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Peripheral arterial disease and critical limb ischaemia: still poor outcomes and lack of guideline adherence

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Aims Only few and historic studies reported a bad prognosis of peripheral arterial disease (PAD) and critical limb ischaemia (CLI). The contemporary state of treatment and outcomes should be assessed.

Methods and results From the largest public health insurance in Germany, all in- and outpatient diagnosis and procedural data were retrospectively obtained from a cohort of 41 882 patients hospitalized due to PAD during 2009–2011, including a follow-up until 2013. Patients were classified in Rutherford categories 1–3 ($n = 21\,197$), 4 ($n = 5353$), 5 ($n = 6916$), and 6 ($n = 8416$). The proportions of patients with classical risk factors such as hypertension, dyslipidaemia, and smoking declined with higher Rutherford categories (each $P < 0.001$) while diabetes, chronic kidney disease, and chronic heart failure increased (each $P < 0.001$). Angiographies and revascularizations were performed less often in advanced PAD (each $P < 0.001$). In-hospital amputations increased continuously from 0.5% in Rutherford 1–3 to 42% in Rutherford 6, as also myocardial infarctions, strokes, and deaths (each $P < 0.001$). Among 4298 amputated patients with CLI, 37% had not received any angiography or revascularization neither during index hospitalization nor the 24 months before. During follow-up (mean 1144 days), 7825 patients were amputated and 10 880 died. Kaplan–Meier models projected 4-year mortality risks of 18.9, 37.7, 52.2, and 63.5% in Rutherford 1–3, 4, 5, and 6, and for amputation of 4.6, 12.1, 35.3, and 67.3%, respectively. In multivariable Cox regression models, PAD categories were significant predictors of death, amputation, myocardial infarction, and stroke (each $P < 0.001$). Length of in-hospital stay (5.8 ± 6.7 days, 10.7 ± 11.1days, 15.2 ± 13.8 days and 22.1 ± 20.3 days; $P < 0.001$) and mean case costs (3662 ± 3186 €, 5316 ± 6139 €, 6021 ± 4892 €, and 8461 ± 8515 €; $P < 0.001$) increased continuously in Rutherford 1–3, 4, 5, and 6. While only 49% of the patients suffered from CLI, these produced 65% of in-hospital costs (141 million €), and 56% during follow-up (336 million €).

Conclusion Regardless of recent advances in PAD treatment, current outcomes remain poor especially in CLI. Despite overwhelming evidence for reduction of limb loss by revascularization, CLI patients still received significantly less angiographies and revascularizations.

Keywords Peripheral arterial disease • Critical limb ischaemia • Endovascular • Amputation • Mortality

Introduction

Peripheral arterial disease (PAD) is a markedly emerging and severe disease as outlined by the current ACC/AHA[1,2] and ESC guidelines[3] as well as a number of other related publications.[4–8] This concerns especially the advanced stage of PAD which is critical limb ischaemia (CLI).[1,3,5,9] A recent nationwide analysis of all PAD-related hospitalizations in Germany demonstrated a continuous increase in PAD

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burden of 21% from 401 000 cases in 2005 to 484 000 cases in 2009, and also an increase of the proportion of CLI from 40.6 to 43.5%.[10]

Despite the relevant medical and socio-economic burden, knowledge about the prognosis and optimal treatment of PAD and CLI is very limited as recently pointed out.[8,11] The few available outcome reports are derived from data which are about a decade old with low frequencies of revascularizations,[5,6,12–14] or from few contemporary trials with small numbers of included patients.[15,16] Nevertheless, they all show concordantly that patients with symptomatic PAD have a markedly increased risk for death, cardiovascular events and, especially in those with CLI, life-changing limb loss. This poor outcome might also be due to the fact that PAD and CLI are often underdiagnosed and undertreated.[17,18]

It is not known in how far recent changes in awareness and detection of PAD, the continuously rising number of revascularizations, and the substantial progress in medication[19,20] and technical devices used for endovascular revascularization have affected the prognosis of these patients. Therefore, we now sought to analyse a large and contemporary patient cohort to characterize the outcomes of PAD in its distinct stages with special regard to endovascular and surgical revascularization.

Methods

In 2004, the system for hospital reimbursement in Germany underwent a fundamental change by the introduction of a diagnosis and procedure-related reimbursement system (German Diagnosis Related Groups, G-DRG system).[21,22] Detailed and mandatory coding guidelines were implemented, and all hospitals were obligated to transfer all data about baseline patient characteristics, diagnoses, comorbidities, procedures, and complications to the health insurances. Otherwise no reimbursement is paid for the respective hospital treatment. All transferred cases are cross-checked by special software, and additionally ~20% are reviewed and corrected by special physicians (Medizinischer Dienst der Krankenversicherung) who work independent from hospitals and health insurances.

Of note, in Germany all inhabitants must by law be insured by a private or public health insurance.

Principles of the German Diagnosis Related Groups system

In brief, the German remuneration system requires the coding of one main diagnosis for all in-hospital patients which must thoroughly be chosen after discharge with concern to the underlying cause for hospital admission. Furthermore, an unlimited number of secondary diagnoses can be coded to reflect comorbidities and complications being present or occurring during in-hospital stay. Secondary diagnoses increase the patient's comorbidity and complexity level and have some impact on reimbursement.

Each diagnosis has to be coded according to the German Modification of the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10). In addition to the WHO ICD-10, some diagnoses are more detailed in the German Version due to the coding requirements of the G-DRG-System. This allows to separate subgroups such as Rutherford categories.

Similar to the ICD for diagnoses, all diagnostic, endovascular, and surgical procedures have to be coded according to the German procedure classification ('Operationen und Prozedurenschlüssel', OPS).

Each case is then allocated into a specific G-DRG depending on its main diagnosis and combination of secondary diagnoses and procedures, and induces a certain reimbursement.

Data source

The BARMER GEK is the largest public German health insurance which is currently responsible for >8 million people representing ~10% of the entire German population. All patients' data are stored in a central computerized database, from which we obtained anonymised data of all patients who fulfilled the following inclusion criteria.

Patients' inclusion and allocation

Patients qualified for this analysis if they had an index hospitalization between January 1st, 2009 and December 31st, 2011 (Supplementary material online, *Figure S1*). Moreover, in-hospital patients were included if they had a main diagnosis of lower limb PAD (ICD-10 codes I70.20–I70.24), or a secondary diagnosis of lower limb PAD in combination with one of the following main diagnoses: diabetes with vascular complications, other peripheral vessel disease, arterial embolism and thrombosis, or ulcers (ICD codes in Supplementary material online, *Table S1*). Frequencies and combinations of these main and secondary diagnoses in the study subset are presented in Supplementary material online, *Table S2*. Patients were then allocated in accordance to their PAD codes as follows: patients were classified as Rutherford Category 6 if I70.24 was coded as main or secondary diagnosis; I70.23 as Rutherford 5; I70.22 as Rutherford 4, and I70.20 or I70.21 as Rutherford 1–3 (Supplementary material online, *Figure S2*). In accordance to current guidelines,[1–3,18] patients with Rutherford 4, 5, or 6 were classified to suffer from CLI.

In-hospital complications were assessed from specific secondary diagnoses in accordance to strict coding rules (Supplementary material online, *Table S1*); e.g. sepsis can only be coded if a systemic inflammatory response syndrome was present as defined in detail.[23]

Types and anatomic locations of procedures were classified with regard to their OPS code (Supplementary material online, *Table S3*).

Previous treatments before index hospitalization and follow-up

From all patients also all in- and outpatient cardiovascular diagnoses and procedure codes during 24 months *before* their index hospitalization were obtained (Supplementary material online, *Figure S1*). Moreover, all in- and outpatient diagnoses and procedures *after* the index hospitalization until December 31st, 2012 were also recorded as a follow-up. This included also all major adverse events such as death, amputation, myocardial infarction, and stroke.

Costs and reimbursement

An independent institute (Institut für das Entgeltsystem im Krankenhaus) calculates annually the total actual costs in all distinct DRGs for entire Germany as described previously.[21,22] On this real-life basis, DRG cost weights are calculated for each DRG. These are then used for the reimbursement of in-hospital care in the next year. Thus, in Germany reimbursement is based on actual costs and is specific for those health care services which are conducted. The here presented costs included all in-hospital measures including drugs, catheters, and blood products. Any costs resulting from outpatient care are not included in the analysis.

Statistics

Categorical variables are presented as absolute numbers (n) and percentages (%) of the total numbers for each Rutherford subgroup; statistical comparisons for these were made by the χ^2 test. Continuous variables

were presented as mean ± standard deviation (SD) and compared by the ANOVA *F*-test. Events during follow-up were displayed by Kaplan–Meier models; differences between the distinct Rutherford subgroups were compared by the log-rank test. The predictive value of baseline parameters concerning long-term outcomes were tested by multivariable cox regression models; results were displayed as hazard ratios (HRs) and 95% confidence intervals (CIs). Furthermore, concordance indices (Harrell's C) of the Cox models were calculated and the proportional hazards assumption examined graphically for potential violations. All tests were performed two-sided, and *P*-values of <0.05 were considered statistically significant.

Results

A total of 41 882 patients fulfilled the inclusion criteria and represented the cohort for this analysis (Supplementary material online, *Figure S1* and *S2*). Baseline characteristics and comorbidities of these patients are shown in *Table 1*. The proportions of patients with classical risk factors such as hypertension, dyslipidaemia, and smoking declined with higher Rutherford categories (each $P < 0.001$). Conversely, diabetes, chronic kidney disease, and chronic heart failure increased with higher Rutherford categories (each $P < 0.001$).

In-hospital treatment and complications

Details of in-hospital treatment and outcomes during the index hospitalization are shown in *Table 2*. The frequencies of arterial angiographies and endovascular revascularization decreased with higher Rutherford categories (each $P < 0.001$). Surgery was most frequent in Rutherford 4, but decreased in Categories 5 and 6 ($P < 0.001$).

Major complications during the index hospitalization are also summarized in *Table 2*. Thus, acute renal failure, myocardial infarctions, infections, sepsis, and death occurred more frequently in higher Rutherford categories (each $P < 0.001$). Frequencies of ischaemic stroke were comparable in all subgroups except a peak in those with Rutherford 6 ($P < 0.001$).

Vascular procedures in amputated patients

A total of 4401 patients were amputated during their index hospitalization (*Table 2*). Of these, 4298 amputees had CLI (Rutherford Categories 4–6) and represented the basis for a subgroup analysis about previously applied vascular procedures. The 103 patients with amputations in Rutherford Categories 1–3 were not included because amputations in these may represent more likely a rare complication of current treatment rather than a manifestation of the underlying disease.

Thus, 44% of all amputees with CLI ($n = 1887$) had not received at least a diagnostic angiography in hospital before amputation (*Figure 1*). Even if for these 1887 patients all previous in- and outpatient vascular procedures during the 24 months before were additionally taken into account, 1571 of 4298 patients (37%) with an amputation due to CLI had neither during the index hospitalization nor the 2 years before received any angiography or revascularization.

Long-term outcome

During a mean follow-up time of 1144 days (95% CI 1138–1149 days), a total of 10 880 patients died. Another 1039 patients (2.5% of the entire cohort) changed to another health insurance. However, until they left the insurance, all events and procedures were recorded. *Figure 2* shows Kaplan–Meier probabilities of long-term outcomes.

Mortality risks after 4 years (95% CIs given in parentheses) were significantly different between the subgroups with 18.9% (18.0–19.8%), 37.7% (35.7–39.7%), 52.2% (50.4–54.0%), and 63.5% (62.0–65.1%) in Rutherford Categories 1–3, 4, 5, and 6, respectively ($P < 0.001$). The curves display also how rapidly mortality rose: 34.2% (33.2–35.3%) of the patients in Rutherford Category 6 deceased within the first 12 months after index hospitalization (*Figure 2A*).

Including the 4401 amputations which were performed during the index hospitalization, a total of 7825 patients were amputated. The

Table 1 Baseline characteristics and comorbidities with regard to Rutherford categories

	RF 1–3	RF 4	RF 5	RF 6	Total	*P*
Patients, *n* (% of all)	21 197 (50.6)	5353 (12.8)	6916 (16.5)	8416 (20.1)	41 882 (100.0)	
Age, mean ± SD (years)	68.5 ± 10.4	72.2 ± 11.8	75.6 ± 11.1	74.9 ± 11.8	71.4 ± 11.4	**<0.001**
Women, *n* (%)	8765 (41.4)	2697 (50.4)	3413 (49.3)	3716 (44.2)	18 591 (44.4)	**<0.001**
Hypertension, *n* (%)	14 667 (69.2)	3695 (69.0)	4686 (67.8)	5437 (64.6)	28 485 (68.0)	**<0.001**
Obesity, *n* (%)	1557 (7.3)	364 (6.8)	547 (7.9)	605 (7.2)	3073 (7.3)	0.118
Dyslipidaemia, *n* (%)	7941 (37.5)	1669 (31.2)	1670 (24.1)	1674 (19.9)	12 954 (30.9)	**<0.001**
Smoking, *n* (%)	3127 (14.8)	637 (11.9)	433 (6.3)	508 (6.0)	4705 (11.2)	**<0.001**
Diabetes, *n* (%)	4976 (23.5)	1416 (26.5)	3061 (44.3)	4108 (48.8)	13 561 (32.4)	**<0.001**
CAD, *n* (%)	5115 (24.1)	1423 (26.6)	1735 (25.1)	2192 (26.0)	10 465 (25.0)	**<0.001**
Chronic heart failure, *n* (%)	1021 (4.8)	569 (10.6)	1063 (15.4)	1470 (17.5)	4123 (9.8)	**<0.001**
CKD, *n* (%)	3023 (14.3)	1196 (22.3)	2139 (30.9)	2797 (33.2)	9155 (21.9)	**<0.001**
Malignancies, *n* (%)	261 (1.2)	131 (2.4)	142 (2.1)	240 (2.9)	774 (1.8)	**<0.001**

CAD, coronary artery disease; CKD, chronic kidney disease; RF, Rutherford category, SD, standard deviation.
Significant *P*-values were presented in bold.
Comorbidities were defined on the basis of given ICD-10 codes, and are presented in detail in Supplementary material online, *Table S1*.

Table 2 Treatment, complications, and outcomes during index hospitalization

	RF 1–3	RF 4	RF 5	RF 6	Total	*P*
Patients, *n* (% of all)	21 197 (50.6)	5353 (12.8)	6916 (16.5)	8416 (20.1)	41 882 (100.0)	
Angiography, *n* (%)	12 339 (58.2)	3128 (58.4)	3567 (51.6)	4032 (47.9)	23 066 (55.1)	**<0.001**
Endovascular, *n* (%)	11 602 (54.7)	2043 (38.2)	2450 (35.4)	2481 (29.5)	18 576 (44.4)	**<0.001**
Surgery, *n* (%)	5068 (23.9)	2130 (39.8)	1312 (19.0)	2083 (24.8)	10 593 (25.3)	**<0.001**
TEA, *n* (%)	2736 (12.9)	932 (17.4)	514 (7.4)	807 (9.6)	4989 (11.9)	**<0.001**
Bypass, *n* (%)	2068 (9.8)	1000 (18.7)	816 (11.8)	1326 (15.8)	5210 (12.4)	**<0.001**
Any revascularization, *n* (%)	15 963 (75.3)	3817 (71.3)	3518 (50.9)	4140 (49.2)	27 438 (65.5)	**<0.001**
Acute renal failure, *n* (%)	76 (0.4)	73 (1.4)	127 (1.8)	235 (2.8)	511 (1.2)	**<0.001**
MI, *n* (%)	68 (0.3)	44 (0.8)	58 (0.8)	147 (1.7)	317 (0.8)	**<0.001**
Ischaemic stroke, *n* (%)	33 (0.2)	21 (0.4)	29 (0.4)	63 (0.7)	146 (0.3)	**<0.001**
Infections, *n* (%)	491 (2.3)	270 (5.0)	1987 (28.7)	3001 (35.7)	5749 (13.7)	**<0.001**
Sepsis, *n* (%)	88 (0.4)	81 (1.5)	323 (4.7)	491 (5.8)	983 (2.3)	**<0.001**
Amputations, *n* (%)	103 (0.5)	88 (1.6)	679 (9.8)	3531 (42.0)	4401 (10.5)	**<0.001**
Deaths, *n* (%)	93 (0.4)	189 (3.5)	234 (3.4)	701 (8.3)	1217 (2.9)	**<0.001**
In-hospital stay, mean ± SD (days)	5.8 ± 6.7	10.7 ± 11.1	15.2 ± 13.8	22.1 ± 20.3	11.2 ± 14.0	**<0.001**
Costs, mean ± SD (€)	3662 ± 3186	5316 ± 6139	6021 ± 4892	8461 ± 8515	5227 ± 5650	**<0.001**

Endovascular, endovascular revascularization; MI, myocardial infarction; TEA, thrombendatherectomy; RF, Rutherford category; SD, standard deviation.
Significant *P*-values were presented in bold.
Comorbidities, complications, and procedures were defined on the basis of given ICD-10 and OPS codes, and are presented in detail in Supplementary material online, *Tables S1* and *S3*.

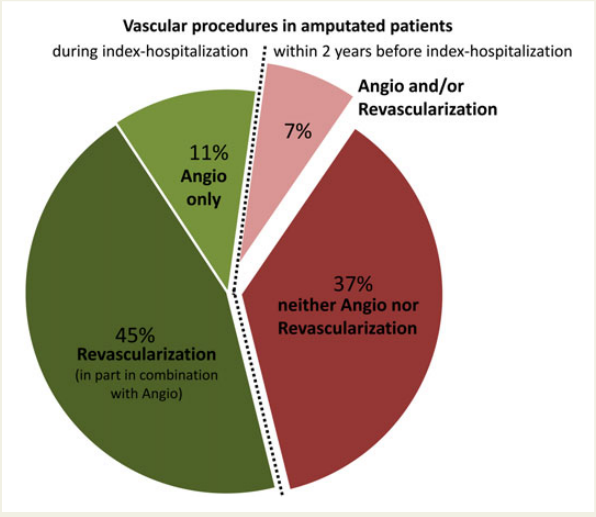

Figure 1 Vascular procedures in amputated patients. In a subgroup analysis, patients with critical limb ischaemia (Rutherford Categories 4, 5, and 6) who underwent an amputation during index hospitalization were selected. From these 4298 patients, 45% ($n = 1917$) underwent a surgical and/or endovascular revascularization procedure (Rx) during index hospitalization (in part in combination with a diagnostic angiography). Another 11% ($n = 494$) received a diagnostic angiography (Angio). But 44% ($n = 1887$) received neither angiography nor revascularization. From these latter 1887 patients, 316 patients had received a revascularization or a diagnostic angiography during the 2 years before amputation, but the remaining 1571 patients (37%) with critical limb ischaemia were amputated without any revascularization or diagnostic angiography neither during index hospitalization nor the 2 years before.

projected amputation risks after 4 years in Rutherford Categories 1–3, 4, 5, and 6 were 4.6% (4.2–5.0%), 12.1% (11.0–13.4%), 35.3% (33.6–37.0%), and 67.3% (65.8–68.8%), respectively (*Figure 2B*). The amputation risk was already 59.6% (58.6–60.7%) within 1 year in patients with Rutherford 6.

A total of 15 155 patients suffered from the combined endpoint of death or amputation, with 4-year risks of 21.4% (20.5–22.3%), 42.1% (40.2–44.1%), 66.1% (64.4–67.8%), and 85.7% (84.6–86.8%) in Rutherford Categories 1–3, 4, 5, and 6, respectively (*Figure 2C*).

During follow-up, 1952 patients suffered from acute myocardial infarction with 4-year risks of 6.6% (6.0–7.1%), 9.4% (8.1–10.9%), 10.9% (9.6–12.4%), and 10.3% (9.0–11.7%) in Rutherford Categories 1–3, 4, 5, and 6, respectively (*Figure 2D*).

Acute ischaemic stroke occurred in 1646 patients, with projected event rates at 4 years of 5.4% (4.9–5.9%), 7.4% (6.4–8.6%), 9.1% (7.9–10.5%), and 8.3% (7.4–9.4%) in Rutherford Categories 1–3, 4, 5, and 6, respectively (*Figure 2E*). Thus, event rates for myocardial infarction and stroke were similar in Rutherford Categories 4, 5, and 6, but significantly lower in patients with Rutherford Categories 1–3 (*Figure 2D* and *E*).

Predictors for long-term outcomes

All baseline parameters and co-morbidities from *Table 1* were entered into separate Cox regression models to identify factors which were associated with death, amputation, myocardial infarction, and stroke during follow-up (*Table 3*). In all models, Rutherford Categories 4, 5, and 6 increased the risk for the respective event significantly and independently from all other comorbidities. There were moreover marked stepwise increases of the HRs between the distinct Rutherford categories with regard to death and amputation. Furthermore, patients with CLI (Rutherford 4, 5, and 6) had a

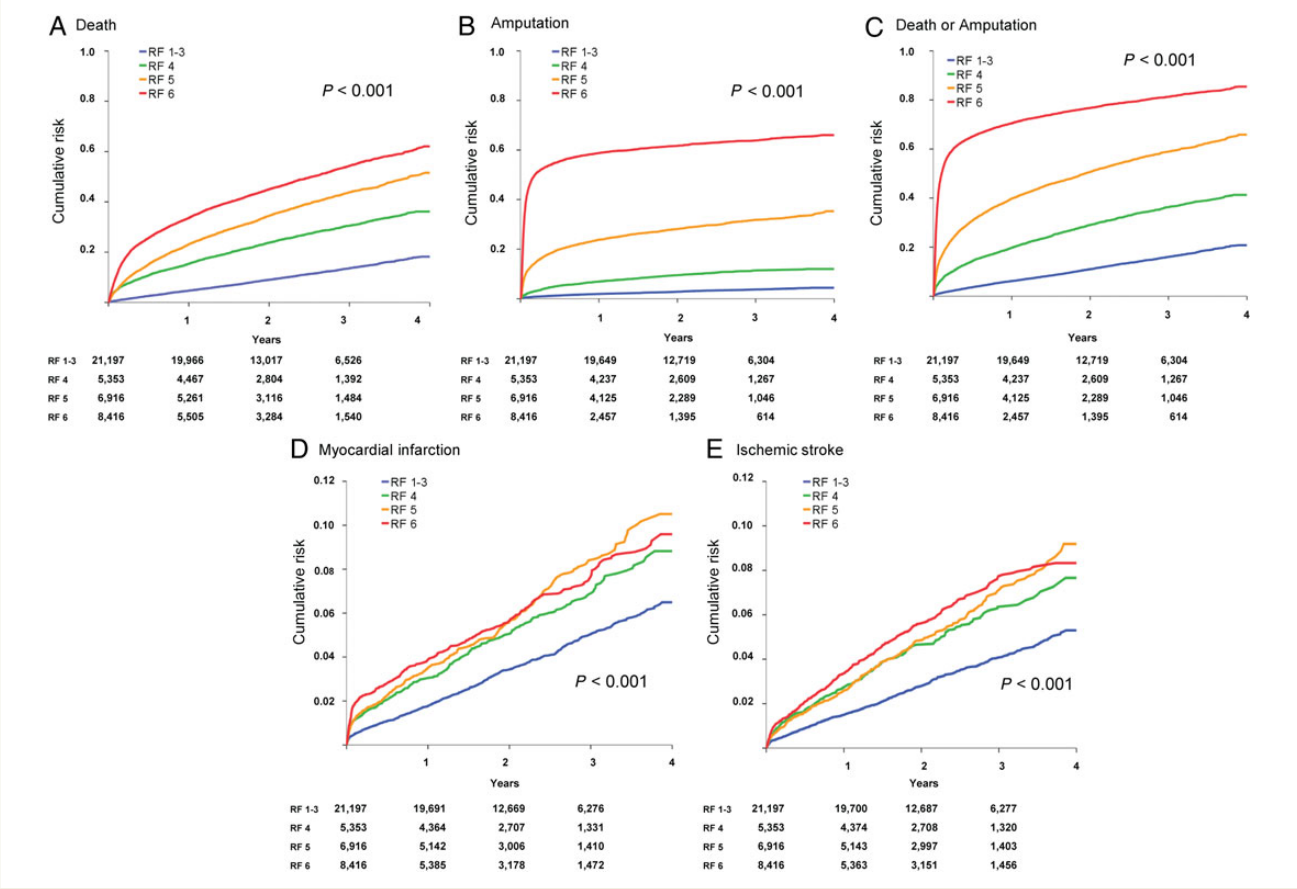

Figure 2 Major adverse events during follow-up. Kaplan–Meier probabilities for death (*A*), amputation (*B*), a combined endpoint of death or amputation (*C*), myocardial infarction (*D*), and ischaemic stroke (*E*) are presented, with the number of patients at risk given below each chart. Between the distinct Rutherford categories highly significant differences were observed (each $P < 0.001$).

higher risk for myocardial infarction and stroke compared with claudicants (Rutherford 1–3) but there were no additional increases between Rutherford categories 4, 5, and 6.

We determined concordance indices by Harrell's C as an overall estimate of model fit (*Table 3*). Moreover, we examined the proportional hazards assumption graphically for the two main outcomes death and amputation by checking the survival plots (survival curves by time). For amputation, no violation of the proportional hazards assumption was observed. Regarding death, there were crossing survival curves for the covariate hypertension indicating a violation of the proportional hazards assumption for this single covariate. Therefore, we performed several sensitivity analyses, including a Cox Regression model without the variable hypertension, a stratified model, and a model including an additional time-dependent covariate term. In all these additional analyses, the effect of the Rutherford categories on death remained consistently high and statistically significant. The model without the variable hypertension gave almost the same hazard ratios as reported in *Table 3* (data not shown).

Finally, especially age and higher Rutherford categories were closely related, and this may have resulted in a residual confounding of the results in spite of statistical adjustment for age. Therefore, in addition to the multivariate Cox models in *Table 3* just including age as one factor, we also used age as a stratification factor thus subdividing patients in quintiles of age. However, in these Cox models stratified by age quintiles regarding the two main outcomes measures death (Supplementary material online, *Table S4*) and amputation (Supplementary material online, *Table S5*) there were only slight variations in HRs: in all quintiles Rutherford categories had consistently a marked impact on outcome as well as the stepwise increase in HRs from Rutherford category to category also remained.

Costs for index hospitalization and during follow-up

The mean length of in-hospital stay and treatment costs increased with higher Rutherford categories ($P < 0.001$, *Table 2*). The costs for the index hospitalization added up to 78 million € for patients with Rutherford 1–3, 29 million € in Rutherford 4, 42 million € in Rutherford 5, and 71 million € in patients with Rutherford 6 (in total 219 million €). Thus, ~65% of all paid reimbursement (141 million €) was allocated to patients with CLI in Rutherford categories 4, 5, and 6, although they represented only 49% of the cohort.

Table 3 Multivariate Cox regression analyses of predictors for long-term outcomes

	Death (n = 41 873)		Amputation (n = 41 860)		MI (n = 41 860)		Ischaemic stroke (n = 41 873)	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
RF 1–3	1		1		1		1	
RF 4	2.04 (1.91–2.18)	**<0.001**	3.11 (2.76–3.49)	**<0.001**	1.32 (1.15–1.51)	**<0.001**	1.43 (1.23–1.65)	**<0.001**
RF 5	2.53 (2.39–2.68)	**<0.001**	9.28 (8.47–10.17)	**<0.001**	1.29 (1.14–1.47)	**<0.001**	1.32 (1.15–1.51)	**<0.001**
RF 6	3.75 (3.56–3.96)	**<0.001**	29.00 (26.67–31.55)	**<0.001**	1.29 (1.14–1.46)	**<0.001**	1.50 (1.32–1.72)	**<0.001**
Age	1.06 (1.06–1.06)	**<0.001**	1.00 (1.00–1.00)	0.157	1.02 (1.02–1.03)	**<0.001**	1.03 (1.03–1.04)	**<0.001**
Male	1.21 (1.16–1.25)	**<0.001**	1.33 (1.27–1.39)	**<0.001**	1.27 (1.16–1.40)	**<0.001**	1.07 (0.96–1.18)	0.226
Hypertension	0.83 (0.79–0.86)	**<0.001**	0.93 (0.89–0.98)	**0.003**	0.91 (0.82–1.00)	0.059	1.07 (0.96–1.20)	0.229
Obesity	0.88 (0.81–0.95)	**0.002**	0.93 (0.86–1.01)	0.104	1.03 (0.88–1.21)	0.729	0.98 (0.81–1.18)	0.825
Dyslipidaemia	0.74 (0.70–0.77)	**<0.001**	0.84 (0.80–0.89)	**<0.001**	0.92 (0.83–1.01)	0.091	0.91 (0.81–1.01)	0.083
Smoking	1.05 (0.97–1.14)	0.265	0.835 (0.76–0.92)	**<0.001**	0.99 (0.85–1.18)	0.989	1.07 (0.90–1.28)	0.446
Diabetes	1.05 (1.00–1.09)	**0.033**	1.473 (1.41–1.54)	**<0.001**	1.28 (1.17–1.41)	**<0.001**	1.30 (1.17–1.44)	**<0.001**
CAD	1.24 (1.19–1.30)	**<0.001**	1.00 (0.95–1.05)	0.976	2.02 (1.84–2.22)	**<0.001**	0.97 (0.86–1.09)	0.554
CHF	1.62 (1.54–1.70)	**<0.001**	1.10 (1.03–1.17)	**0.003**	1.64 (1.44–1.85)	**<0.001**	1.27 (1.09–1.49)	**0.002**
CKD	1.47 (1.41–1.53)	**<0.001**	1.12 (1.07–1.18)	**<0.001**	1.30 (1.17–1.44)	**<0.001**	1.05 (0.93–1.18)	0.439
Malignancies	2.16 (1.96–2.38)	**<0.001**	0.91 (0.78–1.05)	0.203	1.14 (0.82–1.58)	0.428	0.97 (0.65–1.44)	0.874
Harrell's C[a]	0.78		0.85		0.68		0.64	

CAD, coronary artery disease; CHF, chronic heart failure, CKD, chronic kidney disease; CI, confidence interval; HR, hazard ratio; MI, myocardial infarction; RF, Rutherford category. Comorbidities were defined on the basis of given ICD-10 codes, and are presented in detail in Supplementary material online, *Table S1*.
Significant *P*-values were presented in bold.
[a]A value for Harrell's $C = 0.5$ suggests no discrimination; $0.7 \leq C < 0.8$ is considered acceptable discrimination; $0.8 \leq C < 0.9$ is considered as excellent discrimination; $C \geq 0.9$ is considered as outstanding discrimination.

During follow-up, all costs for further in-hospital treatments were also recorded. Thus, the totally paid reimbursement added up to 261 million € for patients with Rutherford categories 1–3, 78 million € in Rutherford 4, 123 million € in Rutherford 5, and 135 million € in patients with Rutherford 6 (in total 598 million €). Thus, 56% of all costs (336 million €) were allocated to CLI patients.

Discussion

Current guidelines[1,3,18] and contemporary reviews[7,8,11,17] consistently outline the lack of data about treatment and outcomes in PAD and especially CLI, despite the high number of affected patients. The limited available data derive from observations which are more than a decade old[5,6,13,24,25] and do not reflect recent improvements in PAD detection and management. The handful of current studies were not only just small sized ($n < 200$) but also focused on specific interventional techniques and reported short-term outcomes of those patients eligible for a distinct revascularization.[15,16]

In the present study, contemporary data from 41 882 patients with all stages of PAD including CLI and the complete variety of real-life treatment are presented. This included a 2-year pre-treatment period and a follow-up up to 4 years which both represent one strength of this analysis.

Trends in mortality

We found a high mortality especially in Rutherford Categories 5 and 6 which was only comparable with that of some aggressive types of cancer.[26] The here observed 1-year mortality risk in patients with CLI of 16–35% depending on Rutherford categories remained unchanged compared with the 25% in CLI patients from TASC II >10 years ago.[5] Our mortality projections were also in line with the 5-year mortality of 46% from a pooled analysis of several small studies about CLI (50 studies with a total of 28 517 patients).[24] In contrast, 1-year mortality in the large REACH registry (including only outpatients) was very low with 1.5% in all PAD patients;[13] but in a subgroup of 1160 individuals who had previously undergone amputations, the 3-year mortality of 22% was similar to our study.[25] In the *getABI* trial,[6] mortality was given with 46.3 per 1000 patient-years for all PAD patients without concerning CLI. This also is lower than in our study but comparable with REACH, which might be due to the fact that in *getABI* as in REACH also many outpatients and asymptomatic individuals were included, while our analysis comprised only symptomatic, hospitalized patients.

Trends in amputations

We observed also high numbers of amputations at 1 year after index hospitalization but within a wide range from 5 to 57% in Rutherford 4–6, respectively. These are again in good accordance to the average frequency of 30% amputations in CLI patients at 1 year after index treatment in TASC II;[5] even more since in TASC II only the frequency of the patients were reported who were amputated and alive. In another study with 564 diabetics with CLI, amputation frequencies ranged also from 5 to 70% depending on the treatment which was applied.[27] In contrary, 1 year amputation frequencies in REACH

were only 1.6% in the entire PAD cohort;[13] and even in the CLI subgroup with previous amputations the 3-year re-amputation frequencies were with 12.4% markedly lower.[25] This could on one hand be attributed to the fact that only outpatients were included, and on the other hand that the amputation subgroup had reduced amputation frequencies since they had already undergone a previous one. Regrettably, the few other studies concerning long-term outcomes of PAD[6] and CLI[24] do not present amputation numbers.

Confounding factors for the observed trends

The question is why these results are still so unfavourable and unchanged over more than a decade. One reason probably is that PAD and CLI represent not only a disease of peripheral arteries but include multiple systemic alterations including heart, brain, and kidney, and also inflammation and haemostasis as precisely pointed out in a recent editorial.[8] This multiorgan disorder causes markedly higher systemic adverse events and could hardly be reversed, especially not by peripheral revascularization.

Another key factor particularly concerning amputations might be that vascular procedures have indeed increased markedly[10,28,29] but as seen in this study they were highest in patients with exercise pain and were utilized less frequently in CLI. Other reports support this evidence for underuse of vascular procedures in CLI: MEDICARE data from different regions across the USA also found that of 20 464 amputees, 54% did not have any vascular procedure (diagnostic angiography or any revascularization) before amputation, with a wide range between specific regions.[30] Beside geographic differences, there appeared also to be major ethical disparities[31] which however play no role in our analysis since the vast majority of patients in Germany are Caucasians. Moreover, our analysis also provided data ~2 years before amputation and found that even then still 37% of amputees had not undergone any vascular procedure.

Our findings are in good accordance to a recent report from the *Nationwide Inpatient Sample* of the USA which also showed that revascularizations have markedly risen but amputations also increased[29] which is in contrast to a previous report from the same database which had observed declining amputations.[28] In another recent nationwide observation from Germany also patients with CLI were less likely to undergo revascularization compared with claudicants;[10] additionally, that study showed that important comorbidities in PAD and CLI patients increased markedly from 2005 to 2009.

In summary, the advanced systemic alterations in CLI patients at the time when they become symptomatic,[8] the increases of relevant comorbidities such as diabetes and heart failure in PAD patients over time,[10] and the underutilization of vascular procedures to reduce amputations may represent important causes for the unchanged poor outcomes.

Limitations

Diagnosis- and procedure-based reports cause always concern because of the data quality. Therefore, the focus of our study was on 'hard' endpoints such as amputations and death which are very unlikely to be miscoded. Precise coding rules concerning main and secondary diagnoses as well as procedures have been in use now for >10 years in Germany and were not changed with regard to the topics of this study. Concerning potential undercoding, complete coding is obligatory for correct reimbursement and therefore an essential interest of the hospitals. With regard to possible overcoding, ~20% of all cardiovascular DRGs are proven and corrected by independent physician task forces; these cases are not selected randomly but computer-assisted with regard to coding abnormalities. However, since only hospitalized patients were analysed, they present in so far a selection of patients with more severe grade of disease.

Smoking, obesity, dyslipidaemia, and hypertension had at no time any impact on DRG grouping and reimbursement. Therefore, their frequencies are surely underestimated in this analysis. However, it is unlikely that non-coding in one Rutherford subgroup might be different to that in another. Other diagnoses, such as chronic kidney disease, diabetes, and chronic heart failure, increase the patients' comorbidity and complexity level and in many cases also reimbursement. Therefore, completeness of these secondary diagnoses could be assumed to be high. Nearly, all procedures directly influence reimbursement and could therefore be expected to be almost complete.

Finally, the nature of our study is purely observational limitating any conclusions about underlying causes.

Conclusion

The high proportions of death and amputations appear surprisingly unimproved compared with the few available historical data.[5,6] Although conclusions with regard to treatment cannot be drawn due to the observational character of this study, the lower frequency of angiographies and revascularizations in CLI patients and the high number of amputated patients without any previous vascular procedures during index hospitalization or the 24 months before may represent one reason for unfavourable outcomes. Since this underuse is in clear contrast to current guidelines and trials[1,3,15,16,18] which provided good evidence that amputation-free survival can be improved, consequent vascular diagnostics, and revascularization (regardless whether endovascular or surgical, depending on what is best suitable[3,12]) should be more strictly recommended in all patients with CLI or a risk for amputation.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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