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

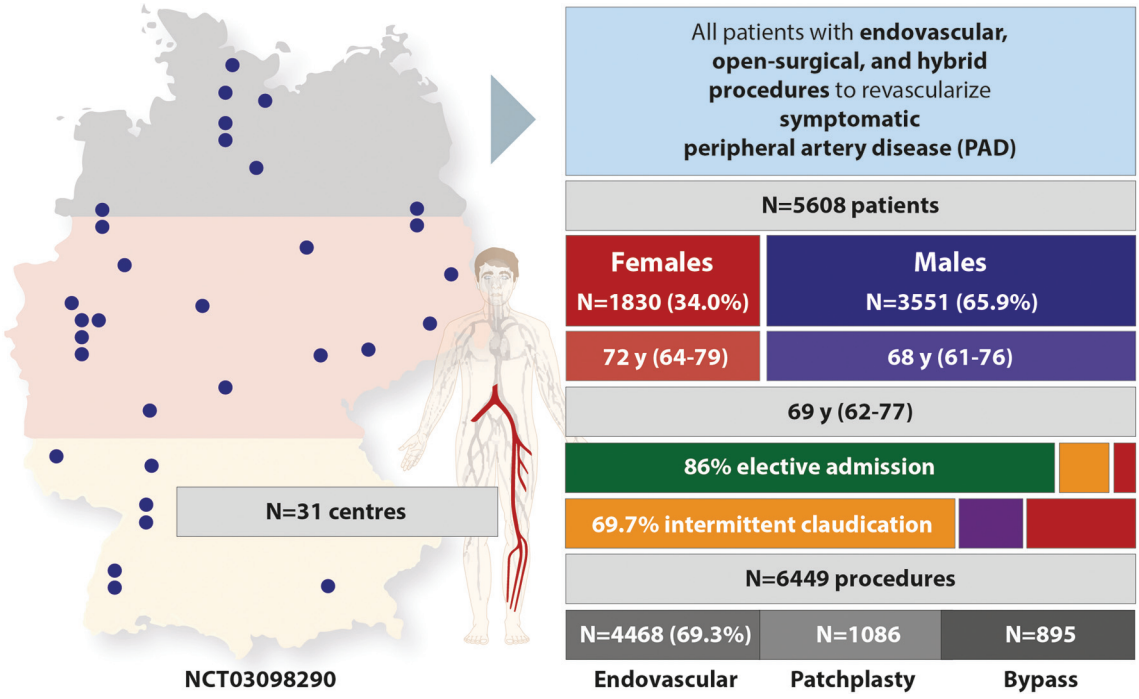

Figure 1. Central Illustration of this prospective multicentric cohort study of 5608 patients.

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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