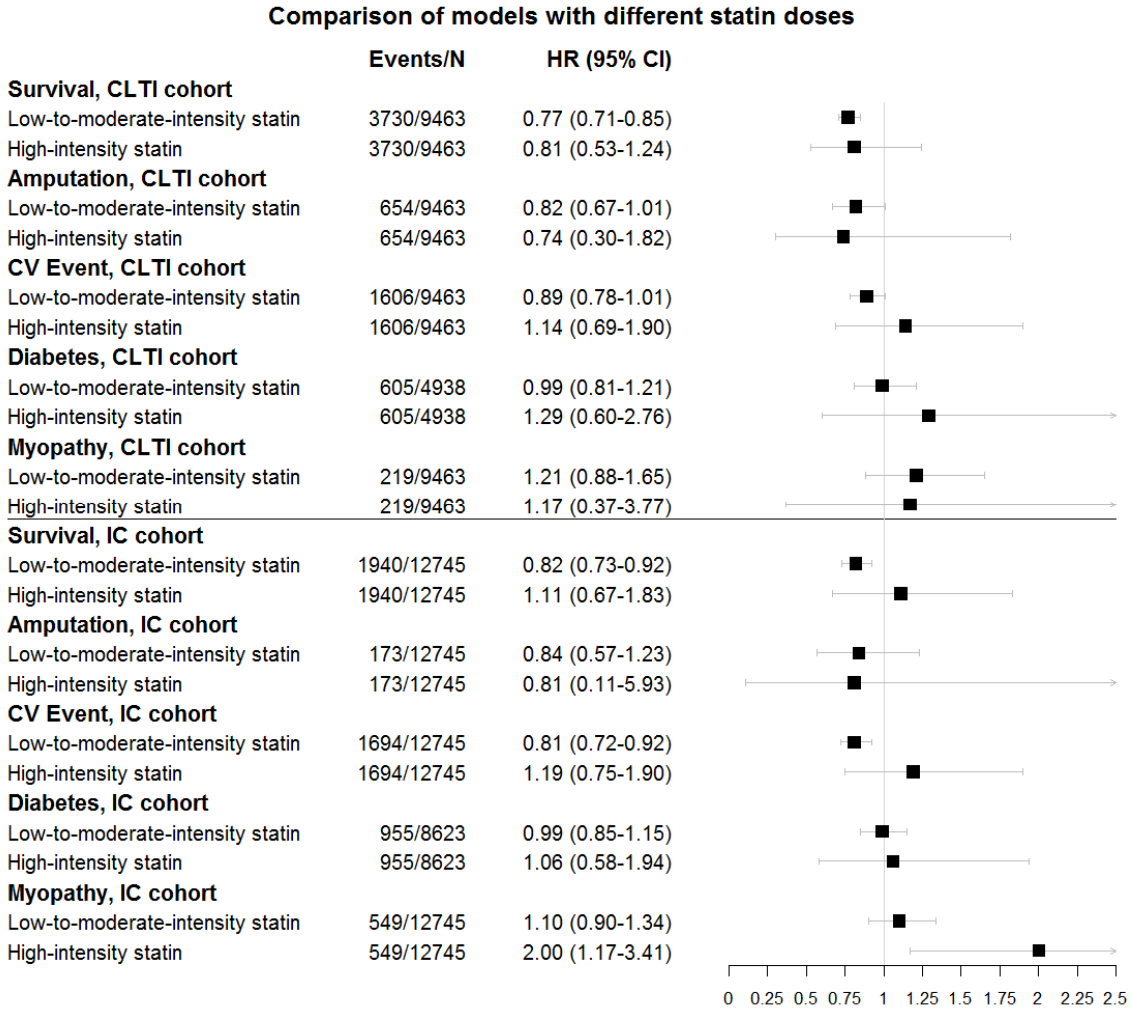
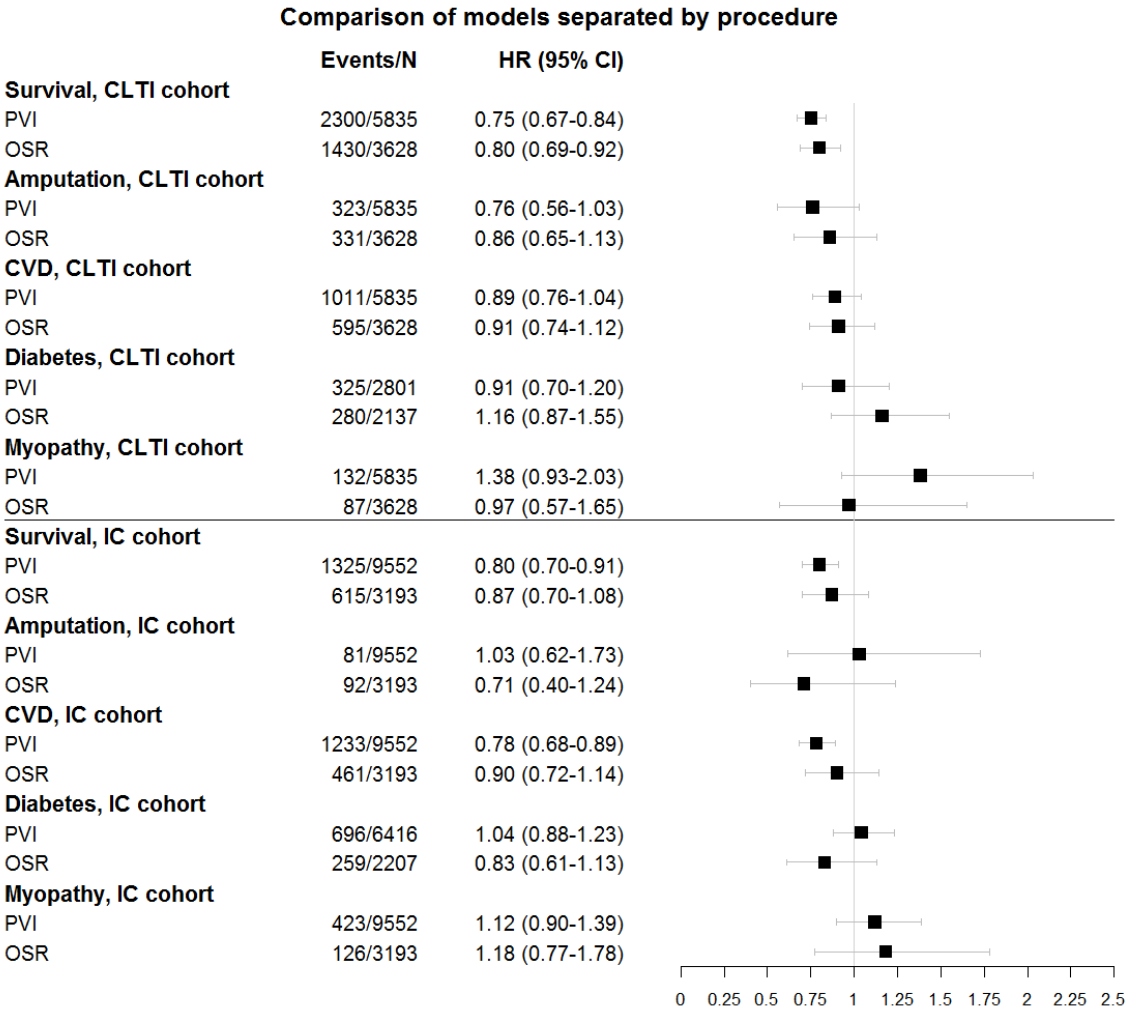


*Figure S10: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; Low-to-moderate statin intensity vs. high intensity; HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular*




*Note: Statin intensity was extracted from linking the pharmaceutical registration number (PZN) of each prescription with public databases on dose and agent; Following to 2013 AHA/ACC lipid guidelines, we grouped atorvastatin 40-80 mg and rosuvastatin 20-40 mg as high intensity treatment (N=415, 6.2%) and all other prescriptions as moderate and low intensity treatment (N=6179, 93.8%).*

*Figure S11: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; Peripheral vascular intervention (PVI) vs. open surgical repair (OSR) at index revascularization; HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular*



Eur J Vasc Endovasc Surg (2019) 58, 738–745

SYSTEMATIC REVIEW

# Quality Indicators in Peripheral Arterial Occlusive Disease Treatment: A Systematic Review

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**WHAT THIS PAPER ADDS**

A systematic review was conducted to identify evidence based quality indicators for invasive revascularisation of symptomatic peripheral arterial occlusive disease (PAOD). Only three indicators from two publications were identified. A further search involving databases of professional vascular medical organisations revealed an additional 31 indicators to be used for quality improvement programmes. The results of this systematic review could help to improve updates of clinical practice guidelines. Currently available guidelines do not contain specific quality indicators, nor do they state that it would be important to develop suitable and feasible indicators to measure structure, process, and outcome quality in PAOD treatment.

**Objectives:** This systematic review aimed to identify evidence based quality indicators for invasive revascularisation of symptomatic peripheral arterial occlusive disease (PAOD).

**Methods:** A systematic search of clinical practice guidelines, consensus statements, systematic reviews, and meta-analyses reporting quality indicators in patients undergoing invasive open and percutaneous revascularisations for symptomatic PAOD (PROSPERO registration number: CRD42019116317) was performed. Furthermore, a grey literature search was conducted involving databases of professional vascular medical organisations. The identified publications were screened independently by two reviewers for possible inclusion and full texts of potentially relevant records were independently evaluated for eligibility. Disagreement was resolved by discussion involving a third reviewer.

**Results:** From 685 articles initially identified, one systematic review and one consensus statement focusing on quality indicators were selected for inclusion in the review. From these sources, a total of three process quality indicators matched the search criteria: one on pharmacological intervention, another on smoking cessation, and a third on surveillance of lower extremity vein bypass grafts. The grey literature search revealed an additional 31 structure, process, and outcome quality indicators.

**Conclusions:** This study revealed a lack of published evidence based quality indicators concerning invasive treatment for PAOD in the literature. An additional 31 indicators from the databases of professional societies and organisations have not been incorporated in prior guidelines. Interestingly, no indicator related to patient reported outcomes could be identified from either high quality sources or grey literature. Further research and harmonisation of different quality indicators is needed to enhance their evidence and subsequently improve patient centred decision making on invasive treatment.

**Keywords:** Systematic review, Quality indicators, Chronic peripheral arterial disease, Intermittent claudication, Chronic limb threatening ischaemia, Outcomes

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## INTRODUCTION

Although demographic developments and the widespread adoption of endovascular techniques have led to a considerable increase in the number of revascularisations in patients with peripheral arterial occlusive disease (PAOD),[1–3]

clinical practice guidelines lack clear recommendations concerning suitable indicators to measure quality of care.[4–6] In fact, there are only few quality indicators which are broadly accepted by clinicians, such as amputation rates for treatments of chronic limb threatening ischaemia (CLTI) or quality of life (QoL) for treatment of intermittent claudication (IC). Quality indicators in prospective trials and retrospective studies commonly involve technical measures such as technical success rate, patency, or freedom from re-intervention. Patient related outcomes are often underrepresented in these studies. However, it is vital to prescribe and to define suitable and feasible quality indicators to improve clinical effectiveness and efficiency. Furthermore, quality indicators developed and validated by a commonly accepted methodology would help to align patients' preferences to the objectives of care givers in times of patient centred medicine.[7]

Quality of health care is based on a complex interaction of different factors and can be subdivided into structure, process, and outcome quality.[8] While structural indicators basically describe the resources and overall infrastructure used in the treatment of patients, process indicators typically involve the clinical pathways in patient care. Suitable and valid structure and process indicators can be used to predict outcomes as the third type of quality measures.

The objective of this systematic review was to identify quality indicators for the invasive treatment of patients with PAOD recommended in the available literature.[9]

## METHODS

The German language study protocol was developed and published online in June 2017 (www.idomeneo.de). It was registered in the International Prospective Register of Systematic Reviews (PROSPERO CRD42019116317) in December 2018. The reporting of this review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards.[10]

Methodological quality was evaluated by Scottish Intercollegiate Guidelines Network (SIGN) criteria for systematic reviews[11] and by the Checklist for the Quality Assessment of Guidelines (AGREE II)[12] by three evaluators independently.

### *Criteria for considering studies*

**Types of studies.** Systematic reviews, meta-analyses, consensus statements, and clinical practice guidelines recommending quality indicators for invasive treatment of chronic PAOD of the lower extremities were reviewed. Furthermore, a grey literature search was conducted to identify quality indicators from databases and websites of professional vascular medical organisations (Tables S1 and S2).

The following criteria were used for exclusion: acute peripheral arterial disease and embolic occlusions of the lower extremities, non-invasive treatment and conservative or pharmacological treatment, primary amputation without revascularisation, and stem cell treatment. Narrative reviews, case reports, clinical studies, and (controlled) clinical trials were also excluded.

**Types of participants.** Male and female patients of any age presenting with IC or CLTI that was assumed to have been caused by chronic PAOD and was treated by invasive revascularisation.

**Types of interventions.** The interventions of interest were any peripheral vascular intervention (PVI), such as percutaneous transluminal angioplasty (PTA), open surgical endarterectomy (EA), or bypass surgery (BS).

**Types of outcome measures.** The primary outcomes of this systematic review were recommended quality indicators in the care of patients including process, structure, and outcome indicators.

### *Search strategy*

An electronic search was performed using the search engine PubMed (US National Library of Medicine) to access databases from MEDLINE, OLDMEDLINE, and PubMed Central. Additionally, databases of professional societies and organisations were searched for publications and quality indicators in patients with PAOD that fulfilled the inclusion criteria for types of participants and types of interventions, and were available in German or English language (Tables S1 and S2). The search was run in December 2017 and April 2019. Hence, all publications included were published before March 31, 2019 in either English or German. A detailed search strategy using a combination of the following three terms with corresponding synonyms and MESH terms was used: chronic peripheral arterial disease AND quality indicator AND systematic review/guideline (Electronic Supplemental File 1).

### *Study selection*

The identified publications were screened independently by two reviewers (MB and SH) for possible inclusion and full texts of potentially relevant records were independently evaluated for eligibility. Disagreement was resolved by discussion. The selected studies were then sent to a third review author (CAB), who assessed and confirmed their suitability for inclusion and acted as an adjudicator in the event of substantial disagreement.

Included studies and other types of sources were described by providing information on the author(s), title and year of publication, language/country, short description of the context, and number of extracted relevant quality indicators (Table 1).

### *Data extraction*

Suitable quality indicators were collected and described using the following: title, description, indicator type, numerator, denominator, exclusion criteria, indicator variations, target range, risk adjustment, and source (Table 2).

German language quality indicators were translated into English

**Table 1. Publications and additional sources included in this systematic review of quality indicators of invasive management of peripheral arterial occlusive disease**

| Source | Author | Year | Language/ country | Type of publication | Description | Indicators included |
|---|---|---|---|---|---|---|
| Healthcare quality indicators of peripheral artery disease based on systematic reviews[13] | Bellmunt *et al.* | 2014 | English | Systematic review | 6 indicators are defined "*to evaluate the quality of healthcare provided in PAD*" | 2 |
| ACCF/AHA/ACR/SCAI/SIR/ SVM/ SVN/SVS 2010 performance measures for adults with peripheral artery disease[14] | Olin *et al.* | 2010 | English | Consensus document | Seven performance measures and two test measures are presented by the ACCF/AHA Task Force on Performance Measures | 1 |
| German National Institute for Quality Measurement in Health Care (BQS)[31] | Federal Office of Quality Assurance (BQS) | 2008 | Germany | Database | The BQS Institute provides quality assurance in the German health care system up to 2008 | 13 |
| CMS Measures Inventory[32] | Centres for Medicare and Medicaid Services (CMS) | 2017 | USA | Database | Centres for Medicare & Medicaid Services (CMS) regularly publishes the CMS Quality Measures Inventory to provide a compilation of measures used by the CMS | 12 |
| External Quality Assurance Hamburg (EQS)[33] | Quality indicator database of the External Quality Assurance Hamburg | 2015 | Germany | Database | The external quality assurance Hamburg is a mandatory quality improvement registry that records and compares the quality of medical services in Hamburg to improve patient care continuously. | 10 |
| National Association of Statutory Health Insurance Funds (GKV-Spitzenverband)[34] | Quality indicator thesaurus of the Statutory Health Insurance Funds Association (QUINTH) | 2017 | Germany | Database | Since 2009, the GKV-Spitzenverband provides "QUINTH" a database of quality indicators for health care developed in German-speaking countries by various authors and institutions | 20 |
| Quality Positioning System (QPS)[35] | National Quality Forum (NQF) | 2017 | USA | Database | NQF started 2012 the QPS as an interactive searchable database of NQF endorsed quality measures | 2 |
| List of 2017 Vascular Quality Initiative (VQI) Qualified Clinical Data Registry (QCDR) Measures *and* List of 2017 Non-Quality Payment Program (QPP) Measures[36,37] | Vascular Quality Initiative (VQI) | 2017 | USA | Database | The VQI is a patient safety organisation to improve the quality, safety, effectiveness and cost of vascular health care by collecting and exchanging information | 8 |

ACCF = American College of Cardiology Foundation; ACR = American College of Radiology; AHA = American Heart Association; BQS = Federal Office of Quality Assurance; CMS = Centers for Medicare and Medicaid Services; SCAI = Society for Cardiac Angiography and Intervention; SIR = Society for Interventional Radiology; SVM = Society for Vascular Medicine; SVN = Society for Vascular Nursing; SVS = Society for Vascular Surgery; PAD = peripheral arterial disease.

## RESULTS

A literature search via the database PubMed and a search of additional online sources identified 729 articles. After 44 duplicates were removed, the titles and abstracts of 685 articles were screened. Of these, 601 articles did not fulfil the inclusion criteria and were excluded leaving 84 articles shortlisted for full text review, of which 82 were excluded for the following reasons: unsuitable outcome ($n = 49$), unsuitable study design ($n = 28$), unsuitable patient population ($n = 3$), and unsuitable intervention ($n = 2$). Ultimately, two studies were selected for inclusion in the qualitative synthesis: Bellmunt *et al.*[13] and Olin *et al.*[14] as shown in the flow diagram (Fig. 1).

### *Quality indicators identified by this systematic review*

In the included studies, three process quality indicators were identified that met the inclusion criteria: 1) proportion of patients with history of bypass grafting to whom antiplatelet agents are prescribed,[13] 2) proportion of current smokers with history of bypass grafting to whom a smoking cessation intervention is prescribed,[13] and 3) lower extremity vein bypass graft surveillance.[14]

**Table 2. List of 34 identified quality indicators by different categories**

| | Quality indicator for invasive therapy | Type of indicator | Source | Reference |
|---|---|---|---|---|
| *Indicators concerning quality of diagnostic work up* | | | | |
| 1 | Determination of the Fontaine stage | Process | BQS, GKV | 31,34 |
| 2 | Indication for PTA according to Fontaine stage | Process | BQS, EQS, GKV | 31,33,34 |
| 3 | Multidisciplinary team decision prior to invasive therapy | Process | BQS, EQS, GKV | 31,33,34 |
| 4 | Treadmill testing | Process | BQS | 31 |
| 5 | Pre-interventional ankle brachial index | Process | BQS, EQS, GKV | 31,33,34 |
| 6 | Primary stenting of the pelvic region | Process | BQS, EQS, GKV | 31,33,34 |
| *Indicators concerning quality of concomitant medical therapy and lifestyle modification* | | | | |
| 7 | Statin therapy at discharge after lower extremity bypass | Process | CMS, NQF, VQI, | 32,35–37 |
| 8 | Procedures with statin and antiplatelet agents prescribed at discharge | Process | VQI | 36,37 |
| 9 | Proportion of patients with history of bypass grafting to whom antiplatelet agents are prescribed | Process | Bellmunt | 13 |
| 10 | Anticoagulant medication during PTA | Process | BQS, GKV | 31,34 |
| 11 | Proportion of current smokers, with history of bypass grafting, to whom a tobacco cessation intervention is prescribed | Process | Bellmunt | 13 |
| *Indicators concerning quality of follow up after invasive therapy* | | | | |
| 12 | Lower extremity vein bypass graft surveillance | Process | Olin | 14 |
| 13 | Rate of surgical conversion from lower extremity endovascular revascularisation procedure | Outcome | CMS | 32 |
| 14 | Amputation free survival assessed at least nine months following infra-inguinal bypass for intermittent claudication | Outcome | VQI | 36,37 |
| 15 | Amputation free survival assessed at least nine months following supra-inguinal bypass for claudication | Outcome | VQI | 36,37 |
| 16 | Amputation free survival assessed at least nine months following peripheral vascular intervention for intermittent claudication | Outcome | VQI | 36,37 |
| 17 | Infra-inguinal bypass for claudication patency assessed at least nine months following surgery | Process | VQI | 36,37 |
| 18 | Peripheral vascular intervention patency assessed at least nine months following infra-inguinal peripheral vascular intervention for claudication | Process | VQI | 36,37 |
| 19 | Post-interventional angiography after PTA | Process | BQS, EQS, GKV | 31,33,34 |
| 20 | Post-interventional ankle brachial index after PTA | Process | BQS, EQS, GKV | 31,33,34 |
| 21 | Improvement of the ankle brachial index following PTA | Outcome | BQS, EQS, GKV | 31,33,34 |
| 22 | Post-interventional residual stenosis following PTA | Outcome | BQS, EQS, GKV | 31,33,34 |
| 23 | Post-interventional complications following PTA | Outcome | BQS, EQS, GKV | 31,33,34 |
| *Indicators concerning quality of invasive therapy (adverse events)* | | | | |
| 24 | Absence of serious technical complications during peripheral arterial intervention | Outcome | VQI | 36,37 |
| 25 | Wound infection rate (total) after arterial reconstruction of the lower extremity | Outcome | GKV | 34 |
| 26 | Wound infection rate (in hospital) after arterial reconstruction of the lower extremity | Outcome | GKV | 34 |
| 27 | Risk adjusted in hospital measure of mortality and major complications following lower extremity bypass grafting. | Outcome | NQF | 35 |
| *Indicators concerning quality of invasive therapy (re-interventions)* | | | | |
| 28 | Re-intervention within 12 months after PTA | Process | BQS, GKV | 31,34 |
| *Interventional radiology indicators* | | | | |
| 29 | Professional qualification in interventional radiology | Structure | GKV | 34 |
| 30 | Technical prerequisites for interventional radiology | Structure | GKV | 34 |
| 31 | Structural requirements for interventional radiology | Structure | GKV | 34 |
| 32 | Structural requirements for follow up care in interventional radiology | Structure | GKV | 34 |
| 33 | Maintaining professional qualification in interventional radiology | Structure | GKV | 34 |
| 34 | Documentation of diagnostic catheter angiography or therapeutic interventions | Process | GKV | 34 |

BQS = Federal Office of Quality Assurance; CMS = Centers for Medicare and Medicaid Services; GKV = German statutory health insurance; NQF = The National Quality Forum; EQS = External Quality Assurance Hamburg; PTA = percutaneous transluminal angioplasty; VQI = Vascular Quality Initiative.

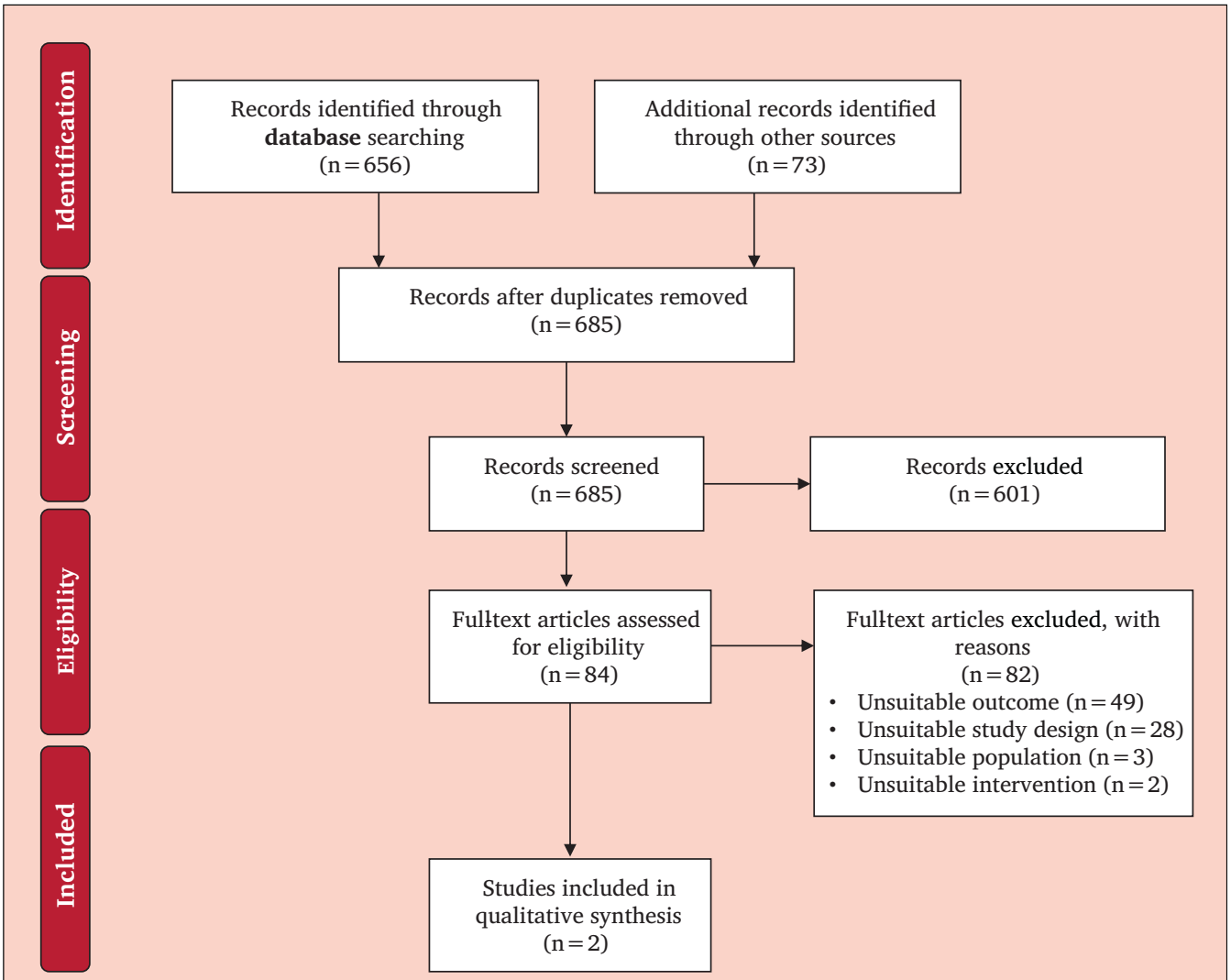


**Figure 1.** PRISMA 2009 flow diagram of this systematic review. Among 685 records identified through this systematic review, 685 records were screened. After excluding 601 records, 84 full-text articles were assessed for eligibility. Two studies were included in the qualitative synthesis. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Furthermore, 54 indicators were identified from the databases of various professional societies. After 23 duplicates were removed, 31 indicators were left. The characteristics of the sources of the extracted indicators are shown in Table 1.

The sources and types of the 34 identified quality indicators are listed in Table 2. Of these, 18 are process indicators, five structure indicators, and 11 outcome indicators. Their characteristics are described in detail in Table S3.

Most indicators concern the follow up period or adverse events following the index revascularisation. No patient reported outcome (PRO) was recommended as a quality indicator (Table 2).

The methodological quality of both studies was assessed with SIGN (for systematic reviews) and AGREE II (for practice guidelines) criteria. All three authors (SH, MB, CAB) independently assessed high quality (++) of the systematic review by Bellmunt *et al.*[13] and a mean score of 4.5/7 of the guideline by Olin *et al.*[14]

## DISCUSSION

In this systematic review on quality indicators in invasive treatment of PAOD, only two of 685 publications containing three quality indicators were of high methodological quality and could be included in the qualitative synthesis. An additional 31 quality indicators could be identified through other sources including structure, process, and outcome quality. These results emphasise the need for further research and reflection to find a consensus on suitable and feasible quality indicators in the medical care of PAOD.

Measuring the performance of vascular health care is important for national quality improvement programmes, statutory pay per quality initiatives, or research projects. However, because of the paucity of high quality evidence in clinical practice guidelines, vascular specialists often face the task pondering achievable patient benefit and the underlying risks of treatment. They should be capable of reflecting and improving their own treatment quality by comparative methods using evidence based quality

indicators. The term "quality of health care" is often described non-homogeneously making quality improvement projects challenging.[15–18]

In 2010, the American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) Performance Measure Sets were extended by the Performance Measures for Adults with Peripheral Artery Disease published by Olin *et al*.[14] The authors identified a total of seven process and outcome quality indicators involving not only PAOD of the lower extremities, but also other cardiovascular diseases and abdominal aortic aneurysms. Four of the recommended indicators concern pharmacological (e.g., cholesterol lowering medication or antiplatelet therapy) or lifestyle factors (e.g., smoking cessation, supervised exercise). Bellmunt *et al*. identified 1809 reviews, including 29 high quality systematic reviews to ultimately generate six quality indicators for PAOD focussing on pharmacological and lifestyle issues.[13] Ultimately, three quality indicators from these two publications were identified and subsequently included into the qualitative synthesis of the current review. Among them, no indicator concerns outcome quality.

Interestingly, no patient reported quality indicators such as QoL could be identified by this review, although these are often recommended as a primary treatment aim especially for IC.[19,20] PROs and patient centred treatment are key aspects of modern evidence based care because PAOD is known to decrease the disease related QoL and might lead to social isolation or even depression.[21–23] However, prior Delphi studies involving vascular specialists and real world evidence experts demonstrate that limited practicability in collecting data on PROs might counteract their clinical relevance.[7,24] Furthermore, heterogeneous use of variables and often comprehensive QoL assessing instruments complicate their comparability and validation.[25,26]

Conte *et al*. suggested objective performance goals (OPG) for catheter based treatment of CLTI including nine measures of outcome quality.[15] The authors used various retrospective cohort studies to suggest OPGs primarily for market access studies complementing randomised and controlled trials (RCT). However, there are important differences between OPGs and traditional quality indicators. Quality indicators are developed from clinical practice guidelines, consensus statements, or systematic reviews. Subsequently, their practicability, reliability, and validity will be evaluated by expert consensus.[27]

Recently, the Global Vascular Guidelines (GVG) on CLTI were published by the Society for Vascular Surgery (SVS) and the European Society for Vascular Surgery (ESVS).[28] Although not specifically containing quality indicators per se, these guidelines involve an entire chapter concerning trial endpoints and outcome measures for studies including patients with CLTI. These valuable recommendations may help specialists in vascular care and they will probably aid future study projects focusing on the development of evidence based quality indicators for the treatment of PAOD.

This study demonstrates a lack of quality indicators published in the literature to be used for revascularisations of PAOD. Although databases of professional vascular medical organisations contain an additional 31 quality indicators, these indicators have not been incorporated in prior clinical practice guidelines. Meanwhile, there is a growing global community such as the VASCUNET committee or the International Consortium of Vascular Registries (ICVR) active in comparative health services research and quality improvement using real world evidence.[24,29] The existing data standards for real world evidence research on patients with PAOD need to be followed, to have the possibility of developing indicators in the future.[30] That allows international comparison of the quality of health care. Patients with symptomatic PAOD remain the central target population of vascular specialists emphasizing the need of future research and reflection. This review will help to develop evidence based structure, process, and outcome quality indicators to be used for quality improvement in the future.

This study has limitations. Firstly, although quality improvement is a key task in medical care, the methodology and terminology are used non-homogeneously in the literature. Publications and quality indicators were only included if the development and terminology followed commonly accepted standards. Secondly, although an extensive review of the grey literature such as societal websites, databases, and additional sources was performed to identify quality indicators, there might be sources it was not possible to identify. Lastly, searches were only performed in English and German, and the search was limited to the PubMed search engine accessing the largest databases MEDLINE, OLDMEDLINE, and PubMed Central. However, there may be quality indicators available through other databases such as the EMBASE. A multilingual approach and a more inclusive search term could have identified a broader picture.

## CONCLUSIONS

Only three quality indicators for invasive treatment and medical care of patients with PAOD are available in the published literature and an additional 31 quality indicators from databases of professional societies and organisations have not been incorporated in prior clinical practice guidelines. Non-homogeneous definitions and methodological discrepancies emphasise the need for further reflection and actions to develop commonly accepted process, structure, and outcome quality indicators in PAOD treatment.

## ACKNOWLEDGEMENTS

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## CONFLICTS OF INTEREST

None.

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## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2019.06.029.

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## COUP D'OEIL

# False Aneurysm After Gamma-nail Surgery: A Rare Complication

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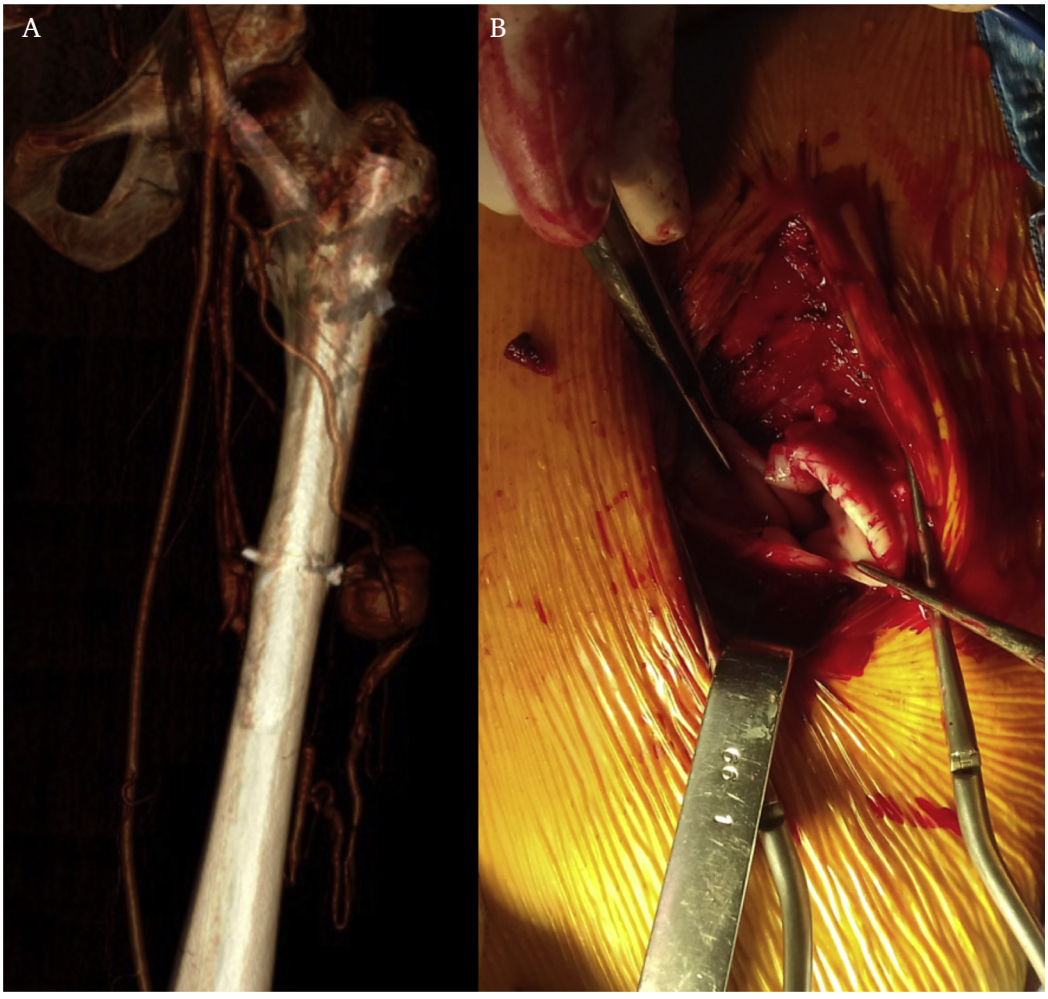


The case of a 29 year old patient who underwent a gamma nail (Stryker, Portage, MI, USA) procedure is reported. Four months after surgery, he presented with a pulsatile mass in the left thigh. Computed tomography angiography showed a 44 mm false aneurysm of a muscular branch of the profunda femoris artery supplying the vastus lateralis, probably due to traumatic injury by the distal screw (A). Open surgical repair was carried out (rather than embolisation, based on patient choice) with proximal and distal ligation to control the false aneurysm which was evacuated (B), and the damaged arterial segment oversewn. The patient was discharged on Day 1.

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# International Consortium of Vascular Registries Consensus Recommendations for Peripheral Revascularisation Registry Data Collection

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**WHAT THIS PAPER ADDS**

This paper presents the first international consensus on creation of a minimum and optimum core data set for registries devoted to peripheral arterial revascularisation. A modified Delphi approach with online interaction was used to achieve consensus among international experts from multiple countries. The concept of simple to more complex levels of data capture allows harmonisation at all levels, despite variation among registries. Adoption of a standard variable set by the national registries within the International Consortium of Vascular Registries will provide opportunities for more advanced collaborations, including amalgamation of large scale international data for assessment of outcomes after the introduction of new techniques and devices.

**Objective/Background:** To achieve consensus on the minimum core data set for evaluation of peripheral arterial revascularisation outcomes and enable collaboration among international registries.

**Methods:** A modified Delphi approach was used to achieve consensus among international vascular surgeons and registry members of the International Consortium of Vascular Registries (ICVR). Variables, including definitions, from registries covering open and endovascular surgery, representing 14 countries in ICVR, were collected and analysed to define a minimum core data set and to develop an optimum data set for registries. Up to three different levels of variable specification were suggested to allow inclusion of registries with simpler versus more complex data capture, while still allowing for data aggregation based on harmonised core definitions.

**Results:** Among 31 invited experts, 25 completed five Delphi rounds via internet exchange and face to face discussions. In total, 187 different items from the various registry data forms were identified for potential inclusion in the recommended data set. Ultimately, 79 items were recommended for inclusion in minimum core data sets, including 65 items in the level 1 data set, and an additional 14 items in the more specific level 2 and 3 recommended data sets. Data elements were broadly divided into (i) patient characteristics; (ii) comorbidities; (iii) current medications; (iv) lesion treated; (v) procedure; (vi) bypass; (vii) endarterectomy (viii) catheter based intervention; (ix) complications; and (x) follow up.

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**Conclusion:** A modified Delphi study allowed 25 international vascular registry experts to achieve a consensus recommendation for a minimum core data set and an optimum data set for peripheral arterial revascularisation registries. Continued global harmonisation of registry infrastructure and definition of items will overcome limitations related to single country investigations and enhance the development of real world evidence.

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**Keywords:** Consensus development, Delphi technique, Health services research, Peripheral arterial disease, Registries

## INTRODUCTION

Although peripheral arterial disease (PAD) remains an increasing burden for national healthcare systems with >200 million people affected worldwide,[1] many questions regarding treatment of this disease cannot be answered using evidence from trials. Thus, in the absence of such evidence, many recommendations in international practice guidelines are built on expert consensus.[2–4] As there are only a few randomised controlled trials (RCTs) with well known problems of selection bias and limited external validity, with reasonable efforts registries and registry based cohort studies can help to fill the gaps. Registries allow evaluation of treatment practice patterns, medical device evaluation, and can assess convergence of real world and RCT evidence.[5] Although multiple national vascular registries exist, lack of consensus around variables (and their definitions) makes aggregation and comparison of findings difficult.

International collaborations such as the International Consortium of Vascular Registries (ICVR; www.icvr-initiative.org) can help harmonise cross border research. The ICVR is comprised of countries with vascular surgery registries, including the Vascular Quality Initiative (VQI; www.vqi.org) in the USA and the Vascunet Collaboration, consisting of vascular registries from 12 countries in Europe and Australasia (www.vascunet.org). The ICVR was launched in 2014 with the goal of establishing a collaborative platform across registries to share data in order to improve the quality of vascular health care.[6] Contributions regarding abdominal aortic aneurysms (AAA) and carotid artery stenosis were recently published by this collaboration.[6–9] For this project, ICVR members aimed to apply a modified Delphi approach to achieve agreement on a minimum core data set and to create an optimum data set for registries capturing surgical and interventional PAD treatments.

## METHODS

The Delphi approach is widely accepted and used to gain consensus among a panel of experts,[10] and has previously been used in various specialties, including vascular surgery.[11–15] Representatives of 14 national vascular registries participating in the ICVR from Australia (Australasian Vascular Audit), Denmark (Karbase), Finland (HUSvasc), Germany (GermanVasc and Aortic Registry of the German Vascular Society), Hungary (Hungarian Vascular Registry), Iceland (Isvasc), Italy (Italian Vascular and Endovascular Registry), New Zealand (Australasian Vascular Audit), Norway (NORKAR), Spain, Sweden (Swedvasc), Switzerland (Swissvasc), and the USA (VQI) submitted their registries' current data sheets and definitions of data elements. An extensive narrative review of the literature was conducted to identify additional items in registry based studies on PAD. All participants in this study agreed to the scope of items identified through the abovementioned process. Members of the ICVR were then invited to participate in web based anonymised electronic questionnaires. Open source software (www.limesurvey.org) was used to generate the questionnaires. The participants could only submit one set of answers in each Delphi round. Following each round, a structured report, including anonymised group responses, mean results with SDs, as well as comments, were forwarded to the participants by email before they were invited to the next round. Each participant was asked to indicate whether they agreed that individual variables should be included in the consensus data set, and each item was scored on a five point Likert scale comprising "strongly agree", "agree", "neutral", "disagree", and "strongly disagree". Additionally, a free text comment could be submitted for each item. Items repeatedly rated with "strongly agree" or "agree" were recommended for the minimum data set. Items repeatedly rated with "strongly disagree" or "disagree" were eliminated from consideration. If consensus was not achieved after three rounds, the remaining items were discussed by the experts in two face to face ICVR meetings and added to the minimum data set if 80% of the experts supported the variable.

During this evaluation, it became apparent that it was important to determine not only which variables to include, but also what level of detail was needed for each variable included. By analysing each current national registry, it was determined that considerable variation existed in the level of detail collected, and in some cases the definition of the variables. In order to allow different levels of detail to be collected by different registries, but still allow harmonisation, three "levels" of variable recording detail but with common core definitions were created. Thus, reporting levels were stratified for data elements as level 1, 2, and 3, ranging from minimum to optimum. Reporting level 1 for variables were considered the minimum information necessary and typically have a simple input (yes, no) or simple numeric range. Level 2 and 3 variables have additional increasing specificity and granularity. For example, reporting the comorbidity of diabetes includes yes/no in reporting level 1. The more specific reporting level 2 includes the type of medical treatment (insulin, oral antidiabetic, etc.), whereas reporting level 3 includes HbA1c level

**Table 1.** Seventy-nine items in the minimal core and optimal data set for registries evaluating peripheral arterial revascularisation.

| Category | Variable | Reporting Level 1 | Reporting Level 2 | Reporting Level 3 | Comments | *Reference* |
|---|---|---|---|---|---|---|
| 1) Patient Characteristics | Birth Date | Day (dd), month (mm), and year (yyyy) of birth | | | Used to calculate age at time of procedure for subsequent analysis and de-identified data sharing. If regulations do not allow date collection, age (years) can be substituted. | |
| | Sex | Female, Male | Female, Male, Trans female, Trans male | | Sex at birth. Trans female has transitioned from female sex to male gender; Trans male has transitioned from male sex to female gender. | |
| | Weight | Body Weight in kg | | | | |
| | Height | Body Height in cm | | | | |
| | Functional Status | | Full activity, Light Work, Self Care, Assisted Care, Bedbound | Add disease specific quality of life survey, such as Vascu-Qol-6 | A person's level of functioning in terms of their ability to care for them self, daily activity, and physical ability (walking, working etc.). | *Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET,* et al. *Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649—55.* |
| | | | | | | *Nordanstig J, Wann-Hansson C, Karlsson J, Lundström M, Petterson M, Morgan MBF. Vascular Quality of Life Questionnaire-6 faciliates health related quality of life assessment in peripheral arterial disease. J VascSurg 2014;59:700-7.* |
| | Ambulation | | Fully Ambulatory, Ambulate with Prosthesis, Ambulate with Assistive Device, Wheelchair, Bedbound | Add walking distance survey such as Walking Improvement Questionnaire or GPS monitored walking | | |
| | ASA Grade | Normal healthy patient (1), mild systemic disease (2), severe systemic disease (3), severe systemic disease that is a constant threat to life (4), moribund patient who is not expected to survive without the operation (5), declared brain dead patient | | | | *Owens WD, Felts JA, Spitznagel EL. ASA Physical Status Classifications: A Study of Consistency of Ratings.Anesthesiology 1978;49:239-243. Recent update:* https://www.asahq.org/resources/clinical-information/asa-physical-status-classification-system |

*Continued*

**Table 1-*continued***

| Category | Variable | Reporting Level 1 | Reporting Level 2 | Reporting Level 3 | Comments | *Reference* |
|---|---|---|---|---|---|---|
| 2) Patient Co-morbidities | Diabetes | No, Yes | If Yes: Treated with: Insulin, Oral Antidiabetic, Both, Diet alone, No Treatment | HbA1c in % | Yes = clinical diagnosis documented in medical record based on Fasting $\geq$ 7 mmol/L or post glucose $\geq$ 11.1 mmol/L and/or HbA1c $\geq$ 6.5% and/or antidiabetic medication. | *Stoner MC, Calligaro KD, Chaer RA, Dietzek AM, Farber A, Guzman RJ,* et al. *Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. J Vasc Surg. 2016;64(1):e1-e21.* |
| | | | | | | *Kumar R, Nandhini LP, Kamalanathan S, Sahoo J, Vivekanadan M. Evidence for current diagnostic criteria of diabetes mellitus. World J Diabetes. 2016;7(17):396—405.* |
| | Current Renal Function | Normal, Abnormal | Serum Creatinine (in µmol/l or mg/dl) | Glomerular filtration rate (GFR) in ml/min (Cockcroft-Gault calculation) | As defined by the National Kidney Foundation::eGFR $<$60 mL/min/1.73 $m^2$ on two occasions separated by 3 months and that is not associated with a transient, reversible condition such as volume depletion. | *National Kidney F. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2002;39(2 Suppl 1):S1-266.* |
| | Current Dialysis | No, Yes | Duration of dialysis dependence (years) | | | |
| | Tobacco Use | Current Smoker, Former Smoker, Never Smoked | If Former Smoker: Quit Date | If Current or Former Smoker: Pack Years (py) Smoked | | *Stoner MC, Calligaro KD, Chaer RA, Dietzek AM, Farber A, Guzman RJ,* et al. *Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. J Vasc Surg. 2016;64(1):e1-e21.* |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Current Ischaemic Heart Disease | No, Yes | If Yes: Asymptomatic, Angina only during Strenuous or Prolonged Physical Activity, Symptoms with Everyday Living Activities, Inability to Perform any Activity Without Angina or Angina at Rest | | Yes = current angina or positive stress test indicating ischaemic heart disease | *Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF,* et al. *Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10): 1043—9.* |
| | Prior Myocardial Infarction | No, Yes | Add Prior Revascularisation: CABG, PCI | Add timing of MI and CABG/PCI: MI $\leq$ 6 Months, $>$ 6 Months; CABG/ PCI $<$ 5 years, CABG/ PCI $>$ 5 years | Yes = clinical history documented in medical record | *Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF,* et al. *Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10): 1043—9.* |
| | Congestive Heart Failure | Never, Former, Current | If Current: New York Heart Association (NYHA)-Classification for heart failure (Class I to IV) | Current Ejection Fraction in % | Current/former = clinical diagnosis/history documented in medical record, based onPonikowski et al. (2016) andLee et al. (1999): Patient has a history of or current symptoms of congestive heart failure, pulmonary oedema, or paroxysmal nocturnal dyspnea, physical examination showing bilateral rales or S3 gallop, or chest radiograph showing pulmonary vascular redistribution. | *Lee TH, Marcantonio ER, Mangione CM, Thomas EJ, Polanczyk CA, Cook EF,* et al. *Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation. 1999;100(10): 1043—9.* |

*Continued*

**Table 1-*continued***

| Category | Variable | Reporting Level 1 | Reporting Level 2 | Reporting Level 3 | Comments | *Reference* |
|---|---|---|---|---|---|---|
| | | | | | | *Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, CoatsAJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European journal of heart failure. 2016;18(8): 891—975.* |
| | Cardiac Arrhythmia | Never, Former, Current | If Current: Atrial, Ventricular, Previous Ablation, AV-Block with Pacemaker, Defibrillator (ICD), Previous Ablation and Pacemaker or ICD, Other | | Yes = clinical diagnosis documented in medical record, including atrial fibrillation, bradycardia, conduction disorders, premature contraction, tachycardia, ventricular fibrillation, other rhythm disorders. | |
| | Chronic Obstructive Pulmonary Disease | Never, Former, Current | If Current: No Treatment, Medical Treatment, Home Oxygen | | Yes = clinical diagnosis documented in medical record of chronic obstructive pulmonary disease or pulmonary medical treatment. As defined byStoner et al. (2016). | *Stoner MC, Calligaro KD, Chaer RA, Dietzek AM, Farber A, Guzman RJ,* et al. *Reporting standards of the Society for Vascular Surgery for endovascular treatment of chronic lower extremity peripheral artery disease. J Vasc Surg. 2016;64(1):e1-e21.* |
| | Hypertension | Never, Former, Current | If Current: Treated controlled, treated uncontrolled (blood pressure > 140/90 despite treatment) | | Blood pressure > 140/90 or medical treatment. | *Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M,* et al. *2013 ESH/ESC Guidelines for the management of arterial hypertension. Eur Heart J. 2013;34:2159-2219.* |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Prior PAD Revascularisation | No, Yes | If Yes: Interventional, Surgical, Both | Location: Inflow, Outflow; Type: Intervention, Bypass, Endarterectomy; Leg: R/L/Aorta | | |
| | Prior Amputation | Minor, Major | If Yes: Level: Toe(s), transmetatarsal, below knee, through knee, above knee, higher of R/L leg | | | *Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL,* et al. *Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg. 2009;50(6):1462−73 e1-3.* |
| 3) Current Medication | Aspirin | No, Yes | If Yes: $\leq$ 100 mg/d, 101 −320 mg/d, >320 mg/d | Add medication prescribed at discharge. | Medication in effect at time of procedure. | |
| | Other Platelet Inhibitor | No, Yes | if Yes, medication name | Add medication prescribed at discharge. | Medication in effect at time of procedure. | |
| | Statin | No, Yes | If Yes: Low Dose, High Dose | Add medication prescribed at discharge. | Medication in effect at time of procedure. | |
| | Anticoagulant | No, Yes | If Yes: Vitamin K Antagonist, Thrombin Inhibitor, Factor Xa Inhibitor, Other | Add medication prescribed at discharge. | Medication taken chronically before procedure (even if stopped in preparation for procedure). | |
| 4) Lesion treated | Symptoms for Right/Left Leg | Modified Rutherford-Classification: Asymptomatic, Mild Claudication, Moderate Claudication (>200m), Severe Claudication (<200m), Ischaemic Rest Pain, Ulcer/Necrosis, Non-healing Amputation, Both Ulcer/Non-healing Amputation, Acute Ischaemia | | | | will include ref RAPID for the modified Rutherford when published |

*Continued*

**Table 1-*continued***

| Category | Variable | Reporting Level 1 | Reporting Level 2 | Reporting Level 3 | Comments | *Reference* |
|---|---|---|---|---|---|---|
| | Foot Infection for Right/Left Leg | No, Yes | Grade 0 None, Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe | | | *Mills, Joseph L. Sr., MD,* et al. *(2014). The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk Stratification Based on Wound, Ischaemia, and Foot Infection (WIfI). Journal of Vascular Surgery, Volume 59 (Issue 1) pp.220-pp.234.e2,* https://doi.org/10.1016/j.jvs.2013.08.003 |
| | Tissue Loss Severity for Right/ Left Leg | | None, Grade 1, Shallow, Grade 2, Deep, Grade 3, Extensive | | | *Mills, Joseph L. Sr., MD,* et al. *(2014). The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk Stratification Based on Wound, Ischaemia, and Foot Infection (WIfI). Journal of Vascular Surgery, Volume 59 (Issue 1) pp.220-pp.234.e2,* https://doi.org/10.1016/j.jvs.2013.08.003 |
| | Ankle brachial index for Right/ Left Leg | Highest ABI$\geq$ 1.3, ABI $<$ 1.3 and $\geq$ 0.9, ABI $<$ 0.9 and $\geq$ 0.7, ABI $<$ 0.4, treated leg | ABI exact measurement R/L leg | ABI and TBI exact measurement R/L leg | | *Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C,* et al. *Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126(24):2890—909.* |
| | Artery vs. Graft | Native Artery, Bypass Graft | Graft Conduit: Vein, Prosthetic; Location: Supra-Inguinal, Infra-Inguinal | Add Graft Origin and Insertion | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Artery Treated or Bypassed | Aorta, iliac, femoral, popliteal, tibial | Aorta, common Iliac, external iliac, common + external iliac, internal iliac, common femoral, superficial femoral, profunda femoral, popliteal, SFA + popliteal, anterior tibial, posterior tibial, peroneal, tibioperoneal trunk, dorsal pedal, plantar | Add Artery Segment: Prox, Mid, Distal, as in Popliteal P1, P2, P3 segments | | |
| | Side for each Lesion Treated | Right, Left, Aorta | | | | |
| | Lesion Length | Short (<5cm for aorto-iliac and <25cm for femoropopliteal lesions), Long (≥5cm for aorto-iliac and ≥ 25cm for femoropopliteal lesions) | Length (cm) | | | *Acin F, de Haro J, Bleda S, Varela C, Esparza L. Primary nitinol stenting in femoropopliteal occlusive disease: a meta-analysis of randomized controlled trials. Journal of endovascular therapy: an official journal of the International Society of Endovascular Specialists. 2012;19(5):585—95.* |
| | | | | | | *Aboyans V, Ricco J, Bartelink MEL, Björck M, Brodmann M, Cohnert T et al., 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS), European Journal of Vascular and EndovascularSurgery (2017),* http://dx.doi.org/10.1016/j.ejvs.2017.07.018 |
| | Most Severe Stenosis | | Stenosis, Occlusion | Bollinger Score: Complete occlusion, Stenosis >50% of lumen, Stenosis of 25—50% of lumen, ≤25% stenosis of lumen | | *Bollinger A, Breddin K, Hess H, Heystraten FM, Kollath J, Konttila A,* et al. *Semiquantitative assessment of lower limb atherosclerosis from routine angiographic images. Atherosclerosis. 1981;38 (3—4):339—46.* |

*Continued*

**Table 1-*continued***

| Category | Variable | Reporting Level 1 | Reporting Level 2 | Reporting Level 3 | Comments | *Reference* |
|---|---|---|---|---|---|---|
| | Outflow from Treated Artery | | No outflow, one vessel, two vessels, three vessels | Modified Society for Vascular Surgery (SVS) runoff score: from 0 to 19 points | | *Davies MG, Saad WE, Peden EK, Mohiuddin IT, Naoum JJ, Lumsden AB. Impact of runoff on superficial femoral artery endoluminal interventions for rest pain and tissue loss. J Vasc Surg. 2008;48(3):619—25; discussion 25—6.* |
| 5) Procedure | Procedure Date | Day (dd), month (mm), and year (yyyy) of the procedure | | | Used to calculate length of hospital stay for subsequent analysis and de-identified data sharing. If regulations do not allow date collection, length of stay (days) can be substituted. | |
| | Living Location | | Home, Nursing Care Facility, Homeless | | | |
| | Admission Date | Day (dd), month (mm), and year (yyyy) of admission if hospitalised | | | Used to calculate length of hospital stay for subsequent analysis and de-identified data sharing. If regulations do not allow date collection, length of stay (days) can be substituted. | |
| | Discharge Date | Day (dd), month (mm), and year (yyyy) of discharge if hospitalised | | | Used to calculate length of hospital stay for subsequent analysis and de-identified data sharing. If regulations do not allow date collection, length of stay (days) can be substituted. | |
| | Discharge Destination | | Home, Nursing Care Facility, Rehabilitation Facility, Homeless, Other | | | |
| | Performance Site | | Hospital Outpatient, Hospital Inpatient, Ambulatory Centre, Office | | | |

| | | | | | |
|---|---|---|---|---|---|
| | Urgency of the Procedure | Elective, Urgent, Emergent | | | Elective = planned/ scheduled procedure; urgent = surgery within 24 hrs of admission or patient can't be discharged; emergency = surgery within 6 hrs of admission |
| | Provider Specialty | | Angiologist/Vascular Medicine, Cardiologist, Radiologist, Surgeon, Other | Multidisciplinary Team Decision (MTD) achieved prior to the Procedure? | |
| | Type of Procedure | Surgical Bypass, Endarterectomy, Catheter based Intervention, Hybrid | | | |
| 6) Bypass | Surgical Bypass Location for Right/Left Leg | Ax-fem, Ax-bifem, Aorto-fem, Aorto-bifem, Fem-fem, fem-ATK popliteal, Fem-BTK popliteal, Fem-tibial, Pop-tibial, Fem/Pop-DP/plantar | Proximal and Distal anastomosis location: Supra-aortic, Thoracic Aorta, Abdominal Aorta, Common Iliac Artery, External Iliac Artery, Internal Iliac Artery, Common Femoral Artery, Deep Femoral Artery, Superficial Femoral Artery, Popliteal Artery Above Knee, Popliteal Artery BelowKnee, Tibioperoneal Trunk, Anterior Tibial Artery, Posterior Tibial Artery, Peroneal Artery, Pedal Artery, Plantar, Other | | |
| | Conduit | Prosthetic, Vein | Prosthetic: Polyester, PTFE, heparin bonded; Cryopreserved allograft; Vein: great saphenous reversed, in situ, translocated; femoral vein; small saphenous; arm vein | Add number of vein segements used or UDI identification of prosthetic graft | |
| 7) Endarterectomy | Endarterectomy Location for Right/Left Leg | Aorta, common iliac, external iliac, common femoral, profunda femoral, superficial femoral, Popliteal | | | |

*Continued*

**Table 1-*continued***

| Category | Variable | Reporting Level 1 | Reporting Level 2 | Reporting Level 3 | Comments | *Reference* |
|---|---|---|---|---|---|---|
| | Patch Used | No, Yes | None, Polyester, PTFE, heparin bonded, Bovine pericardium, Autogenous vein | UDI identification of prosthetic patch | | |
| 8) Catheter based Intervention | Access Site(s) | | Femoral, Popliteal, Pedal, Arm | Femoral Retrograde, Femoral Antegrade, SFA, Popliteal, Dorsal Pedal, Posterior Tibial, Brachial, Radial, Axillary, Graft, Femoral Retro to Antegrade, Femoral Ante to Retrograde | | |
| | Largest Sheath Size | | French size number | | | |
| | Intervention Type | Balloon angioplasty, drug coated balloon, bare metal stent, drug eluting stent, covered stent, atherectomy, other | Balloon angioplasty, drug coated balloon, bare metal stent, drug eluting stent, mechanical thrombectomy, covered stent, brachytherapy, atherectomy, laser assisted angioplasty, aspiration, scoring balloon, cutting balloon, cryoplasty, other | GUDID identification of device | | |
| | Planned Adjunct Procedure | No, Yes | None, Thrombolysis Pharmacological, Thrombolysis Mechanical, Suction Thrombectomy, Embolic Protection Device, IVUS, CTO-Device, Bypass, Endarterectomy | GUDID identification of device | | |
| | Closure Device | No, Yes | If Yes: List Device Name | GUDID identification of device | | |
| | Unplanned Procedure for Complication | Bailout Stent, Bailout Stent graft | None, Thrombolysis Pharmacological, Thrombolysis Mechanical, Suction Thrombectomy, Embolic Protection Device, IVUS, CTO-Device, Bypass, Endarterectomy | GUDID identification of device | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Final Technical Result | Successful (Stenosis $\leq$ 30%), Stenosis $>$ 30% or 10mm Gradient, Target Lesion Occlusion, Failure (unable to cross or deploy device) | Bollinger Score: Complete occlusion (1), Stenosis $>$ 50% of lumen (2), Stenosis of 25—50% of lumen (3), $\leq$ 25% stenosis of lumen (4), Failure (unable to cross or deploy device) | | Including only treated region | *Bollinger A, Breddin K, Hess H, Heystraten FM, Kollath J, Konttila A,* et al. *Semiquantitative assessment of lower limb atherosclerosis from routine angiographic images. Atherosclerosis. 1981;38 (3—4):339—46.* |
| 9) Complications | Unplanned Amputation for Right/Left Leg | No, Minor Amputation, Major Amputation | Level: Toe(s), transmetatarsal, below knee, through knee, above knee, higher of R/L leg | | Amputation that resulted from a complication or abrupt change in disease severity that was not anticipated at the time of the procedure | |
| | Site or Graft Thrombosis for Right/Left Leg | No, Yes | If Yes: No Treatment, Medical Treatment, Interventional Treatment, Surgical Treatment | | | |
| | Site or Graft Stenosis for Right/Left Leg | | No, Yes | If Yes: No Treatment, Medical Treatment, Interventional Treatment, Surgical Treatment | Graft Stenosis is defined as $\geq$ 70% diameter reducing stenosis by Doppler Ultrasonography, CT Angiography, MR Angiography or Fluoroscopy | |
| | Distal Embolisation for Right/Left Leg | No, Yes | If Yes: No Treatment, Medical Treatment, Interventional Treatment, Surgical Treatment | | | |
| | Target Lesion Dissection for Right/Left Leg | No, Yes | If Yes: No Treatment, Medical Treatment, Interventional Treatment, Surgical Treatment | | | |
| | Device Failure | No, Yes | If Yes: Failure to Deploy, Fracture, Rupture, Other | | | |
| | Bleeding, Hematoma, Pseudoaneurysm | No, Yes | If Yes: Minor, Transfusion, Thrombin Injection, Surgical Treatment | | | |
| | Compartment Syndrome | No, Yes | If Yes: Medical, Surgical Treatment | | | |
| | Wound Infection | No, Yes | If Yes: Medical, Surgical Treatment | | | |
| | Myocardial Infarction | No, Yes | If Yes: Troponin only (NSTEMI), ECG (STEMI) or Clinical Symptoms | | | |

*Continued*

**Table 1-*continued***

| Category | Variable | Reporting Level 1 | Reporting Level 2 | Reporting Level 3 | Comments | *Reference* |
|---|---|---|---|---|---|---|
| | Stroke | No, Yes | If Yes: Minor, Major | Modified Rankin level | As defined byEaston et al. (2009). | *Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E,* et al. *Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/ American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists. Stroke; a journal of cerebral circulation. 2009;40(6):2276—93.* |
| | New Dialysis Required | No, Yes | No, Acute In hospital only, Chronic Dialysis | | Any acute renal replacement therapy for acute kidney injury (intermittent/ continuous, haemodiafiltration, haemofiltration, haemodialysis etc.). | |
| | Death | No, Yes | If Yes: Death caused by procedure? | | | |
| 10) Follow up | Follow up Date | Day (dd), month (mm), and year (yyyy) of the procedure | | | Used to calculate duration of follow up for subsequent analysis and de-identified data sharing. If regulations do not allow date collection, follow up duration (months) can be substituted. | |
| | Death | No, Yes | If Yes: Date of Death | If Yes: Procedure related, Not Procedure related | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Functional Status | | Full activity, Light Work, Self Care, Assisted Care, Bedbound | Add disease specific quality of life survey, such as Vascu-Qol-6 | A person's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working etc.). | *Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET,* et al. *Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649 —55.* |
| | | | | | | *Nordanstig J, Wann-Hansson C, Karlsson J, Lundström M, Petterson M, Morgan MBF. Vascular Quality of Life Questionnaire-6 faciliates health-related quality of life assessment in peripheral arterial disease. J VascSurg 2014;59: 700-7.* |
| | Ambulation | | Fully ambulatory, Ambulate with Prosthesis, Ambulate with Assistive device, Wheelchair, Bedbound | Add walking distance survey such as Walking Improvement Questionnaire or GPS monitored walking | | |
| | Symptoms for Right/Left Leg | Modified Rutherford-Classification: Asymptomatic, Mild Claudication, Moderate Claudication (> 200m), Severe Claudication (< 200m), Ischaemic Rest Pain, Ulcer/Necrosis, Non-healing Amputation, Both Ulcer/Non-healing Amputation, Acute Ischaemia | | | Level 1 Modified Rutherford | !need to ref RAPID for the modified Rutherford! |
| | Foot Infection for Right/Left Leg | No, Yes | If Yes: Grade 0 None, Grade 1 Mild, Grade 2 Moderate, Grade 3 Severe | | | *Mills, Joseph L. Sr., MD,* et al. *(2014). The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk Stratification Based on Wound, Ischemia, and Foot Infection (WIfI). Journal of Vascular Surgery, Volume 59 (Issue 1) pp.220-pp.234.e2,* https://doi.org/10.1016/j.jvs.2013.08.003 |

*Continued*

**Table 1-*continued***

| Category | Variable | Reporting Level 1 | Reporting Level 2 | Reporting Level 3 | Comments | *Reference* |
|---|---|---|---|---|---|---|
| | Tissue Loss Severity for Right/ Left Leg | | If Yes: None, Grade 1, Shallow, Grade 2, Deep, Grade 3, Extensive | | | *Mills, Joseph L. Sr., MD,* et al. *(2014). The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Risk Stratification Based on Wound, Ischemia, and Foot Infection (WIfI). Journal of Vascular Surgery, Volume 59 (Issue 1) pp.220-pp.234.e2,* https://doi.org/10.1016/j.jvs.2013.08.003 |
| | Amputation for Right/Left Leg | No, Minor, Major | If Yes: Level: Toe(s), Transmetatarsal, Below Knee, Through Knee, Above Knee, Higher if Right/Left Leg | If Yes: Date of Amputation | | |
| | Graft/Site Patency for Right/Left Leg | No, Yes | Method of Assessment (Clinical Examination, ABI, Ultrasound, MRA, CTA, Fluoroscopy, Other) | | Patency of the treated index lesion. | |
| | Graft/Site Re-Intervention for Right/Left Leg | No, Yes | If Yes: Interventional, Surgical, Both | If Yes: Date of Re-Intervention | | |
| | Major Adverse Cardiac Events (MACE, MACCE) | No, Yes | If Yes: Stroke, MI, CABG, PCI | If Yes: Date of Coronary Procedure or Death | Composite endpoint: Any major adverse cardiac or cerebrovascular event (MACE, MACCE) such as all cause death, myocardial infarction, stroke, or coronary vessel revascularisation. | *Conte MS, Geraghty PJ, Bradbury AW, Hevelone ND, Lipsitz SR, Moneta GL,* et al. *Suggested objective performance goals and clinical trial design for evaluating catheter-based treatment of critical limb ischemia. J Vasc Surg. 2009;50(6):1462—73 e1-3. Kip KE, Hollabaugh K, Marroquin OC, Williams DO. The problem with composite end points in cardiovascular studies: the story of major adverse cardiac events and percutaneous coronary intervention. Journal of the American College of Cardiology. 2008;51(7):701—7.* |
| | Procedure related Re-Admission | No, Yes | If Yes: For infection, Treatment Failure, Systemic Complication | If Yes: Date of Re-Hospitalisation | Any hospital readmission or rehospitalisation after discharge. | |

(see Table 1). Some data elements, such as urgency of treatment and type of procedure were judged sufficiently important to always be required (level 1).

Statistical analyses were performed with SPSS Statistics software version 23.0 (IBM, Armonk, NY, USA).

## RESULTS

Thirty-one experts were contacted and 25 accepted and completed the first online survey. In total, 187 items were submitted by them and were included in the panel discussion (Table 2). The items were reviewed by the expert panel and subsequently sorted into 11 main topics: (i) patient characteristics; (ii) comorbidities; (iii) current medications; (iv) lesion treated; (v) procedure; (vi) bypass; (vii) endarterectomy; (viii) catheter based intervention; (ix) complications; (x) follow up. The panel comprised vascular surgeons representing their national registry in ICVR, from three continents, 14 countries, and 18 institutions. The final number of data elements was not specified a priori. All panel experts (100%) completed rounds 1—4 and 18 (90%) completed round 5. The Delphi process (Fig. 1) resulted in the ICVR suggested data set for PAD revascularisation registries with different levels of potential detail for each variable (Table 1). After two Delphi rounds, 68 items were designated twice as "agree" or "strongly agree", whereas 60 items were designated twice as "disagree" or "strongly disagree". After five Delphi rounds, a total of 79 items were included in the recommended data set, of which 65 were included in the level 1 version, with an additional 14 included with more data specificity at the level 2 and 3 versions (Table 1). For example interventional device data can be recorded as level 1, which reports devices by class (plain angioplasty, drug coated balloon angioplasty, atherectomy, stent, etc.); level 2, which includes adjuncts such as embolic protection; and level 3, which records the Global Unique Device Identification Database.

It was recommended that all registries create an option to indicate that the state of the variable is "unknown", in order to differentiate omitted from unknown data, and not force users to choose an option when it is unclear. For simplicity, the "unknown" options for each variable have not been included in Table 1.

## DISCUSSION

In this modified Delphi study with international experts, consensus was achieved on items to be collected in registries on peripheral arterial revascularisation. Sixty-five items were recommended for a minimum core (level 1) data set with an additional 14 variables with increased specification recommended for the optimum dataset (level 2—3). According to the existing literature and methodological recommendations, the minimum and optimum number for Delphi studies is two rounds. Regarding the panel size, at least 6—11 members are usually recommended to work efficiently. In this Delphi study more experts were included ($n = 25$) and there were more rounds ($n = 5$), emphasizing the rigor of the approach to address the complexity of the

| | | | |
|---|---|---|---|
| Ankle brachial index for Right/ Left Leg | Highest ABI $\geq$ 1.3, ABI $<$ 1.3 and $\geq$ 0.9, ABI $<$ 0.9 and $\geq$ 0.7, ABI $<$ 0.4, treated leg | ABI exact measurement R/L leg | ABI and TBI exact measurement R/L leg |

*Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al. Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation. 2012;126(24):2890—909.*

**Table 2.** 187 items submitted by the expert panel or identified by the literature review.

| |
|---|
| Date of admission |
| Date of procedure |
| Date of discharge |
| Mode of admission (e.g. emergency vs. elective)/ Urgency of the procedure |
| Performance site |
| Intensive care unit LOS |
| Special discipline responsible for hospital treatment |
| Hospital capacity/volume/teaching status |
| Discharge destination |
| Age (Birth Date) |
| Sex/Gender |
| Income |
| Occupation |
| Housing |
| Functional status |
| Ambulation |
| Nursing status |
| Migration background |
| Race and ethnicity |
| Education |
| Health insurance status |
| Walking distance |
| Existence of rest pain |
| Existence of ulcers |
| Existence of gangrene |
| Existence of infection |
| Fontaine classification (symptoms of index leg) |
| Rutherford classification (symptoms of index leg) |
| Tissue loss severity (for index leg) |
| WIfI Score |
| Texas classification |
| Wound depth |
| Angiosome |
| Acute limb ischaemia (ALI) |
| Ankle brachial index (ABI) |
| Toe pressure |
| Oscillographics |
| Transcutaneous oxygen measurement (tcp O2) |
| Duplex ultrasound |
| Contrast enhanced CT angiography (SCTA) |
| Contrast enhanced MR angiography (MRA) |
| Invasive digital subtraction angiography (DSA) |
| TASC classification |
| Exact location of treated lesions/artery treated or bypassed |
| Side for each lesion treated |
| Exact location of all lesions (even untreated) |
| Grade of stenosis |
| Length of stenosis |
| Inflow quantification |
| Outflow quantification (from treated artery) |
| Genuine vessel or graft/artery vs. graft |
| Pretreatment of lesion |
| Laboratory findings (e.g. cholesterol, HDL, platelet count, haemoglobin) |
| Ever smoked/Tobacco use |
| Current smoking/Tobacco use |
| Diabetes type 1 |
| Diabetes type 2 |
| Hypertension |
| Hyperlipidemia |
| Weight (or Body Mass Index) |
| Height (or Body Mass Index) |
| ASA Grade (Risk score: American Society of Anesthesiologists) |
| Renal function |
| Dialysis |
| Chronic obstructive pulmonary disease (COPD) |
| Myocardial infarction (MI) |
| Congestive heart failure (CHF) |
| Atrial fibrillation or flutter (AF) |
| Cardiac arrhythmia |
| Pacemaker, defibrillator, orthopedic endoprosthesis or other artificial material |
| Coronary artery disease (CAD)/Ischaemic heart disease |
| History of stroke or TIA |
| History of PAD revascularisation |
| History of acute limb ischaemia |
| History of amputation |
| Open wound or wound infection |
| History of vascular procedures |
| Aspirin |
| P2Y12/Clopidogrel/Other platelet inhibitor |
| Other platelet inhibitors |
| Vitamin K antagonists |
| New oral anticoagulants |
| Low dose heparin (not procedural) |
| High dose heparin (not procedural) |
| Beta blockers |
| ACE inhibitors or sartans |
| Statin/Lipid lowering agents |
| PGE1 infusions |
| Cilostazol |
| Naftidrofuryl oxalate |
| Pentoxifylline |
| Inositol nicotinate |
| Special discipline performing the procedure |
| Level of residency supervision |
| Pre-treatment of lesion |
| Side of intervention |
| Principal anaesthesia technique |
| Intra-procedural heparin |
| Additional anaesthesia technique |
| Operation time |
| Type of main endovascular procedure |
| Hybrid procedure |
| Type of devices used |
| Instructions for Use (IFU) followed |
| Detailed device information (includes length and diameter of different devices) |
| Atherectomy device |
| PTA device |
| Stent device |
| Distal protection device |
| Embolic protection device |
| Chronic total occlusion (CTO) device |
| Access site and approach |
| Access guidance |
| Largest sheath size |
| Use of duplex ultrasound (access) |
| Information about sheath used |
| Information about guidewire used |
| Planned adjunctive procedure |

| |
|---|
| Thrombolysis |
| Mechanical thrombectomy |
| Additional approach (e.g. Nitro) |
| Completion angiography performed |
| Final technical result (includes technical success) |
| Dose area product (DAP)/Radiation dosage |
| Treatment aborted or incomplete |
| Acute conversion to open surgery |
| Patency |
| Closure device |
| Type of main open procedure |
| Hybrid procedure |
| Access site and approach |
| Diathermia or ligature used for cut down |
| Existence of infection |
| Conduit |
| Type of bypass |
| Type of prosthetic grafts used |
| Type and location of vein graft |
| Instructions for Use (IFU) followed |
| Type of surgical suture material |
| Proximal anastomosis |
| Distal anastomosis |
| Blood loss |
| Re-intervention of bypass |
| Completion angiography performed |
| Treatment aborted or incomplete |
| Acute conversion to endovascular procedure |
| Patency |
| Dissection |
| (Pseudo)Aneurysm |
| Arteriovenous fistula |
| Distal embolisation |
| Perforation |
| Bleeding |
| Myocardial infarction (MACE) |
| Death (MACE) |
| Stroke or TIA (MACE) |
| Major amputation (MALE) |
| Minor amputation (MALE) |
| Re-operation or re-intervention |
| Transfusion |
| Acute limb ischaemia/Lower extremity ischaemia |
| Device fracture or rupture |
| Compartment syndrome |
| Nerve injury |
| Wound infection or graft infection |
| Lymphoedema |
| Lymph fistula or seroma |
| Re-intervention open surgery |
| Re-intervention endovascular |
| Pneumonia |
| Deep venous thrombosis (DVT) |
| Pulmonary embolism |
| Acute renal replacement therapy |
| Delirium |
| Stent or graft thrombosis |
| Gastrointestinal complications |
| MACE |
| MALE |
| Patency |
| Limb salvage |
| Quality of life |
| Walking distance |
| Rehospitalisation |
| Re-intervention |
| Infection |
| Ankle brachial index (ABI) |
| Destination at discharge/discharge destination |

research questions. For example, the additional three rounds resulted in 58 positive or negative recommendations that influenced the final result. An existing and well established international research collaboration of ICVR was used in order to include a high proportion of vascular registry experts. In addition to two face to face meetings, all comments of the panel experts were shared electronically. This innovative approach made the processes rigorous and efficient, considering the fact that international experts from different time zones participated in this Delphi study.

Importantly, the Delphi process resulted in a reduction from 187 items originally included in PAD registries across the ICVR to 79 items in the optimum data set. This is still a large number of variables after the consensus process and may pose a hurdle owing to the burden of data collection. However, considering the complexity of the PAD, and the abundance of medical and surgical treatment alternatives, a more comprehensive data collection is necessary to allow meaningful data analysis. Ultimately, the trade-off between complexity and practicality was challenging and proved to be even more difficult when designing a registry database for PAD than for AAA or carotid artery disease.

The key to collaboration and data sharing among registries is harmonisation of data elements, definitions, and method for similarly recording each variable. While each registry would prefer to register the most detailed data possible, real world practice and current lack of ability to easily extract uniform data from all electronic medical record (EMR) systems makes this impractical. For this reason, it is valuable to recommend not only a minimum core data set (and uniform definitions) that can be used by all registries, but also to recommend more detailed categories (levels) for data recording as registries mature and EMR extraction becomes more feasible. It is important that these higher levels of data collection harmonise with core levels so that all data can be merged at some level. The authors believe that the current proposal of core to optimum data collection “levels” is a novel contribution that could be valuable for other specialties.

It is recognised that the number and selection of data elements is contingent on the intended uses of the registry. A PAD revascularisation registry designed for quality improvement would probably have different elements or fewer granular data than one established for clinical research or device evaluation. In this work there was an attempt to balance the competing interests of inclusiveness with the practicality of data entry. The concept of different levels of modern web based registries with contingent variables already enables efficient data entry, but there is much work to be done. In the future, it is expected that

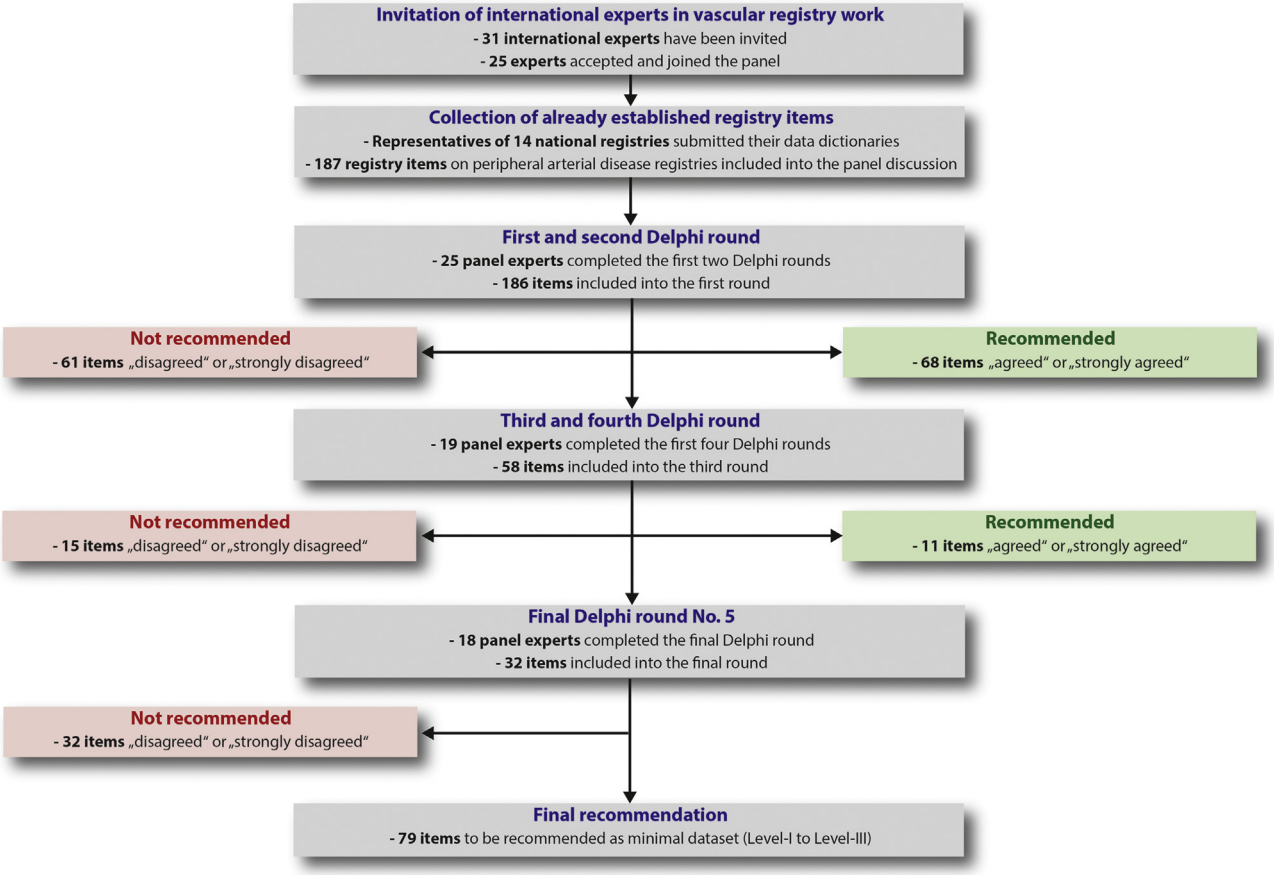


**Figure 1.** Flow chart of the modified Delphi study.

registries will integrate with EMR systems and claims data to allow more automated data capture to minimise the work of data entry. Clearly, such future developments facing big-data applications will need to meticulously deal with data privacy and safety concerns.[16]

Harmonisation of registries will allow for more meaningful comparisons of practice patterns, medical device performance, and outcomes across countries. Such collaboration will improve our ability to generate real world evidence and design registry based studies of peripheral vascular interventions. In the future, registry based studies may supplement the evidence gained from RCTs and prospective cohort studies. Similar work has been reported by the Registry Assessment of Peripheral Arterial Devices (RAPID) group for multispecialty collaboration within USA.[17,18] The ICVR-recommended data set has many agreements with data elements and definitions in RAPID, which is focused on device evaluation for peripheral vascular intervention in USA. The current ICVR database recommendations extend those of RAPID to encompass both open and endovascular revascularisation and for international studies, while still allowing device evaluation. These efforts provide an important opportunity for global harmonisation of clinical data to improve vascular health care. Existing ICVR registry members are committed to adopting these data elements as the next stage of evolution for ICVR.

## CONCLUSIONS

This large scale modified Delphi study among international vascular registry specialists achieved a consensus agreement on a minimum core and optimum data set for registries evaluating peripheral arterial revascularisation. It reduced the overall number of initially suggested variables by nearly half. Global harmonisation of registry infrastructure and definition of items will overcome limitations related to single country investigations and has the potential to speed up and enhance acquisition of real world evidence. National registries in the ICVR plan to incorporate these core data elements into their PAD registries to increase the opportunity for future collaboration.

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# Editor's Choice — Recommendations for Registry Data Collection for Revascularisations of Acute Limb Ischaemia: A Delphi Consensus from the International Consortium of Vascular Registries

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**WHAT THIS PAPER ADDS**

This international Delphi process has generated a core set of items to be captured by vascular quality registries that are specific for acute limb ischaemia (ALI) and supplement previous recommendations for chronic peripheral arterial occlusive disease. This core set can be used to standardise data collection for comparability across registries and thereby facilitate amalgamation of real world data, and comparisons between centres, regions, and countries. Ultimately, harmonised registries will provide a base for international collaboration to fill evidence gaps and contribute to improving the care of patients with ALI.

**Objective:** To develop a minimum core data set for evaluation of acute limb ischaemia (ALI) revascularisation treatment and outcomes that would enable collaboration among international registries.

**Methods:** A modified Delphi approach was used to achieve consensus among international multidisciplinary vascular specialists and registry members of the International Consortium of Vascular Registries (ICVR). Variables identified in the literature or suggested by the expert panel, and variables, including definitions, currently used in 15 countries in the ICVR, were assessed to define both a minimum core and an optimum data set to register ALI treatment. Clinical relevance and practicability were both assessed, and consensus was defined as $\geq$ 80% agreement among participants.

**Results:** Of 40 invited experts, 37 completed a preliminary survey and 31 completed the two subsequent Delphi rounds via internet exchange and face to face discussions. In total, 117 different items were generated from the various registry data forms, an extensive review of the literature, and additional suggestions from the experts, for potential inclusion in the data set. Ultimately, 35 items were recommended for inclusion in the minimum core data set, including 23 core items important for all registries, and an additional 12 more specific items for registries capable of capturing more detail. These 35 items supplement previous data elements recommended for registering chronic peripheral arterial occlusive disease treatment.

**Conclusion:** A modified Delphi study allowed 37 international vascular registry experts to achieve a consensus recommendation for a minimum core and an optimum data set for registries covering patients who undergo ALI revascularisation. Continued global harmonisation of registry infrastructure and definition of items allows international comparisons and global quality improvement. Furthermore, it can help to define and monitor standards of care and enable international research collaboration.

**Keywords:** Acute limb ischaemia, Consensus development, Delphi technique, Health services research, Registries
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## INTRODUCTION

Although more widespread antithrombotic treatment of atrial fibrillation (one of the most important causes) has led to a decreasing incidence of acute limb ischaemia (ALI), this limb and life threatening condition remains a great challenge for vascular surgeons and interventionists.[1] Like all emergency conditions, ALI is difficult to study. To date, the evidence base regarding open surgical vs. thrombolytic therapy is limited to a few outdated randomised controlled

[†] The full list of Acute Limb Ischaemia Collaborators is available in Appendix S1 (Supplementary Material).

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trials.[2] Thus there is a need to gather real world data on risk factors, treatment, and outcome at the time when novel pharmaceutical agents and interventional techniques have entered clinical practice. Patient registries can provide valuable contemporary data to address open questions. However, there is no consensus among national registries regarding which data elements are critical or how to categorise these to allow harmonisation.

International collaborations such as the International Consortium of Vascular Registries (ICVR; www.icvr-initiative.org) are intended to promote cross border research. The ICVR includes countries with vascular surgery registries such as the Vascular Quality Initiative (www.vqi.org) in the USA and the Vascunet collaboration of vascular registries from 20 countries in Europe and Australasia (www.vascunet.org).[3,4] The ICVR was established in 2014 with the goal of implementing a collaborative platform across registries to share data in order to improve the quality of vascular health care.[5] Contributions regarding abdominal aortic aneurysms,[6] carotid artery stenosis,[7] and recommendations on chronic peripheral arterial occlusive disease (PAOD) revascularisation registries were recently published by this collaboration.[8,9] In the current project, ICVR members applied a modified Delphi approach to achieve agreement on both a minimum core and optimum dataset for registries capturing risk factors, treatment patterns, and outcome for patients treated for ALI in addition to prior recommendations on chronic PAOD. The results of the current study aim to supplement the European Society for Vascular Surgery (ESVS) practical guidelines on ALI (to be published in 2020). Furthermore, the results of the current study aim to amplify prior recommendations on chronic PAOD. Registries already collecting patients with chronic PAOD can extend their scope by using the current recommendations.

## METHODS

The Delphi approach is widely accepted and used to gain consensus among a panel of experts,[10] and has previously been used in various specialties, including vascular medicine.[8,11–15] The registry data forms of all 14 registries participating in the ICVR were reviewed to identify relevant items for ALI needed to supplement current ICVR recommendations on registration of chronic PAOD revascularisations.[8] Additionally, a narrative literature review was conducted to identify potential additional items to record for ALI. Medline was searched for meta-analyses, systematic reviews, and guidelines, using a combination of keywords referring to ALI (acute limb ischaemia, acute limb ischaemia, acute arterial occlusion, acute leg ischaemia, acute leg ischaemia, ischaemic foot) and quality improvement measurement (registry, registries, outcome, end point, follow up, measures, performance measures, items). In addition, a grey literature search was performed: websites concerning ALI or indicators of outcome were searched by hand for guidelines, statements, and quality indicators. The search was restricted to the English language. No restriction regarding publication date was used. All ICVR experts were invited to evaluate the list of items identified during this process and to suggest additional items to be included in the Delphi process. All participants agreed to the scope of items identified through the above mentioned process. Members of the ICVR and members of the writing committees of the 2017 European Society of Cardiology Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the ESVS,[16] as well as the ESVS guidelines on ALI (to be published in 2020), were then invited to participate in web based, anonymised electronic questionnaires. Open source software (Limesurvey, Hamburg, Germany; www.limesurvey.org) was used to generate the questionnaires and there was no further quality control of the software by the authors. The participants could only submit one set of answers in each Delphi round. Following the preliminary survey and first round, a structured report, including distribution of the group responses using bar charts, as well as comments, was forwarded to the participants via email before they were invited to the next round. In the first round, each participant was asked to score each item in terms of clinical relevance, as well as practicability in clinical practice. Each item was scored for both parameters on a five point Likert scale, comprising “strongly agree”, “agree”, “neutral”, “disagree”, and “strongly disagree”. Items received a consensus recommendation for the minimum dataset if at least 80% of the participants voted “strongly agree” or “agree” for clinical relevance and practicability. Items with $<$60% agreement for clinical relevance or practicability were eliminated from further consideration. In line with prior recommendations,[8] a set of minimum core data elements felt necessary for any registry (level 1) were defined, as well as an optimum set of additional data elements (level 2) recommended for registries capable of collecting more detailed information. In general, level 1 variables typically had simple options (e.g., yes, no), while level 2 variables had increasing specificity. For example, only a history of a peripheral aneurysm was recommended for level 1, while the specific location and diameter of a peripheral aneurysm were recommended for level 2 reporting (see Table 1). Level 1 data elements were judged sufficiently important to always be registered. The median time for the experts to answer a question in the modified Delphi process (duration between opening the questionnaire and saving the results) is displayed as median time in minutes, including interquartile range (IQR).

### *Statistical analysis*

The agreement of individual experts’ answers in both Delphi rounds was tested using the Student *t* test and mean difference for the tendency of answering. Missing data due to non-participation in one round were not imputed. Statistical analyses were performed with software R version 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria).

## RESULTS

Of 40 experts invited, 37 (93%) accepted and completed the preliminary survey. The panel comprised vascular surgeons

**Table 1. Thirty-five items in five categories (risk factors, medication, clinical presentation, procedure details, outcome) to be recommended for acute limb ischaemia revascularisation registries**

| Item | Level 1 | Level 2/3 |
|---|---|---|
| *Risk factors* | | |
| History of malignancy | Yes/no | If yes: type of malignancy, type of treatment |
| History of atrial fibrillation or atrial flutter | Yes/no | If yes: paroxysmal vs. permanent |
| History of arterial embolisation | Yes/no | |
| History of peripheral aneurysm | Yes/no | If yes: location and diameter of peripheral aneurysm |
| History of stroke | Yes/no | |
| History of aortic aneurysm or dissection | Yes/no | |
| Prior revascularisation/ reconstruction of affected leg | Yes/no | Type of prior revascularisation/ reconstruction; if any: prior catheter based intervention |
| *Medication* | | |
| If any: type of anticoagulants at presentation | For example, vitamin K antagonists, direct oral anticoagulants, heparin | If any: name and dose of anticoagulants |
| Any recent stop or switch (change) of anticoagulants | −/− | Yes/no |
| *Clinical presentation* | | |
| Rutherford ischaemia classes | I, IIA, IIB, III | |
| Sensory deficit | Yes/no | |
| Motor deficit | Yes/no | |
| Upper vs. lower extremity | Arm/leg/both | |
| Aetiology or cause of acute limb ischaemia | −/− | Native artery thrombosis, embolus, acute native artery occlusion or thrombosis or embolus, thrombosed arterial aneurysm, occluded previous vascular reconstruction, other (e.g., popliteal entrapment syndrome) or unknown |
| Concomitant embolic focus | −/− | Coronary arteries, carotid or vertebral arteries, visceral arteries, renal arteries, other |
| Level/location of index occlusion | −/− | Upper/lower arm, aorto-iliac/ above the knee/below the knee |
| *Procedure* | | |
| Ischaemia duration: time from first symptom to procedure | In hours and minutes | |
| Type of treatment/procedure Including: open surgical thrombo-embolectomy, catheter directed thrombolysis, catheter guided thrombo-embolectomy | Multiple selection: best medical treatment only, primary amputation only, open surgical thrombo-embolectomy, catheter-directed thrombolysis, catheter guided thrombo-embolectomy | |
| Primary fasciotomy | Yes/no | |
| Intra-operative completion angiography | Yes/no | |
| *Outcome* | | |
| Rutherford ischaemia classes | −/− | I, IIA, IIB, III |
| Residual sensory deficit | −/− | Yes/no |
| Residual motor deficit | −/− | Yes/no |
| Compartment syndrome | Yes/no | If compartment syndrome: unplanned fasciotomy |
| Major bleeding or haemorrhage | Yes/no | |
| If any: intracranial haemorrhage | Yes/no | |
| Haemorrhage at access site | −/− | Yes/no |
| Infection at (surgical) access site | −/− | Yes/no |
| Acute kidney injury | Yes/no | |
| Multi-organ failure | −/− | Yes/no |
| If death: cause of death | −/− | Death related to acute limb ischaemia? |

and interventionists (both internal medicine specialists and radiologists), representing 15 countries and 36 institutions. In total, 76 items potentially useful to register ALI treatment were identified from the available literature, while another 79 items were already recommended for chronic PAOD in a prior study and, accordingly, excluded from this evaluation. Additionally, 41 complementary items were suggested by the expert panel during the preliminary survey. Ultimately, 117 items were included in the panel discussion (Table S1; see Supplementary Material). The final number of data elements was not defined prior to the Delphi rounds. The items were reviewed by the authors, and subsequently sorted into five main categories: risk factors, medication, clinical presentation, procedure details, and outcome.

Thirty-seven panel experts completed round 1 (median 22.6 min, IQR 18.0) and 31 of them also completed round 2 (median 7.7 min, IQR 3.7).

After the first Delphi round, 37 items reached the 80% consensus limit for clinical relevance. Of these, 23 items also reached the 80% consensus limit for practicability (excellent level of agreement) (Fig. 1) and one item failed to reach the 60% limit for practicability. Another 61 items failed to reach the 60% limit for clinical relevance. After a group discussion, 33 items were recommended after the first Delphi round and an additional 23 items with ambiguous results (between 60% and 80% limit of agreement) were forwarded to the second Delphi round.

After two Delphi rounds, two of 23 items with ambiguous results (from round 1) reached the 80% consensus limit for clinical relevance and practicability: "aetiology or cause of ALI" and "time from the first symptom to procedure" reached at least 80% consensus for clinical relevance and practicability. The remaining 21 items included into the second Delphi round failed to reach the 80% limit of agreement.

The Delphi process (Fig. 1) ultimately recommended 35 items (33 items from Delphi round 1 and two items from Delphi round 2) specific to ALI treatment for registry collection (with different levels of potential detail) (Table 1). It was also recommended that all registries create the response alternative "unknown", in order to differentiate omitted from unknown data, and not force users to choose an unclear option. However for simplicity, the "unknown" options for each variable have not been included in Table 1.

## DISCUSSION

In this modified Delphi study involving 37 international experts in multidisciplinary vascular care and registry based research, consensus to recommend 35 additional items specific to ALI treatment for registries was achieved. These items, specific for ALI, supplement prior recommendations on registering patients treated for chronic PAOD (79 items), and will help to harmonise international research using real world data.[8,17] It must be noted that in order to benefit from the current recommendations, registries should capture selected items of interest for ALI from prior recommendations on chronic PAOD. Important risk factors and outcomes such as amputations have not been included in the current ALI Delphi process but were already captured by prior recommendations.

Patients with ALI are known to be elderly, and they frequently suffer from multiple comorbidities. Of 45 different risk factors evaluated in this Delphi study, the expert panel selected seven items to supplement the minimum data set recommended for chronic PAOD. Interestingly, $>$ 10 different laboratory values were considered by the expert panel, but none reached the 60% consensus limit during the two Delphi rounds. As for medication, only treatment with any anticoagulation reached level 1. For example, the use of heparin in the emergency department was not included, despite the fact that this practice is associated with reduced risk of death and amputation.[18,19] The aetiology of ALI was considered clinically relevant but not practicable in $>$80%, and therefore set as a level 2 recommendation, owing to difficulty distinguishing between a non-classical embolism and thrombosis.

Despite changing environments and the widespread adoption of endovascular techniques, the treatment of this urgent condition in daily practice remains challenging. High amputation and mortality rates remain important consequences of ALI, emphasising the need for further research to improve and harmonise care.[20–23] To this end, treatment practices were included as an important component of this study. Ischaemic duration reached a high level of consensus and is a key factor for outcome, but to the authors' knowledge, is not yet included in any registry for ALI. This new indicator may help to reduce time delay and can be used for future quality improvement projects.

To ameliorate this situation and to reach consensus on the treatment of ALI, the ESVS has initiated a process of developing clinical practice guidelines for the treatment of ALI, to be published in early 2020.

This study has limitations. Firstly, the composition of the expert panel may have significantly affected the group discussion and subsequent consensus. As patients with ALI are treated by different medical specialties, there might be disagreement among the panel members on how to treat these patients which could affect the evaluation of items. To address this bias, the panel comprised experts from all medical specialties involving vascular surgery, internists, and radiology. Secondly, the point of including the patient's point of view is essential in modern patient centred medicine. According to that, items considering patient reported outcome measures (e.g., quality of life) were included in the Delphi process but failed to reach the required consensus limit (62% for clinical relevance, but only 38% for practicability in current registries). This result may be explained by the perceived difficulty, right or wrong, of involving patients who are frail and suffering an acute life threatening condition, in the decision making. Lastly, the recommendations of the current study can only reflect the group consensus among countries participating in the Delphi process. The VASCUNET collaboration and the ICVR should raise their efforts to involve more countries in the future.

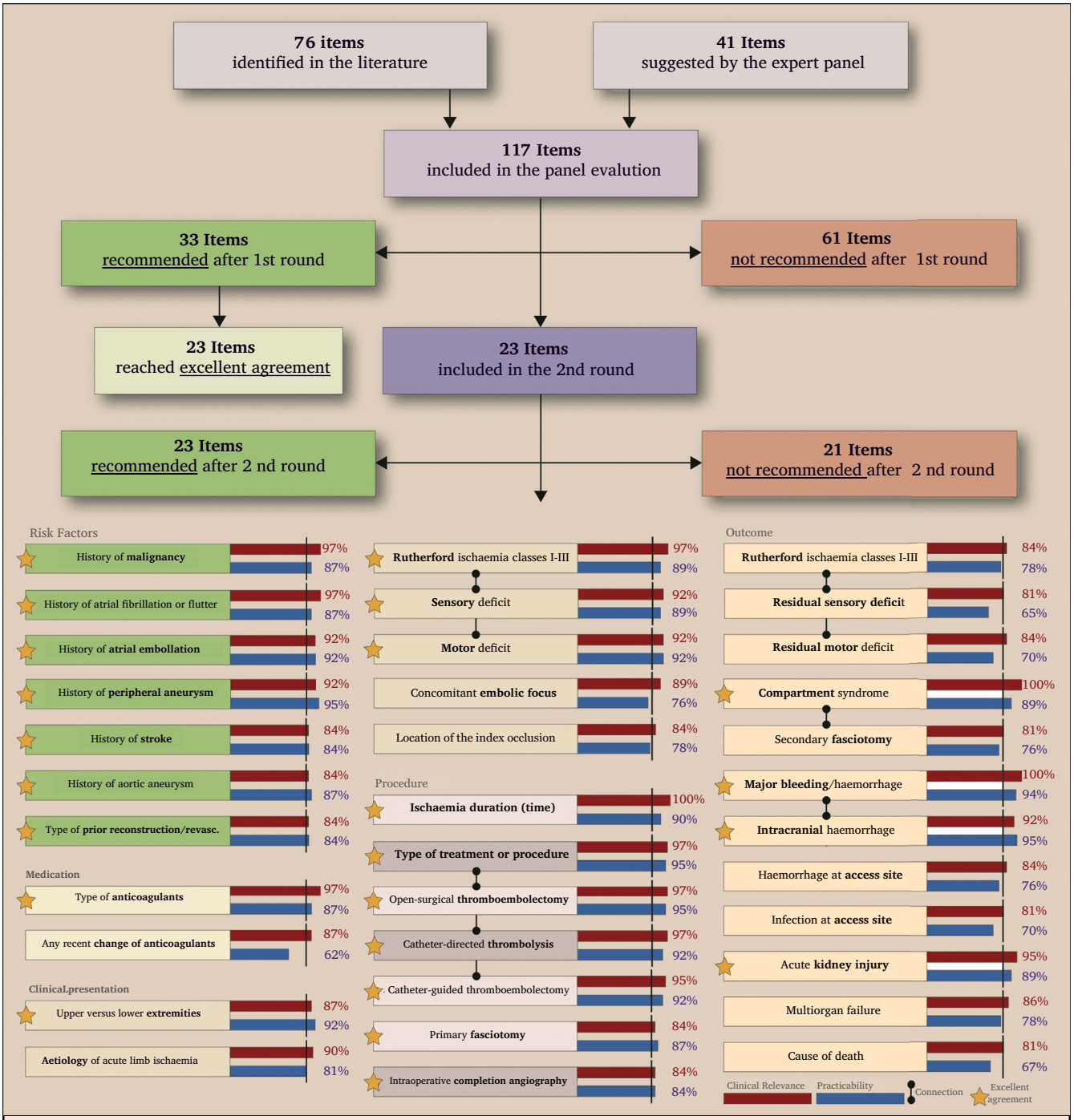


**Figure 1.** Flow chart of the modified Delphi expert consensus process. Of 117 items included in the panel evaluation, a total of 35 registry items were recommended for acute limb ischaemia revascularisation registries. The red bars illustrate the group results for clinical relevance. The blue bars represent the group results for practicability. Twenty-three items reached excellent levels of agreement for both clinical relevance and practicability (star).

Registry based quality improvement projects should in the future result in the collection of self reported patient data after treatment for emergency diseases such as ALI. This would also decrease the rapidly growing documentation burden and improve the practicability of quality improvement registries. There are a number of ways to integrate patient related outcome data into registries. The development of electronic health technology is a rapidly evolving field with easy to use applications that appears to enhance patient care.[24]

## CONCLUSIONS

This modified Delphi study among international vascular registry specialists achieved consensus on a minimum core and optimum dataset for registries evaluating ALI

revascularisation. It reduced the overall number of initial potential variables by nearly half. This core set of items has the potential to standardise data collection between existing and upcoming registries so that clinical data on ALI revascularisation can be merged and compared.

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## CONFLICT OF INTEREST

None.

## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2019.02.023.

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Original communication

# Indicators of outcome quality in peripheral arterial disease revascularisations – a Delphi expert consensus

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**Summary:** *Introduction:* Peripheral arterial disease (PAD) affects a continuously increasing number of people worldwide leading to more invasive treatments. Indication to perform invasive revascularisations usually arises from consensus-based recommendations of practice guidelines and from few randomized controlled trials where outcome measures focus mainly on risk factors associated with mortality and morbidity. To date, no broad consensual agreement of experts on valid indicators of outcome quality exists for PAD. *Methods:* A literature review was conducted to collect indicators of outcome quality from studies of PAD. The Delphi technique was used to achieve a consensual agreement on a set of core indicators. The expert panel of the two-round Delphi approach was formed by leading vascular specialists joining the IDOMENEO study, physician assistants, wound nurses, and patient representatives. Items were scored via a web-based anonymised electronic questionnaire using a five-point Likert-scale. *Results:* Out of 40 invited experts 30 joined the panel and completed round one. Twenty-four experts completed the second and final round. Forty-three indicators of outcome quality were initially identified and validated by the panel. After two Delphi rounds, 12 indicators (27.9 %) achieved the limit of agreement for relevance and four (9.3 %) for practicability. Major adverse limb events (MALE), major amputation, and major re-intervention (or re-operation) were consented as both highly relevant and practicable. Additionally, major adverse cardiovascular events (MACE), myocardial infarction, stroke or transient ischaemic attack, all-cause death, all re-intervention (or re-operation), wound infection, vascular access-related major complication, walking distance, and Rutherford-classification were consented as highly relevant. Ankle-brachial-index was consented as highly practicable. *Conclusions:* This Delphi approach of vascular experts identified three indicators as highly relevant and clinically practicable to be recommended as indicators of outcome quality in invasive PAD treatment. Among others, these consented items may help in harmonising future studies and quality benchmarking increasing their comparability, validity, and efficiency.

**Keywords:** Delphi technique, peripheral arterial disease, registries, health services research, consensus development



## Introduction

The numbers of invasive treatment of peripheral arterial disease (PAD), especially regarding endovascular revascularisations [1, 2], are continuously rising and it is necessary to monitor quality of treatment to improve patient care and safety. Due to the lack of evidence, especially regarding the treatment of intermittent claudication (IC), the choice of treatment should take patients' preferences more into consideration and be supported by shared decision-making [3–5]. Evidence-based quality indicators of structure, process, and outcomes would help to align patients' preferences to enable pragmatic quality improvement in PAD treatment. To date, no broad consensus of indicators evaluating outcome quality of treatment in patients with PAD exists. Indicators available in the literature

mainly focus on identifying risk factors for morbidity, mortality, or failure of treatment [6].

In the present study, we used a Delphi approach. A panel of multidisciplinary and inter-professional experts participating within the multimethodological and multistage IDOMENEO study (www.idomeneo.de) achieved consensual agreement and identified clinically relevant and practicable indicators for outcome quality of invasive PAD treatment. The IDOMENEO study aims to collect data on 10,000 consecutive patients from 40 vascular centres in Germany undergoing invasive endovascular or open-surgical treatment for symptomatic PAD with a follow-up of 12 months [7, 8]. Hence, the aim of the study was to create a set of core indicators for quality measurements that can be consistently utilized for outcome research and quality improvement in PAD treatment. The indicators of outcome quality consented in this Delphi study will in the next stage be field-tested on the 10,000 patients enrolled in the IDOMENEO study.

## Methods

The Delphi approach is widely accepted and used to gain consensus among a panel of experts [9] and has previously been used in various specialties including vascular surgery [10–14]. An extensive literature review was conducted to identify indicators of quality upon studies on PAD. Medline was searched for meta-analyses, systematic reviews, and guidelines, using keywords referring to PAD and quality measurement. In addition, a grey literature search was performed. Websites concerning PAD or indicators of outcome quality were searched by hand for guidelines, statements and quality indicators. The search was restricted to German and English. No restriction to publication date was made.

Furthermore, data variable definitions of peripheral arterial revascularisation registries participating in the International Consortium of Vascular Registries (ICVR) were reviewed and possible indicators of outcome quality were extracted [15].

Leading vascular specialists from different medical specialties including vascular surgery and interventional internal medicine, participating the IDOMENEO study (ClinicalTrials.gov: NCT03098290; German Clinical Trials Registry: DRKS00014649) were invited to take part in this Delphi study. The data privacy compliant GermanVasc registry is used to collect and to validate study data. Additionally, vascular specialists in the outpatient setting, general practitioners, vascular assistants, wound nurses, and the patients' representatives of the largest patient-society in Germany were invited to participate. The final number of quality indicators was not specified a priori. All participants in this study agreed to the scope of items identified through the abovementioned process. The panel experts were then invited to participate in web-based anonymised electronic questionnaires. Open source software (LimeSurvey GmbH, Hamburg, Germany) was used to generate the online 43-item questionnaires. In the first round, each participant was asked to indicate whether the item has a high clinical relevance and a high practicability in daily clinical practice. Each item was scored for both parameters on a five-point Likert scale, comprising "Strongly agree", "Agree", "Neutral", "Disagree", and "Strongly disagree". Items received a consensus recommendation for the minimal dataset if at least 80 % of the participants voted with "Strongly agree" or "Agree" either for relevance or practicability. Items with less than 80 % of agreement were eliminated from consideration. The 80 % criteria were applied in correspondence to valid practical guidelines and specialist society consensus recommendations [16, 17].

Additionally, space for a free text comment for each item was given in the questionnaire for individual arguments, hints or questions. The participants could only submit one set of answers in each Delphi round.

Following the first round, a structured report about the voting results using bar charts for clinical relevance and practicability was given for each item. The charts included graphical highlighting of items having reached the 80 % consensus criteria and anonymised group comments separated in pro and contra arguments (in green/red) (Figure 1).

In the second Delphi round, the participants voted only for quality indicators in order for outcome to achieve a higher response rate. Subsequently, the voting results are presented with bar charts again.

Statistical analyses were performed with IBM SPSS Statistics software version 25.0 (IBM, Armonk, NY, U.S.)

## Results

Forty experts from different medical specialties (vascular surgery, interventional internal medicine) and professions (physicians, vascular nurses with at least six years of clinical practice, physician assistants) as well as the patients' representative of Germany were contacted and 30 (17 vascular surgeons, eight angiologists, one radiologist, one patients' representative, three vascular nurses) accepted and completed the first online survey and 24 of them the second one between November 2017 and March 2018. In total, 43 indicators of outcome quality were identified in the literature or submitted by the experts and were included in the panel discussion (Table I and II). All quality indicators were reviewed and validated by the expert panel. After two Delphi rounds, a total of twelve (27.9 %) quality indicators reached the consensual limit of agreement for clinical relevance and four (9.3 %) quality indicators reached the consensual limit of agreement for practicability (Figure 2). Three composite quality indicators capturing major adverse limb events (MALE), major amputation, and major re-intervention (or re-operation), respectively, were considered to be of both high relevance and high practicability (Table I).

Two out of the twelve consented items can be differentiated into specific quality indicators. Major adverse cardio-

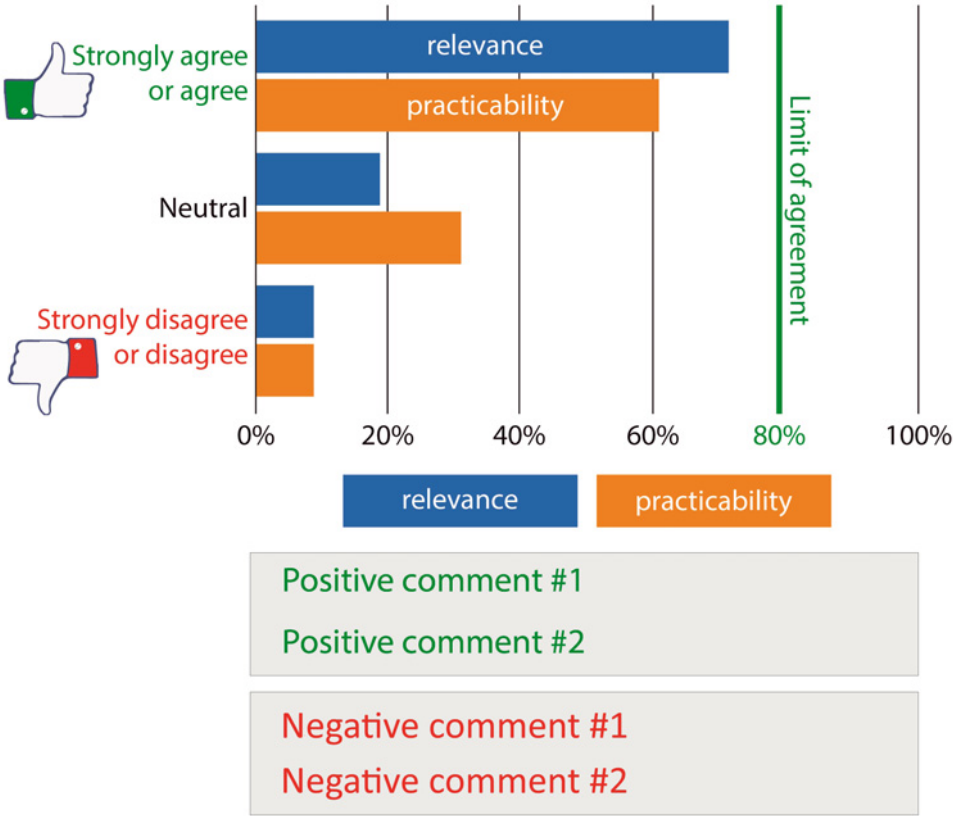


**Figure 1.** Schematic illustration of the structured report about the voting results using bar charts for clinical relevance and practicability. Positive and negative comments are highlighted in green or red colour.

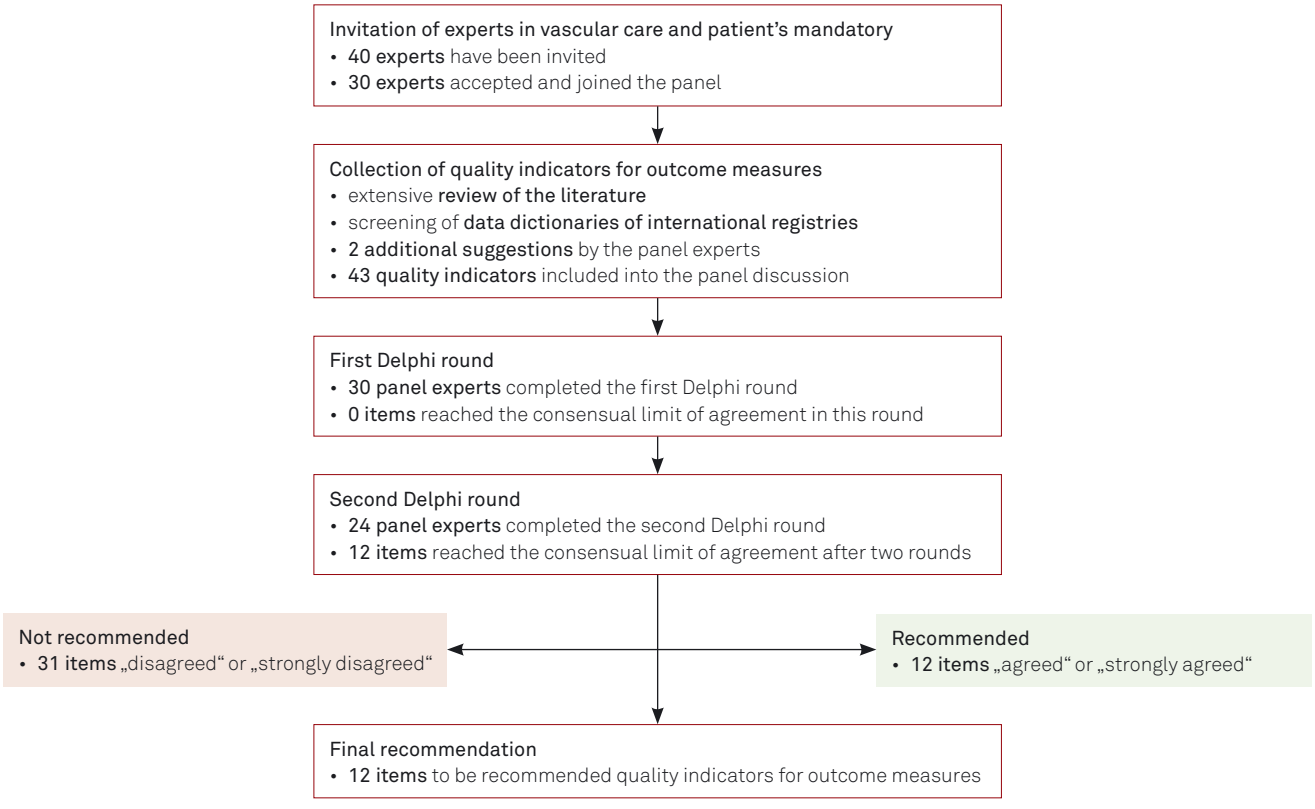


**Figure 2.** Flow chart of this Delphi study. 30 experts accepted and joined the panel.

**Table I.** Results of the Delphi study after two rounds. Twelve out of 43 quality indicators for outcome measures were consented.

| | Relevance after two rounds | Practicability after two rounds |
|---|---|---|
| Major adverse cardiovascular events (MACE/MACCE)<br>Including: myocardial infarction, coronary revascularisation, cardiac hospitalization, stroke or TIA, all-cause death or cardiac death | 92 % | 58 % |
| Major adverse limb events (MALE)<br>Including: major amputation, major re-intervention or re-operation | 96 % | 96 % |
| Myocardial infarction | 88 % | 58 % |
| Stroke or transient ischaemic attack (TIA) | 83 % | 50 % |
| All-cause death | 96 % | 63 % |
| Major amputation (above ankle level) | 96 % | 92 % |
| Major re-intervention (bypass, bypass revision, thrombectomy, thrombolysis) | 88 % | 83 % |
| Re-intervention or re-operation | 96 % | 63 % |
| Wound infection | 88 % | 75 % |
| Vascular access-related major complication | 92 % | 75 % |
| Increase of maximum walking distance | 88 % | 54 % |
| Increase of Rutherford-classification | 92 % | 71 % |
| Increase of ankle-brachial-index | 79 % | 92 % |



vascular or cardiac events (MACE, MACCE) are inconsistently used to describe major health events like myocardial infarction, coronary artery revascularisations, re-hospitalization for cardiac events, stroke or transient ischaemic attack, all-cause or cardiac-related death. Corresponding to that, MALE is commonly used to describe major health events including major amputation above ankle level, major re-interventions or re-operations to retain blood perfusion of the index leg.

In addition to the two abovementioned composite parameters and their components, the rate of wound infections, access-related complications requiring treatment, increase of maximum walking distance, improvement in Rutherford-classification, and improvement in ankle-brachial-index (ABI) found consensual agreement for clinical relevance during this Delphi process.

A total of 31 indicators failed to reach the consensual limit of agreement (six patient-reported outcomes) (Table II).

## Discussion

In this Delphi study with experts, we achieved a consensus on a set of indicators of outcome quality to be used in the treatment of patients with PAD. Twelve quality indicators were recommended, including two composite parameters for major cardiovascular and limb events. The Delphi approach is a widely used and accepted method to find a consensual agreement between a panel of experts on variable questions using at least two rounds of questionnaires with at least six to eleven experts [9].

In the light of rising numbers of procedures performed in patients with PAD, the question remains how to measure outcome quality of vascular care to improve patient safety and to evaluate if aims of treatment have been reached. Quality improvement programs have already been implemented in various fields of multidisciplinary vascular medicine worldwide, using specific indicators as a measurable aspect of care. Against this backdrop, quality indicators can cover aspects of process, structure, and outcome. However, in the field of PAD, the 2017 European Society of Cardiology (ESC) guideline in collaboration with the European Society for Vascular Surgery (ESVS) does not contain recommendations regarding quality indicators [5]. Ploeg et al. systematically reviewed the existing literature to provide an insight into quality improvement initiatives in vascular surgery [6]. Besides several structural and process measures, they identified 31 reports on outcome measures as indicators of quality of care published between 1991 and 2007. These reports mainly focused on identifying risk factors for morbidity, mortality or failure of treatment. Conte et al. suggested a set of objective performance goals (OPG) for evaluating catheter-based treatments in critical limb ischaemia (CLI), including MALE and MACE as important outcome measure [18].

To date, there is a paucity of evidence on valid indicators for measuring outcome quality of care in PAD revascularisations. Mortality and morbidity are certainly the most widely used indicators. However, a growing application of endovascular techniques with decreasing mortality and consequently lower variation between hospitals may prompt the emergence of further valid indicators. An in-

**Table II.** A total of 31 quality indicators were not consented after two rounds of the Delphi study. Patient-reported outcomes in orange colour. Items sorted by relevance.

| | Relevance after two rounds | Practicability after two rounds |
|---|---|---|
| Minor amputations | 79 % | 75 % |
| Primary patency | 79 % | 63 % |
| Secondary patency | 79 % | 67 % |
| Quality of life | 79 % | 17 % |
| Healing of wound infections or wound healing disorders | 79 % | 33 % |
| Cardiac death | 75 % | 25 % |
| Lymphatic fistula | 75 % | 54 % |
| Periprocedural major complications (cardiac, respiratory, renal, neurologic, venous, pulmonary embolic events, allergic complications, nerve lesions) | 75 % | 38 % |
| Ambulation | 75 % | 29 % |
| Re-stenosis | 71 % | 50 % |
| Cardiac events | 67 % | 46 % |
| Primary-assisted patency | 67 % | 58 % |
| Technical success | 63 % | 42 % |
| Patient satisfaction | 63 % | 25 % |
| Contrast-volume applied (Endovascular) | 58 % | 67 % |
| Treatment of wound infection | 54 % | 54 % |
| Dose-area product | 54 % | 67 % |
| Unplanned re-transfer to operating room | 50 % | 42 % |
| Total length of hospital stay | 50 % | 67 % |
| Postoperative length of hospital stay | 50 % | 71 % |
| Experience of pain | 46 % | 21 % |
| Functional status | 46 % | 25 % |
| Coronary revascularisation/interventions | 42 % | 29 % |
| Need for pain medication | 42 % | 8 % |
| Hospital-acquired infections | 42 % | 42 % |
| Catheter-related infections | 42 % | 21 % |
| Cardiac-related rehospitalisation | 38 % | 13 % |
| Toe-Brachial-Index | 29 % | 13 % |
| Pressure/decubitus ulcer | 25 % | 29 % |
| Oxygen pressure (tcpO2) | 25 % | 17 % |



creasing number of procedures is performed in patients suffering from intermittent claudication (IC) [19]. To address differences between both groups, one could claim to stratify this Delphi study into IC and CLI. While limb salvage and wound healing plays a major role in treatment of CLI, patient-reported outcomes and maximum walking distance are usually named as aims for invasive treatments in claudicants. However, even if markedly rare, amputations or deaths following elective revascularisations for IC remain fatal events and therefore deserve to be suggested as quality indicators for both groups. All indicators of outcome quality consented in this study can be measured for both IC and CLI but certainly have specific prevalence. Interestingly, two out of the twelve consented indicators (MACE, MALE) are composite indicators that can be further differentiated into specific quality indicators. In particular, the practicability of indicators for outcome quality seems to make the difference.

Interestingly, no patient-reported outcomes reached the limit of consensual agreement in this Delphi study.

Although indicators such as quality of life and ambulation reached 79 and 75 % clinical relevance, respectively, their practicability was scored notably low by the panel experts (17 % for quality of life, 29 % for ambulation). To be used in daily clinical practice, a brief quality of life instrument such as the VascuQoL-6 by Nordanstig et al. [20] could be helpful but needs to be translated and validated accordingly.

## Limitations

One important limitation of this study is the paucity of commonly accepted definitions for the indicators included into the Delphi process. Some of the expert comments suggested that there are various definitions available in daily clinical practice, making it challenging to compare experts voting. However, all comments and relevant questions have been reported back to the experts before finishing the second Delphi round and we took the most common definition as a basis for panel discussion. Another controversy concerned the duration of follow-up and the exact time-point of measuring the indicators of outcome quality. The fact that especially treatments for IC usually do not exceed two days of hospital stay implies that the in-hospital duration is insufficient. A follow-up duration of 30 days is commonly accepted as minimum but one year of follow-up might bring valid results even for patient-reported outcomes. Furthermore, it was difficult to find a consensual agreement for PAD revascularisations in general, although the scope of quality indicators obviously differs between treatment of IC vs. CLI.

## Funding

The IDOMENEO-study is partially funded by the German Joint Federal Committee (01VSF16008).

## Conclusions

The consented indicators of the present study may help to harmonise future studies and quality benchmarks increasing their comparability, validity, and efficiency. The indicators will in the next stage be field-tested on the 10,000 patients enrolled in the IDOMENEO study.

## IDOMENEO collaborators

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Original communication

# The prospective GermanVasc cohort study

## Endovascular and open-surgical treatment of symptomatic peripheral artery disease

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**Summary:** *Background:* Previous observational studies reported a wide variation and possible room for improvement in the treatment of patients suffering from symptomatic peripheral artery disease (PAD). Yet, systematic assessment of everyday clinical practice is lacking. A General Data Protection Regulation (GDPR) compliant registry was developed and used to collect comprehensive data on clinical treatment and outcomes regarding PAD in Germany. Here, we report baseline characteristics of patients prospectively enrolled until the end of 2020. *Methods:* The GermanVasc registry study is a prospective longitudinal multicentre cohort study. Between 1st May 2018 and 31st December 2020, invasive endovascular, open-surgical, and hybrid revascularisations of patients suffering from chronic symptomatic PAD were prospectively included after explicit informed consent (NCT03098290). For ensuring high quality of the data, we performed comprehensive risk-based and random-sample external and internal validation. *Results:* In total, 5608 patients from 31 study centres were included (34% females, median 69 years). On-site monitoring visits were performed at least once in all centres. The proportion of chronic limb-threatening ischaemia was 30% and 13% were emergent admissions. 55% exhibited a previous revascularisation. Endovascular techniques made 69% among all documented invasive procedures (n=6449). Thirty-five percent were classified as patients with severe systemic disease, and 3% exhibited a constant threat to life according to the American Society of Anaesthesiologists classification. The risk profile comprised of 75% former or current smokers, 36% diabetes mellitus, and in 30% a current ischemic heart disease was present. At discharge, 93% of the patients received antiplatelets and 77% received statins. *Conclusions:* The GermanVasc registry study provides insights into real-world practice of treatment and outcomes of 5,608 patients with symptomatic PAD in Germany. The cohort covers a broader range of disease severity and types of interventions than usually found in trials. In future studies, comparative outcomes will be analysed in more detail.

**Keywords:** Health services research, peripheral artery disease, intermittent claudication, chronic limb-threatening ischaemia, endovascular techniques, bypass surgery

## Introduction

Although peripheral artery disease (PAD) is a common illness with more than 230 million affected worldwide, the existing evidence base to treat this target population is still incomplete in regard of patient selection, best medical treatment, and the best patient-centred approach to revascularise atherosclerotic lesions [1].

A wide variation between countries was previously reported concerning the proportion of patients with claudication, endovascular techniques, females, and octogenarians [2]. In line with this unexplained variation, nearly half of all recommendations in valid practice guidelines are based on low level of evidence [3, 4, 5].

While the vascular community waits with bated breath for the first results of currently recruiting randomized

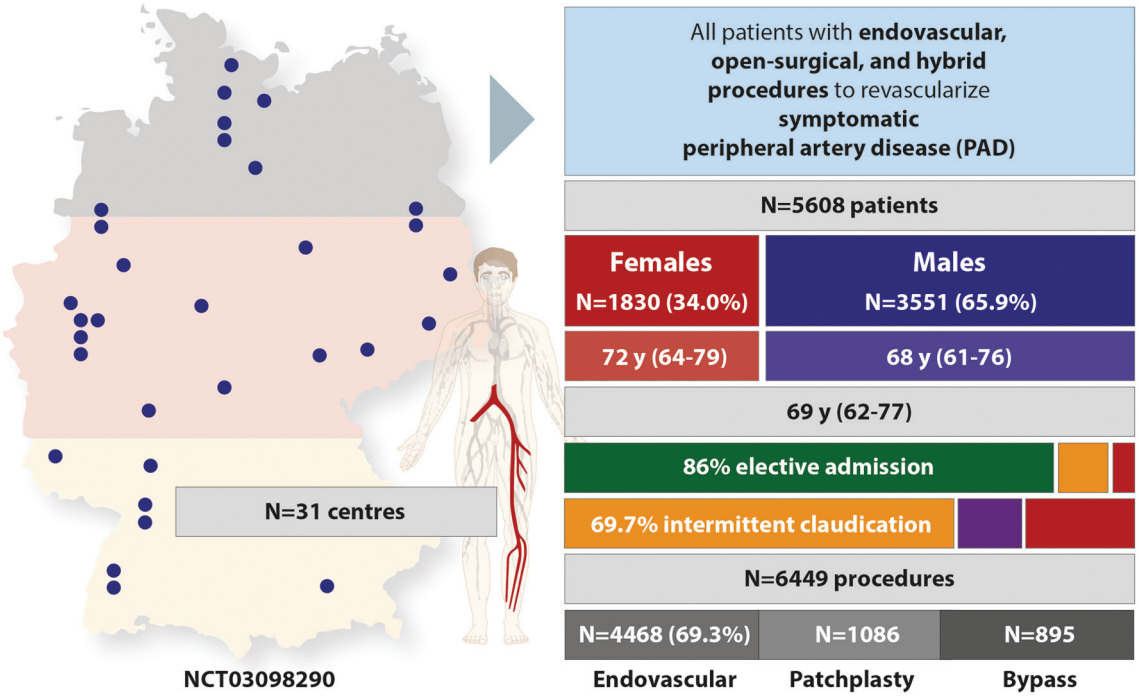


**Figure 1.** Central Illustration of this prospective multicentric cohort study of 5608 patients.

controlled trials (RCT) [6, 7], it appears reasonable to match conclusions derived from RCTs with high quality registry data better reflecting everyday clinical practice. For instance, in an ongoing debate concerning outcomes after drug-coated device treatment, RCTs reported excess long-term mortality while real-world data showed opposite results, emphasizing their complementary value [8, 9]. While health insurance claims data offer particularly large samples for such purpose, clinical registries additionally offer the inclusion of more detailed parameters such as body mass index, lesion characteristics, blood pressure, and ankle-brachial-index.

The GermanVasc study included patients with symptomatic PAD who underwent either endovascular, open-surgical, or hybrid revascularisations between 1st May 2018 and 31st December 2020 at 31 German centres (Figure 1). The rationale and methods were published and registered a priori (clinicaltrials.gov NCT03098290) [10, 11]. All indicators of outcome quality and additional variables collected in the current study were aligned by international Delphi consensus methods [12, 13, 14]. The data collection underwent both an independent random-sample validation and automated quality assurance.

The primary goal of the study was to quantify to which extent real-world treatment follow guideline recommendations.

The current report aims to present the baseline characteristics of the included patients.

## Material and methods

This was a prospective longitudinal multicentre cohort study. The rationale and methods of the GermanVasc registry study were published a priori [10, 11] and additionally registered at Clinicaltrials.gov (NCT03098290) and the German Registry of Clinical Trials (DRKS00014649). A total of 18 ethical committees in affected German federal states confirmed the initial approval by the leading ethical committee at the medical association in Hamburg, Germany (PV5691). The European Union (EU) General Data Protection Regulation (GDPR) compliant GermanVasc registry platform was developed to follow the principles of privacy by design while collecting the personal and medical data relevant for the current study [11, 15, 16]. Results were reported using the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement [17].

### Inclusion and exclusion criteria

All patients above 18 years who underwent either endovascular, open-surgical, or hybrid revascularisation for chronic symptomatic PAD between 1st May 2018 and 31st December 2020 at participating study centres were included if an explicit informed consent was available by the data subject. Patients with embolic acute limb ischaemia without history of chronic PAD were excluded. According to the modified Rutherford classification, patients selected for invasive revascularisation with mild, moderate, and severe claudication were pooled as intermittent claudication (IC). Patients selected with ischaemic rest pain, ulcer or necrosis, and non-healing amputation were pooled as chronic limb-threatening ischaemia (CLTI).

### Study variables

The data collection in the current study followed three previous Delphi consensus studies on registry core elements and quality indicators for peripheral arterial revascularisation. These study variables were published

elsewhere [12, 13, 14]. Variables were collected at baseline, after three, six, and twelve months of follow-up. In the current report, we present baseline characteristics as follow-up data collection is still ongoing.

In short, the following medical variables were collected during the baseline treatment: Age (years), sex (male, female, transgender), admission month and weekday, discharge month and weekday, urgency of the admission, living status, functional status, ambulation, discharge destination, weight (kilogram), height (meter), body mass index (BMI, calculated as $kg/m^2$), American Society of Anaesthesiologists (ASA) class, diabetes mellitus, glycohaemoglobin, renal insufficiency, most recent serum creatinine, current dialysis dependency, tobacco use (active, former), years since last smoking, current ischaemic heart disease, congestive heart failure, ejection fraction, cardiac arrhythmia, history of atrial fibrillation, chronic obstructive pulmonary disease (COPD), hypertension, prior peripheral arterial disease revascularisation, prior lower leg amputations, antiplatelets at the time of admission and at discharge, statins at the time of admission and at discharge, PCSK9-inhibitor at the time of admission and at discharge, vitamin K antagonist at the time of admission and at discharge, new/direct oral anticoagulants at the time of admission and at discharge, modified Rutherford classification (per side), foot infection (per side), ankle-brachial-index (ABI, per side, categorised), tissue loss (per side), postoperative myocardial infarction, postoperative stroke, postoperative new dialysis dependency, postoperative ankle-brachial-index (per side, categorized), postoperative unplanned amputation (per side), postoperative occlusion of index revascularisation, postoperative distal embolization, postoperative dissection, postoperative failure of graft or device, postoperative bleeding including pseudoaneurysm, postoperative compartment syndrome, postoperative wound infection, quality of life (WIQ and SF36).

## Statistical analysis

Normality of data was tested using the Shapiro-Wilk-Test. We summarized the baseline characteristics of the patients with median and interquartile range (IQR) for non-normally distributed variables with mean and standard deviation for normally distributed variables, and with percentages and Wald 95% confidence interval (CI) for categorical variables. Missing values were handled by case exclusion for each analysis.

All statistical analyses were performed with SPSS version 25 (IBM Corporation, New York, USA). Visualization was performed with Adobe Illustrator version 24.1.2 (Adobe, San Jose, CA, USA).

# Results

In total, 5608 patients (34% females, median 69 years, IQR: 62–77) treated in 31 centres with 6449 procedures in total were registered from 1st May 2018 through 31st December 2020. External on-site visits were performed at least once in 100% of all study centres. Core characteristics were complete in 100% of all cases.

The baseline characteristics of the entire cohort and by occurrence of CLTI are presented in Table I. An urgent or emergent presentation at the study centre was documented in 12.5% (95% CI: 11.6–13.4). Among a total of 6449 documented procedures provided to the study cohort, 4468 (69.3%, 95% CI: 68.1–70.4) were endovascular procedures.

Among all patients, 4.9% (95% CI: 4.4–5.5) were referred from another hospital or department to the study centre, and 0.8% (95% CI: 0.6–1.1) were admitted from a nursery or rehabilitation facility. More than half of the cohort (54.9%, 95% CI: 53.5–56.2) exhibited at least one previous revascularisation of the lower extremities, and 5.5% (95% CI: 4.9–6.2) exhibited a previous major lower limb amputation before the index treatment.

In total, 4.6% (95% CI: 4.1–5.2) of the patients needed assisted care or bedridden, while 18.0% (95% CI: 17.0–19.0) were supplied with either prosthesis, assistive device, or wheelchair.

Regarding the overall physical status according to the ASA classification, 65.1% were either classified as a patient with mild systemic disease (30.6%, 95% CI: 29.4–31.8) or severe systemic disease (34.5%, 95% CI: 33.2–35.7). Among all patients, 3.1% (95% CI: 2.7–3.6) exhibited a severe systemic disease that is a constant threat to life.

## Body mass index, hypertension, smoking, and diabetes

The median body mass index (BMI) of the entire cohort was 26.0 $kg/m^2$ (95% CI: 23.4–29.3), and 20% (95% CI: 19.0–21.1) were obese according to the threshold of 30 $kg/m^2$.

82.2% (95% CI: 81.1–83.2) had a history of hypertension. 44.3% (95% CI: 43.0–45.6) of the entire cohort reported current smoking at the time being selected for invasive revascularisation, and 30.7% (95% CI: 29.5–31.9) were former smoker with a median quit time of 15 years (IQR: 6–26).

35.7% (95% CI: 34.5–37.0) were diagnosed with diabetes. Among these patients, the median HbA1C value was 7 (IQR: 6–8).

## Cardiac risk

One third of the cohort was diagnosed with ischemic heart disease. Among all patients, 29.5% (95% CI: 28.3–30.8) were asymptomatic at the time of presentation, 5.3% (95% CI: 4.7–5.9) exhibited angina only during physical activity, and 1.3% (95% CI: 1.1–1.7) exhibited symptoms at everyday living activities or at rest.

14.9% (95% CI: 14.0–15.9) of the patients reported any history of coronary artery revascularisation, and 16.8% (95% CI: 15.8–17.8) had a history of myocardial infarction.

**Table I.** Baseline characteristics of this cohort including 5608 patients with invasive revascularisation for symptomatic peripheral artery disease. If not otherwise indicated, all values are presented as percentage (%) with 95% confidence interval

| | Total cohort | | Chronic limb-threatening ischaemia | | No chronic limb-threatening ischaemia | |
|---|---|---|---|---|---|---|
| Number of patients | 5608 | | 1676 (29.9%) | | 3932 (70.1%) | |
| Patient age, years (median, interquartile range) | 69 | 62–77 | 72 | 64–80 | 68 | 61–76 |
| Octogenarians | 15.7 | 14.8–16.7 | 25.4 | 25.4–27.6 | 11.6 | 10.6–12.6 |
| Females | 34.0 | 32.7–35.3 | 34.3 | 32.0–36.7 | 33.8 | 32.3–35.4 |
| Urgent or emergent presentation | 12.5 | 11.6–13.4 | 31.7 | 29.5–34.0 | 4.2 | 3.6–4.9 |
| Referred from another hospital | 4.9 | 4.4–5.5 | 11.2 | 9.8–12.8 | 2.2 | 1.8–2.7 |
| Admitted from nursery/rehab | 0.8 | 0.6–1.1 | 2.3 | 1.7–3.2 | 0.3 | 0.1–0.5 |
| Needed assisted care/bedridden | 4.6 | 4.1–5.2 | 11.5 | 10.0–13.1 | 1.6 | 1.3–2.1 |
| Ambulation with any assistive device or bedridden | 18.0 | 17.0–19.0 | 39.4 | 37.0–41.8 | 8.7 | 7.9–9.7 |
| ASA Class III | 34.5 | 33.2–35.7 | 39.4 | 37.0–41.8 | 29.8 | 28.4–31.3 |
| ASA Class IV | 3.1 | 2.7–3.6 | 6.6 | 5.4–7.9 | 1.6 | 1.2–2.1 |
| Body mass index (median, interquartile range) | 26.0 | 23.4–29.3 | 25.8 | 22.9–29.3 | 26.1 | 23.7–29.3 |
| Body mass index >30 kg/m$^2$ | 20.0 | 19.0–21.1 | 21.0 | 19.1–23.0 | 19.6 | 18.4–20.9 |
| Diabetes mellitus | 35.7 | 34.5–37.0 | 47.4 | 45.0–49.8 | 30.7 | 29.2–32.1 |
| Chronic renal failure | 22.1 | 21.0–23.2 | 32.5 | 30.2–34.8 | 17.7 | 16.5–18.9 |
| Dialysis dependency | 2.5 | 2.1–2.9 | 5.4 | 4.4–6.6 | 1.3 | 0.9–1.6 |
| Current smoker | 44.3 | 43.0–45.6 | 37.7 | 35.3–40.0 | 46.3 | 44.8–47.9 |
| Former smoker | 30.7 | 29.5–31.9 | 30.5 | 28.3–32.8 | 30.2 | 28.8–31.7 |
| Quit time, years (median, interquartile range) | 15 | 6–26 | 16 | 7–30 | 13 | 5–24 |
| Asymptomatic ischaemic heart disease | 29.5 | 28.3–30.8 | 34.2 | 31.9–36.5 | 27.5 | 26.1–28.9 |
| Angina symptoms during physical activity | 5.3 | 4.7–5.9 | 6.6 | 5.5–7.9 | 4.7 | 4.0–5.4 |
| Angina symptoms at everyday living activities or at rest | 1.3 | 1.1–1.7 | 1.7 | 1.2–2.5 | 1.2 | 0.9–1.6 |
| History of coronary artery revascularisation | 14.9 | 14.0–15.9 | 18.1 | 16.3–20.0 | 13.6 | 12.5–14.7 |
| History of myocardial infarction | 16.8 | 15.8–17.8 | 20.4 | 18.4–22.4 | 15.3 | 14.2–16.4 |
| History of congestive heart failure | 17.0 | 16.0–18.0 | 23.5 | 21.5–25.5 | 13.9 | 12.8–15.0 |
| Ejection fraction, % | 50 | 40–55 | 45 | 35–55 | 51 | 42–55 |
| History of cardiac arrhythmias | 18.7 | 17.7–19.8 | 23.5 | 21.5–25.6 | 14.9 | 13.8–16.0 |
| History of chronic obstructive pulmonary disease | 11.6 | 10.7–12.4 | 12.7 | 11.2–14.4 | 10.9 | 9.9–11.9 |
| History of hypertension | 82.2 | 81.1–83.2 | 74.8 | 73.4–76.2 | 81.9 | 79.9–83.7 |
| History of any lower extremity revascularisation | 54.9 | 53.5–56.2 | 56.1 | 53.7–58.5 | 49.3 | 47.8–50.9 |
| History of any lower extremity amputation | 5.5 | 4.9–6.2 | 13.4 | 11.8–15.1 | 2.1 | 1.7–2.6 |

ASA: American Society of Anaesthesiologists.

A history of congestive heart failure was reported in 17.0% (95% CI: 16.0–18.0), while a median left ventricular ejection fraction of 50% (IQR: 40–55) was documented in these patients. 18.7% (95% CI: 17.7–19.8) reported any history of clinically relevant cardiac arrhythmias.

## Other risk factors

A chronic renal failure was apparent in 22.1% (95% CI: 21.0–23.2) of the cohort, while 2.5% (95% CI: 2.1–2.9) were dependent from chronic dialysis.

A chronic obstructive pulmonary disease was reported by 11.6% (95% CI: 10.7–12.4) of the patients.

## Invasive procedures

A total of 6449 invasive procedures were registered. Among all registered revascularisations, 69.3% (95% CI: 68.1–70.4) were endovascular procedures (n=4468). A total of 1285 drug-coated balloons and 292 drug-eluting stents were registered. Vascular surgeons were actively involved in the procedure in 43.0% (95% CI: 41.5–44.4), interventional radiologists in 33.5% (95% CI: 32.1–34.9), and interventional internists in 34.4% (95% CI: 33.1–35.9) of the procedures. A total of 17.8% (95% CI: 16.7–19.0) of the procedures involved at least two medical specialties. 8.7% (95% CI: 7.9–9.6) of the procedures were performed as hybrid approach with cut down. In 52.6% (95% CI: 51.1–54.1) of the registered procedures, a total of 2351 closure devices were documented.

## Antiplatelets and statins

At the time of admission, 84.7% (95% CI: 83.7–85.6) of the patients were on antiplatelet medication, while 67.5% (95% CI: 66.2–68.7) were taking statins. After discharge, the prescription rate of antiplatelets was 93.5% (95% CI: 92.8–94.1) and 76.5% (95% CI: 75.4–77.6) for statins.

### Risk profile by occurrence of chronic limb-threatening ischaemia

Among the entire cohort, 1676 (29.9%, 95% CI: 28.7–31.1) patients presented with either ischaemic rest pain or ischaemic wound healing disorders. In CLTI patients, the proportion of octogenarians, urgent or emergent presentation, referral from another hospital, and referral from nursery or rehabilitation facilities was higher when compared with patients without CLTI symptoms (Table I). The overall risk profile was more pronounced in CLTI patients concerning higher ASA class, diabetes, chronic renal failure, cardiac disease, and previous lower extremity revascularisation or amputation.

## Discussion

This large prospective observational cohort study evaluated the everyday clinical practice at 31 vascular centres in Germany. More than 5600 patients were treated by approximately 6500 endovascular and open-surgical procedures for chronic symptomatic PAD. The protocol of the current study was published a priori, and the study data underwent a rigorous validation by an external random-sample and risk-based quality assurance.

The included patients, especially those suffering from CLTI, exhibited a severe multimorbidity and multiple cardiovascular risk factors. One third of the cohort were patients with severe systemic disease, and more than three percent were in a life-threatening condition.

There is growing evidence for a wide variation of practice patterns between countries, centres, and registries. The reasons, however, are mostly unknown. In the United Kingdom, the Getting It Right First Time (GIRFT) programme identified such variations as possible room for improvement [18]. The 2018 GIRFT report found that many patients needing urgent surgery face long or uncertain waits, and a "lack of consistency in the approach taken to the same condition – with different providers choosing different surgical methods in apparently similar circumstances" [19]. Globally, a recent comparison of population-based registries in eleven countries revealed that patient selection and treatment modality varied widely for the proportion of patients with intermittent claudication (6% in Italy and 69% in Russia) and endovascular techniques (24% in Russia and 88% in Italy) [2]. Confirming these previous studies, one third of the current study cohort exhibited symptoms of a CLTI and 70% among all procedures included endovascular techniques.

Interestingly, in the current study, more than half of the cohort had a history of any lower extremity revascularisation, confirming previous reports using longitudinal data [18, 20]. This finding further emphasizes the importance to use patient-linked instead of rather procedure-related data since these redundant treatments would otherwise distort results derived from unlinked databases. However, to date, longitudinally linked multicentre registry data from Germany remains scarce. The RECCORD registry of the society for angiology enrolled 1000 patients with endovascular treatment of symptomatic PAD (25% with CLTI, 35% females, mean age 70 years) but the data collection primarily covered treatments performed by a single medical specialty [21]. In the current study, three different medical specialties were almost equally involved in the endovascular procedures, emphasizing the importance to include all specialties in data collections on endovascular treatments. Against that backdrop it appears noteworthy to highlight that all valid practice guidelines recommend a multidisciplinary approach but there is evidence suggesting an insufficient adherence concerning multidisciplinary team decisions in PAD treatment [22]. From 2013 through 2014, the German national registry for first line treatment strategies in patients with critical limb ischemia (CRITISCH register) collected multicentre data on 1200 patients suffering from CLTI from 27 selected centres. However, considering the current treatment reality and increasingly frequent invasive treatment of patients with intermittent claudication, it appears likewise important to cover the full spectrum of disease stages in real-world data [23].

Considering the ongoing COVID-19 pandemic, the unfavourable risk profile of the current study cohort deserves thoroughly reflection. More and more studies report a growing number of predictors for a severe illness. Males, octogenarians, patients with cardiovascular disease, diabetes, chronic liver and renal disease, chronic pulmonary disease, malignancy, and those with obesity and smoking are at higher risk when compared to the healthy population [24]. Notably, the current study included a highly vulnerable cohort affected by almost all of these severe comorbidities. It may be reasonable to focus on tertiary prevention and re-evaluate vaccination strategies to protect this central target population.

Against that backdrop, the fact that nearly half of the study cohort reported active smoking at the time being selected for invasive revascularisation appears striking. The central importance of smoking cessation was not only highlighted in all valid practice guidelines but is commonly accepted to be one of the most important drivers of early mortality in numerous global cohorts [3, 4, 5, 25, 26]. Together with the high proportion of obese patients in the current study, the modifiable risk factors may need more attention by the vascular community.

### Limitations

Besides many strengths, there are also limitations. First, the patient selection and choice of treatment approach was left to the discretion of the physicians. This prospective observational study collected routinely collected data, and the non-random assignment makes it impossible to derive a causal relationship between treatment strategy and outcomes. Second, the study comprises 31 high-volume centres of about 650 hospitals providing vascular health benefits to the target population in Germany. Therefore,

a selection bias cannot be ruled out although centres with a large variety of characteristics from all over Germany were involved.

The GermanVasc data collection will be used for comprehensive outcome research during the following years. With a follow-up of one year and beyond, a meaningful comparison of commonly accepted quality indicators and objective performance goals is planned. The peculiar risk profile of this vulnerable cohort and its interaction with the intervention-outcome relationship will be further evaluated. The impact of renal insufficiency, cardiac comorbidities, female sex, and diabetes is of special interest. In the beginning of 2021, a medical device module was implemented to the registry platform in order to collect unique device identifiers (UDI) for the evaluation of long-term outcomes (www.mdepinet.de).

## Conclusions

This study reports baseline characteristics from a large validated all-comer prospective cohort in Germany. The cohort covers a broader range of disease severity and types of interventions than usually found in trials. In future studies, the relation between treatment at baseline and outcomes will be analysed in more detail.

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**Conflict of interest**
The authors declare that there are no conflicts of interest.

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