Original communication

Rationale and methods of the IDOMENEO health outcomes of the peripheral arterial disease revascularisation study in the GermanVasc registry

Eike Sebastian Debus[1], Levente Kriston[2], Thea Schwaneberg[1], Sandra Hischke[1,2], Henrik Christian Rieß[1], Martin Härter[2], Ursula Marschall[3], Hannes Federrath[4], and Christian-Alexander Behrendt[1]

[1] Working Group GermanVasc, Department of Vascular Medicine, University Heart Center Hamburg, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[2] Department of Medical Psychology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany
[3] BARMER, Wuppertal, Germany
[4] Working Group Security in Distributed Systems, Department of Computer Science, University of Hamburg, Hamburg, Germany

Summary: *Background:* Atherosclerotic disease of the lower extremity arteries (PAD) remains a significant burden on global healthcare systems with increasing prevalence. Various guidelines on the diagnosis and treatment of patients with PAD are available but they often lack a sufficient evidence base for high-grade recommendations since randomized and controlled trials (RCT) remain rare or are frequently subject to conflicts of interest. This registry trial aims to evaluate the outcomes of catheter-based endovascular revascularisations vs. open-surgical endarterectomy vs. bypass surgery for symptomatic PAD on medical and patient-reported outcomes. *Methods and design:* The study is a prospective non-randomized multicentre registry trial including invasive revascularisations performed in 10 000 patients treated for symptomatic PAD at 30 to 40 German vascular centres. All patients matching the inclusion criteria are consecutively included for a recruitment period of six months (between May and December 2018) or until 10 000 patients have been included in the study registry. There are three follow-up measures at three, six, and 12 months. Automated completeness and plausibility checks as well as independent site visit monitoring will be performed to assure high internal and external validity of the study data. Study endpoints include relevant major cardiovascular and limb events and patient-reported outcomes from two Delphi studies with experts in vascular medicine and registry-based research. *Discussion:* It remains unclear if results from RCT can reflect daily treatment practice. Furthermore, great costs and complexity make it challenging to accomplish high quality randomized trials in PAD treatment. Prospective registry-based studies to collect real-world evidence can help to overcome these limitations.

Keywords: Peripheral arterial disease, chronic limb-threatening ischaemia, outcome analysis, patient-reported outcomes, healthcare analysis

Introduction

Atherosclerotic disease of the lower extremity arteries (PAD) without clinical symptoms or causing intermittent claudication (IC) or chronic limb-threatening ischaemia (CLTI) remains a significant burden on global healthcare systems with increasing prevalence. In 2010, more than 200 million patients worldwide were affected [1] suffering from decreased disability-adjusted life years (DALYs) and increased morbidity and mortality [2]. In Germany, total PAD cases, especially for the treatment of CLTI, are increasing continuously [3, 4]. More than 300,000 invasive revascularisations for PAD are performed annually in legally endorsed hospitals [4] leading to disease-related annual health costs of approximately 6,250 € per capita [5, 6]. Various guidelines on the diagnosis and treatment of patients with PAD are available, but they often lack a sufficient evidence base for high-grade recommendations

[7]. Regarding the 2015 German multidisciplinary guideline on PAD, half of all recommendations were based on consensus of opinion of experts [8, 9]. A wide spectrum of different catheter-based endovascular devices and techniques is available to complement open-surgical techniques such as endarterectomy or bypass surgery, but only few studies validly demonstrate the benefit and superiority in a competitive design. Randomized and controlled trials remain rare or are frequently subject to conflicts of interest [10, 11]. Several registry-based trials aimed to collect real-world-data on PAD treatment in Germany but were partly limited by selection bias [12–14].

The objective of this trial is to evaluate the outcomes of catheter-based endovascular revascularisations vs. open-surgical endarterectomy vs. bypass surgery for symptomatic PAD on medical and patient-reported outcomes. Furthermore, this study aims to compare relevant treatment results of available approaches in a long-term setting and allowing possible risk modelling to develop an algorithm to identify the best treatment approach for different groups of patients suffering from symptomatic PAD.

Methodology and design

Study design

The study is a prospective non-randomized registry trial including invasive catheter-based endovascular revascularisation (ER), open-surgical endarterectomy, and bypass surgery for chronic symptomatic PAD performed in legally endorsed multidisciplinary German hospitals (ClinicalTrials.gov: NCT03098290; German Clinical Trials Registry: DRKS00014649) (ESM 1). All patients matching the inclusion criteria are consecutively included for a recruitment period of six months or until 10 000 patients have been included in the study registry. There are three follow-up measures at three, six, and 12 months (Figure 1). Automated completeness and plausibility checks for integrity of submitted data are implemented into the registry system and all data need to be verified by an authorised study physician employed in the participating study centre (www.idomeneo.de). A reimbursement fee of up to 200 € is paid to the study centres for each included patient with completed follow-up.

Inclusion criteria

Participants must be at least 18 years old. Included patients must be diagnosed with chronic symptomatic PAD, corresponding to stage II (intermittent claudication), III (ischaemic rest pain), and IV (ulcers, necrosis or gangrene) of the Fontaine classification or grade I to III of the Rutherford classification, respectively. Additional inclusion criteria will be an invasive catheter-based endovascular or open-surgical revascularisation performed in a legally endorsed hospital (vascular centre) in Germany.

Exclusion criteria

Patients with acute limb ischaemia caused by an embolic occlusion of lower extremity vessels without any history of chronic symptomatic PAD will not be included.

Technical collection of registry data

This multicentre registry relies on a web-based system with data being entered into a data privacy compliant central database [15]. The registry platform is hosted by the

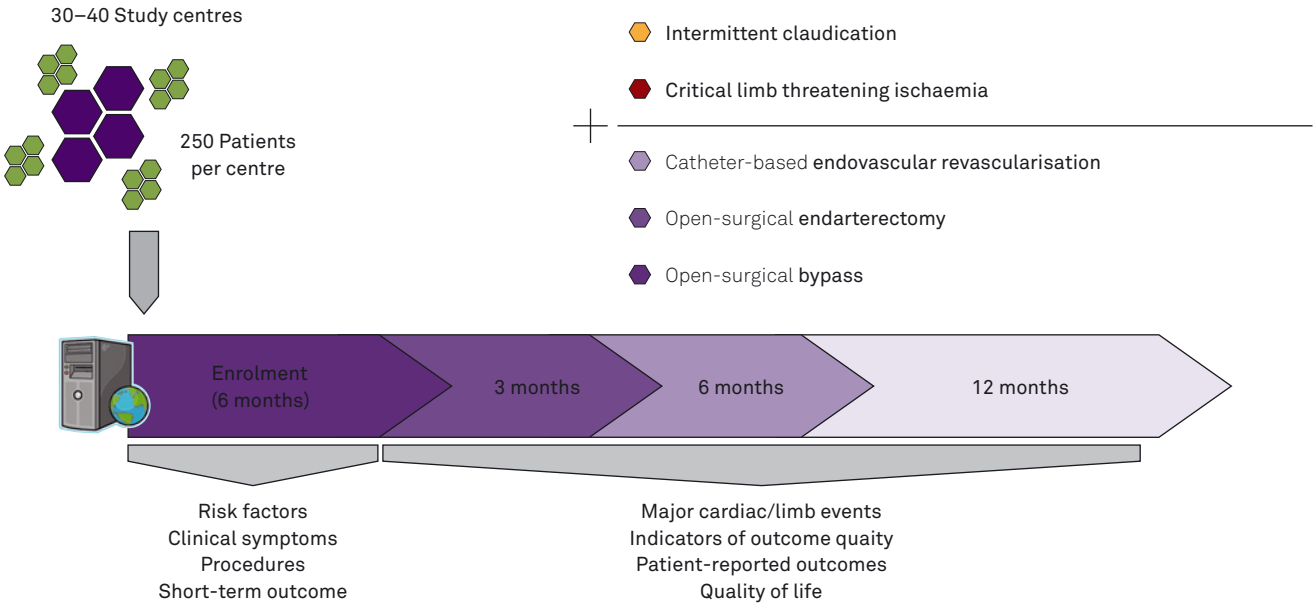

Figure 1. Figure 1 illustrates the enrollment and the follow-up of 10 000 patients. 30 to 40 study centres will include 250 patients with invasive treatment (pink boxes) of symptomatic peripheral arterial disease intermittent claudication (yellow box) or critical limb-threatening ischaemia (red box).

University Medical Center Hamburg-Eppendorf in Hamburg, Germany, and conforms to the 2018 data privacy regulation of the European Union (EU-GDPR) [16, 17]. Individual identifying patient data and pseudonymized medical data are captured by electronic case report forms (eCRFs) and are automatically divided, encrypted, and stored in different databases of the registry system utilizing multi-tenancy functions. The technical concept of the GermanVasc registry system prevents any access to individual patient data for the registry host. The technical concept obviates the need to incorporate the service of an independent (cost-intensive), trusted third party for pseudonymization matters.

Data quality assurance

Data quality assurance is implemented by a) automated completeness and plausibility checks, b) central data monitoring for missing data or invalid data using queries, c) random-sample and risk-based independent site visit monitoring, d) benchmarking between study centres, and e) regular newsletters and frequently asked questions to improve the awareness of potential sources of errors.

Sample size calculation

This study will compare patients undergoing invasive catheter-based endovascular revascularisation (ER), open endarterectomy (EA) or bypass-surgery for chronic symptomatic PAD. We aim to be able to detect minimal standardized, clinically relevant differences between these treatments regarding the outcomes (an explained variance of about 3 %) with a power (1-beta error rate) of 80 % and an alpha error rate of 5 %. (Generalized) linear (mixed) models including 15 covariates to adjust for patient-mix differences between treatments require data from around 600 participants to identify such signals. As a considerable proportion of the variation in the outcome is likely to be attributable to institutional rather than individual differences, we consider the multilevel structure of the data by considering a variance inflation factor of 15 (resulting from a sample of around 250 to 300 individuals in each participating hospital and an intracluster correlation coefficient of 0.05), suggesting the inclusion of around 9,000 participants. To account for longitudinal attrition, design imbalances, and an inflation of power for non-metric outcomes, we aim to include a total of 10 000 patients from around 30 to 40 hospitals in the study. This sampling scheme provides a solid basis for investigating research question both regarding individuals and hospitals [18].

Primary medical outcomes

Table I and II show study endpoints collected via the GermanVasc registry. Additional items collected via the GermanVasc registry are shown in ESM 2. The study outcomes were derived from indicators of outcome quality defined by consensual agreement among experts in the field of vascular medicine [19, 20]. A total of 12 medical outcomes will be assessed at the time of discharge, after three, six, and 12 months, namely major adverse cardio-

Table I. Short-term outcomes collected via GermanVasc (in-hospital duration).

Study endpoints	Description / definition
Acute coronary syndrome	From no myocardial infarction/acute coronary syndrome to ECG changes (STEMI)
Stroke or TIA	From no stroke to major stroke
Acute dialysis	From no new/acute dialysis to new chronic dialysis (beyond discharge)
Ankle-brachial index	For each leg: From > 1.3 to < 0.4
Unplanned amputation	For each leg: From no unplanned amputation to major amputation
Occlusion of target lesion	From no occlusion to occlusion with open-surgical treatment
Distal embolisation	From no distal embolisation to distal embolisation with open-surgical treatment
Postoperative dissection	From no dissection to dissection with open-surgical treatment
Graft/device failure	From no failure to failure with open-surgical treatment
Bleeding complication	From no bleeding to bleeding with open-surgical treatment
Compartment syndrome	From no compartment syndrome to compartment syndrome with open-surgical treatment
Surgical site wound infection	From no wound infection to wound infection with open-surgical treatment
Patient-reported outcomes	Including quality of life (SF12, WIQ, WELCH, PHQ 4), pain experience, health status, employment situation

TIA: Transient ischaemic attack; CABG: coronary artery bypass surgery; PCI: percutaneous coronary intervention; COPD: chronic obstructive pulmonary disease; SIRS: systemic inflammatory response syndrome; STEMI: ST-elevation myocardial infarction.

Table II. Long-term outcomes collected via GermanVasc (after three, six, and 12 months).

Study endpoints	Description / definition
Survival	Survival status; If deceased: Date of death
Functional status	From full activity to bed-bound
Ambulation	From full ambulatory to bed-bound
Modified Rutherford-classification	*For each leg: Asymptomatic, mild claudication, moderate claudication (> 200 m), severe claudication (< 200 m), ischaemic rest pain, ulcer/necrosis, non-healing amputation, both ulcer/necrosis and non-healing amputation, acute limb ischaemia*
Foot infection	For each leg: From no symptoms/signs of infection to grade 3 (SIRS, severe)
Ankle-brachial index	For each leg: From > 1.3 to < 0.4
Tissue loss	For each leg: From no tissue loss to grade 3 (extensive)
Amputation	For each leg: From no amputation to major amputation
Patency of revascularisation	For each leg: No revascularisation, primary patency, primary-assisted patency, secondary patency, occluded; method of evaluation
New revascularisation	For each leg: From no reintervention/reoperation to both endovascular and open-surgical reoperation
Major adverse cardiovascular events (mace)	Yes or no
Major adverse limb events (male)	Yes or no
Readmission to hospital	Yes or no
Myocardial infarction	Yes or no
Stroke or TIA	Yes or no
Surgical site infection	Yes or no
Major bleeding complication	No bleeding complication, gum or nose bleeding, gastrointestinal bleeding, cerebral haemorrhage
Patient-reported outcomes	Including quality of life (SF12, WIQ, WELCH, PHQ 4), pain experience, health status, employment situation

TIA: Transient ischaemic attack.

vascular events (MACE), major adverse limb events (MALE), myocardial infarction, stroke or transient ischaemic attack, all-cause death, major amputation above ankle level, major reintervention or reoperation, all reintervention or reoperation, wound infection, vascular access-related major complication, maximum walking distance, Rutherford classification, and ankle-brachial index (ABI).

Secondary medical outcomes

Several additional outcomes will be assessed: minor amputation, primary and secondary patency, assisted patency, dissection, distal embolisation, device failure, bleeding complication, compartment syndrome, myocardial infarction, acute renal failure, lymphatic fistula, severe periprocedural complications, ambulation, technical success, length of hospital stay, functional status, and failure of closure devices.

Patient-reported outcomes

Several patient-reported outcomes will be assessed at the time of discharge after three, six, and 12 months. The investigated patient-reported outcomes and the measures for assessing them were selected by trading off the following criteria: a) being represented in the seminal conceptual model of patient outcomes by Wilson and Cleary [21] and being aligned with the COMET (Core Outcome Measures in Effectiveness Trials) initiative [22], b) capturing both general and PAD-specific aspects of functioning, health perceptions, and quality of life, c) being psychometrically valid based on reviews of the literature [23–28], and d) being as concise as possible to make an administration in routine care possible. The following measures will be administered in the study: a) the 12-item Short Form Health Survey to assess general physical and mental health-related quality of life and health perceptions [29], b) the 4-item Walking Estimated-Limitation Calculated by History (WELCH) questionnaire to assess walking impairment as

a central aspect of PAD-specific functioning [30], c) one question each for general and specific pain, respectively, d) the 4-item Patient Health Questionnaire for Depression and Anxiety (PHQ-4) to assess symptoms of anxiety and depression [31], and e) one question each to capture occupational status and sick-leave, respectively.

Ethics

The GermanVasc registry trial complies with the Helsinki Declaration 2013. The primary ethics approval was granted by the Hamburg Medical Chamber Ethics Committee (PV5691, January 2018) and the approval was confirmed by the local ethics committees. An insurance contract was concluded for the 10 000 patients included in this registry trial.

Statistical analysis

For the descriptive analyses, prospective registry data will be reported in absolute and relative frequencies for categorical and mean values, standard deviations and quantiles for continuous data.

(Generalized) linear (mixed) models will be used to determine differences between treatments regarding the development of the outcomes across time. Mixed models can be used to take the hierarchical structure of the data into account (individuals clustered within vascular centres, measurements at different time point clustered within individuals). Depending on the specific research question, variation due to vascular centres will be modelled as random effect and/or random slopes. Possible covariates will be modelled as fixed effects for adjustment (patient-mix). Model assumptions will be checked a priori using residual plots.

Findings with a p-value lower than 0.05 will be considered statistically significant.

Discussion

The government-funded registry-based IDOMENEO study will consecutively include 10 000 patients with invasive revascularisations for symptomatic PAD performed at approximately 30 to 40 German vascular centres utilizing the GermanVasc registry system. Because of the primary study focus on invasive treatment approaches, no additional study arm for best-medical-treatment only was implemented.

Due to the paucity of evidence regarding invasive treatment of PAD, the majority of guideline recommendations in current clinical practice guidelines are based on consensus of opinion of the experts [7, 9, 32, 33] and various relevant research questions remain unanswered. Independent randomized and controlled clinical trials (RCT) remain rare in this field of multidisciplinary vascular medicine [10, 11]. This might be explained by several arguments: the high costs and the often irreducible complexity make it challenging to accomplish high quality trials. Patients who undergo pharmacological treatment or invasive revascularisation for lower extremity arterial disease have various risk factors and can exhibit a wide range of clinical symptoms from intermittent claudication to severe tissue loss. Multiple stenoses or occlusions can appear in different locations and in both legs with various severity and complexity. Lastly, a wide and growing range of techniques and devices for open-surgical and endovascular revascularisation is available today with specific instructions for use, making the combination of devices challenging.

Furthermore, it remains unclear if results from RCT can reflect daily treatment practice under real-world conditions [10]. The complementary value of registry-based studies to collect real-world evidence is being controversially discussed these days [34]. Their practical and economic advantages contrast the methodological disadvantages. The non-randomized inclusion of patients and treatments means that possible confounders may affect the parameters of interest and that the validity of results are directly linked to the internal and external validity of the data [11, 35]. To minimize participant selection bias, an independent monitoring is conducted by random-sample cross-checking of patient files with registry data. Collecting multicentric longitudinal data on a large number of individuals directly affects core questions of data privacy and data security. In the light of big data applications in modern medicine and research, it is of utmost importance to deal with this topic [17, 36]. The GermanVasc registry is designed and developed as "Privacy by design", as an essential principle to innovate and develop new projects and methods for the security and protection of personal data.

Recruitment of patients started (first patient in) in May 2018 and is expected to end in December 2018. The last follow-up (last patient out) is expected in December 2019.

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IDOMENEO collaborators

Knöfel T (Bad Berka, Germany), Nolte T (Bad Bevensen, Germany), Zeller T (Bad Krozingen, Germany), Kainer K (Bad Nauheim, Germany), Hinterseher I (Berlin, Germany), Weigang E (Berlin, Germany), Gussmann A (Berlin, Germany), Kuhnert M (Birkenwerder, Germany), Hummel T (Bochum, Germany), Balzer KM (Bonn, Germany),

Remig J (Bonn, Germany), Friedrich O (Bonn, Germany), Waloßek M (Bonn, Germany), Seifert S (Chemnitz, Germany), Mettke R (Cottbus, Germany), Stöbe R (Cottbus, Germany), Bauersachs R (Darmstadt, Germany), Schellong SM (Dresden, Germany), Bergert H (Erfurt, Germany), Hoffmann J (Essen, Germany), Apostolidis S (Frankfurt, Germany), Beyersdorf F (Freiburg, Germany), Czerny M (Freiburg, Germany), Kellersmann R (Fulda, Germany), Debus ES (Hamburg, Germany), Rieß HC (Hamburg, Germany), Atlihan G (Hamburg, Germany), Sonnemann J (Hamburg, Germany), Theodosiou D (Hamburg, Germany), Zanow J (Jena, Germany), Hubert R (Karlsbach, Germany), Storck M (Karlsruhe, Germany), Moussa A (Kassel, Germany), Bürger T (Kassel, Germany), Berg P (Kevelaer, Germany), Hippe H (Kiel, Germany), Teßarek J (Lingen, Germany), Görtz H (Lingen, Germany), Kleemann M (Lübeck, Germany), Tautenhahn J (Magdeburg, Germany), Hribaschek A (Magdeburg, Germany), Tenholt MH (Mannheim, Germany), Reinhold C (Mönchengladbach, Germany), Stehr A (Mühlheim, Germany), Nolte-Ernsting C (Mühlheim, Germany), Ghotbi R (München, Germany), Heider P (München, Germany), Selch A (Neumünster, Germany), Teebken OE (Peine, Germany), Lepique F (Remscheid, Germany), Röttger C (Rheine, Germany), Lulay GR (Rheine, Germany), Nitschmann K (Soest, Germany), Sprenger C (Trier, Germany).

Electronic supplementary material

The electronic supplementary material is available with the online version of the article at http://dx.doi.org/https://doi.org/10.1024/0301-1526/a000730.

ESM 1. Figure.
Localisation of the multidisciplinary vascular centres in Germany. Each centre submitted a letter of intent to participate in the GermanVasc registry on invasive revascularisations of symptomatic peripheral arterial disease.

ESM 2. Table.
Important socio-demographic and medical risk factors collected via GermanVasc.

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Correspondence address
Dr. Christian-Alexander Behrendt
Department of Vascular Medicine
University Heart Center Hamburg
University Medical Center Hamburg-Eppendorf
20246 Hamburg
Germany

behrendt@hamburg.de