European Heart Journal (2013) **34**, 2706–2714
doi:10.1093/eurheartj/eht288

CLINICAL RESEARCH
Coronary artery disease

Recent trends in morbidity and in-hospital outcomes of in-patients with peripheral arterial disease: a nationwide population-based analysis

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Received 11 January 2013; revised 13 June 2013; accepted 1 July 2013; online publish-ahead-of-print 17 July 2013

Aims The prevalence of peripheral arterial disease (PAD) and especially of critical limb ischaemia (CLI) is announced to rise dramatically worldwide, with a considerable impact on the health care and socio-economic systems. We aimed to characterize the recent trends in morbidity and in-hospital outcome of PAD among all hospitalized patients in the entire German population between 2005 and 2009.

Methods and results Nationwide data of all hospitalizations in Germany in 2005, 2007, and 2009 were analysed regarding the prevalence of PAD, comorbidities, endovascular (EVR) and surgical revascularizations (SR), major and minor amputations, in-hospital mortality, and associated costs. From 2005 to 2009, total PAD cases increased by 20.7% (from 400 928 to 483 961), with an increase of CLI subset from 40.6 to 43.5%. Total EVR increased by 46%, while thromb-embolectomy, endarterectomy, and patch plastic increased by 67, 42, and 21%, respectively. Peripheral bypasses decreased by 2%. Major amputation decreased from 4.6 to 3.5%, while minor amputation slightly increased from 4.98 to 5.11%. The crude overall in-hospital mortality remained unchanged in claudicants (2.2%), while it decreased from 9.8 to 8.4% in CLI patients. However, mortality rate according to the Poisson model (*n*/1000 hospital residence days) increased significantly in claudicants ($P < 0.001$). Total reimbursement costs for PAD in-patient care increased by 21% with an average per case costs in 2009 of €4506 in a claudicant and €6791 in a CLI patient.

Conclusion This population-based analysis documents the significant rise of PAD, particularly of the CLI subset, and highlights the malign prognosis associated with PAD as indicated by high amputation and in-hospital mortality rates.

Keywords Peripheral artery disease • Critical limb ischaemia • Revascularization • Amputation • In-hospital mortality

Introduction

Peripheral arterial occlusive disease (PAD) is strongly age-dependent, affecting <3% of the general population ≤50 years of age but this rate increases to >50% with higher ages and extensive cardiovascular risk profiles.[1–4] The clinical status varies from asymptomatic (vast majority of PAD population) to claudicants (exercise-induced symptoms of the lower limbs), and to those having rest pain and/or tissue loss due to critically reduced limb perfusion, categorized as critical limb ischaemia (CLI). Peripheral arterial occlusive disease patients constitute, regardless of their symptomatic status, an extensive high-risk subset for cardiovascular ischaemic events such as myocardial infarction and stroke.[5–7]

The expected dramatic rise in atherosclerotic vascular diseases due to ageing of population and an increased prevalence of atherosclerotic risk factors in Western countries will pose an economic challenge to health systems and healthcare providers. Acquisition of accurate and systematic data on morbidity, mortality, and outcome is a prerequisite for establishment of effective preventive and therapeutic measures to successfully face and overcome those medical and economic challenges. However, contemporary available epidemiological and socio-economic data on PAD are derived from

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small-sized regional and/or restricted cohorts and are extrapolated to ascertain an estimate for a large-scale population. Trend data for an entire healthcare system and nation have not been available until now. Moreover, it is unclear in how far the efforts to enhance the adherence to guidelines-based therapeutic recommendations alongside with increasing endovascular revascularization (EVR) procedures affected the incidence and outcome of PAD. The aim of the current analysis was to provide stage-specific data and trends on hospitalization rates, morbidity, in hospital-mortality, EVR, major and minor amputations, procedural-related mortality, and the individual and global economic burden related to in-hospital treatment of PAD in Germany from 2005 to 2009.

Methods

The introduction of a diagnosis and the procedure-related flat-rate remuneration system (German Diagnosis Related Groups, G-DRG-system) for all somatic in-patient services in Germany in 2003 has led to a uniform 'product-definition' of in-patient care.

In addition, detailed mandatory coding guidelines were implemented and all hospitals were obligated from 2004 on to transfer data on diagnoses, co-morbidities, medical services, procedures-related complications, and patient characteristics to the Institute for the Hospital Remuneration System (InEK) for the annual revision of the G-DRG-system.

Additionally, most variables of this data set are made available for scientific purposes by the Federal Bureau of Statistics. This allows now, for the first time, thorough exploration of the in-hospital characteristics of a certain disease over time for the complete population of Germany.

Data source

We analysed data from the Research Data Centers of the Federal Bureau of Statistics and the statistical offices of the federal states for the years 2005, 2007, and 2009 to obtain PAD characteristics and in-hospital outcomes and trends. The Database contains all in-patient treatments in German hospitals (total population data set) except treatments in psychiatric or psychosomatic hospitals or wards on a case base (i.e. the entire analysis was based on hospitalization cases and not on individual patients).

Analyses were performed by the Research Data Center using a dedicated statistical analysis program written in SAS (SAS 9.2: SAS Institute, Inc., Cary, NC, USA) and the results were sent to the authors.

Diagnoses and procedure codes

The German remuneration system requires the coding of a principal diagnosis for all in-hospital patients, which represents the underlying reason for hospital admission. Furthermore, additional diagnoses are coded to reflect comorbidities and complications co-existing with the principal diagnosis. 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-GM) and the German coding standards. In comparison with the WHO Version of the ICD-10, some diagnoses are more differentiated in the German Version (particularly due to the coding requirements of the G-DRG-System). These give us the possibility to distinguish between different PAD-stages on the basis of claims data.

Similar to the ICD-classification for diagnoses, all diagnostic, endovascular, and surgical procedures have to be coded according to the German Procedure Classification (OPS).

Patients and definitions

All hospitalized patients with PAD (ICD-10 diagnostic codes: I70.20, I70.21, I70.22, I70.23, and I70.24) as their principal or complementary diagnosis were included in the analysis. The Fontaine Classification[8] was used to divide the heterogeneous PAD population into four different clinical stages. Accordingly, patients with ICD I70.20 encompasses asymptomatic patients and those with a pain-free-walking distance >200 m (Fontaine I and IIa). Those with a walking distance <200 m are characterized by ICD I70.21 (Fontaine IIb). Patients with rest pain (ICD I70.22) constitute Fontaine III, while those with ulcers (ICD I70.23) and gangrene (ICD I70.24) are labelled as Fontaine IV. Fontaine III and IV are commonly classified to suffer from CLI.

Major amputations were defined as all amputations above the ankle (OPS codes: 5-864.0 et seqq.) and minor amputations as all amputations below the ankle (OPS code: 5-865.0 et seqq.).Amputations of the upper extremities and amputations due to reasons other than limb ischaemia, such as trauma, venous ulceration, and malignancy, were not included in the analysis.

Statistical analysis

The frequencies of distinct ICD codes characterizing the heterogeneous in-patient population with PAD are given as absolute numbers (*n*) and percentages (%). Amputation data are given in percent and calculated by dividing the number of amputations during the index-hospitalization in each Fontaine group by the number of hospitalizations in that Fontaine group per year. The χ^2 test was used to compare changes in overall and stage-specific hospitalization numbers over time. The in-hospital-mortality rates (95% confidence intervals) for different Fontaine classes were calculated using the Poisson regression model.[9] Values are given as number of deaths/year/1000 residence days.

Statistical analyses were performed using SAS (SAS 9.2: SAS Institute, Inc., Cary, NC, USA). A *P*-value <0.05 was considered significant.

Results

Overall and stage-specific hospitalizations

A total of 1.3 million hospitalizations with PAD were identified and analysed. Baseline characteristics including age, gender and distribution of PAD stages according to Fontaine classification, the prevalence of cardiovascular risk factors and of comorbidities are presented in *Table 1*.

Among 15 million hospitalizations in Germany in 2005, a total of 400 928 (2.67%) had PAD. This figure increased to 483 961 among 16.2 million hospitalizations in 2009 (3.0%). Except for the subgroup of Fontaine III which remained constant, the increase in all other subgroups of PAD was highly significant over time ($P < 0.0001$). The relative increase in overall hospitalizations and in those having PAD from 2005 to 2009 was 8 and 12%, respectively, indicating a disproportionate increase in PAD hospitalizations, particularly among Fontaine IV-subset (+32%). Likewise, the percentage of CLI (Fontaine Class III and IV) among hospitalized PAD cases increased from 40.6 in 2005 to 43.5 in 2009. Compared with asymptomatics and claudicants, patients with CLI were older, with ~50% being >75 years old and had a higher percentage of female gender (*Table 1*).

Cardiovascular risk factors and comorbidities

Diabetes was present in 2005 in 26.7 and 35.7% of claudicants and Fontaine class IV patients, respectively, and increased in 2009 to 30.5 and 39.3%, respectively, indicating a marked increase in the prevalence of diabetes among all PAD stages, particularly among

Table 1 Baseline characteristics and comorbidities of hospitalized patients with prevalence of peripheral arterial disease in 2005, 2007, and 2009

Year	2005					2007					2009				
ICD-10 codes	**I70.20**	**I70.21**	**I70.22**	**I70.23 + I70.24**	**Total**	**I70.20**	**I70.21**	**I70.22**	**I70.23 + I70.24**	**Total**	**I70.20**	**I70.21**	**I70.22**	**I70.23 + I70.24**	**Total**
Hospitalizations with PAD, *n* (%)	82 651 (20.6)	155 371 (38.8)	46 045 (11.5)	116 861 (29.1)	400 928 (100)	77 864* (18.1)	168 262* (39.1)	49 986 (11.6)	134 271* (31.2)	430 383* (100)	92 550* (19.1)	180 792* (37.4)	56 206 (11.6)	154 413* (31.9)	483 961* (100)
Women, *n* (%)	28 764 (34.8)	48 220 (31.0)	17 834 (38.7)	47 943 (41.0)	142 761 (35.6)	26 587 (34.1)	52 051 (30.9)	19 142 (38.3)	54 186 (40.4)	151 966 (35.3)	31 941 (34.5)	56 091 (31.0)	21 720 (38.6)	60 442 (39.1)	170 194 (35.2)
Age, year (mean)	72.0	68.9	71.4	73.3	71.1	72.4	69.2	71.5	73.6	71.4	72.9	69.6	72.1	74.1	71.9
Age ≥60 year	73 286 (88.7)	127 422 (82.0)	39 658 (86.1)	104 774 (89.7)	345 140 (86.1)	69 036 (88.7)	136 974 (81.4)	42 491 (85.0)	119 619 (89.1)	368 120 (85.5)	82 349 (89.0)	147 477 (81.6)	48 235 (85.8)	138 294 (89.6)	416 355 (86.0)
Age ≥75 year	35 842 (43.4)	50 035 (32.2)	19 391 (42.1)	57 035 (48.8)	162 303 (40.5)	34 763 (44.6)	55 307 (32.9)	21 187 (42.4)	67 071 (50.0)	178 328 (41.4)	42 426 (45.8)	60 186 (33.3)	24 496 (43.6)	78 875 (51.1)	205 983 (42.6)
Hypertension, *n* (%)	52 198 (63.2)	99 960 (64.3)	28 207 (61.3)	67 998 (58.2)	248 363 (61.9)	52 220 (67.1)	114 022 (67.8)	32 273 (64.6)	83 089 (61.9)	281 604 (65.4)	65 026 (70.3)	127 180 (70.3)	38 471 (68.4)	100 710 (65.2)	331 387 (68.5)
Diabetes, *n* (%)	26 894 (32.5)	41 416 (26.7)	12 974 (28.2)	41 715 (35.7)	122 999 (30.7)	27 505 (35.3)	47 632 (28.3)	14 964 (29.9)	49 031 (36.5)	139 132 (32.3)	34 581 (37.4)	55 221 (30.5)	18 463 (32.8)	60 735 (39.3)	169 000 (34.9)
Chronic renal failure, *n* (%)	17 013 (20.6)	25 169 (16.2)	8 853 (19.2)	32 684 (28.0)	83 719 (20.9)	18 274 (23.5)	31 802 (18.9)	11 213 (22.4)	42 541 (31.7)	103 830 (24.1)	25 287 (27.3)	40 438 (22.4)	15 628 (27.8)	57 795 (37.4)	139 148 (28.8)
Coronary heart disease, *n* (%)	34 905 (42.2)	57 911 (37.3)	16 358 (35.5)	36 396 (31.1)	145 570 (36.3)	32 263 (41.4)	61 494 (36.5)	17 428 (34.9)	40 679 (30.3)	151 864 (35.3)	39 290 (42.5)	66 881 (37.0)	19 796 (35.2)	47 125 (30.5)	173 092 (35.8)
Chronic heart failure, *n* (%)	8498 (10.3)	13 767 (8.9)	4714 (10.2)	14 828 (12.7)	41 807 (10.4)	10 181 (13.1)	17 278 (10.3)	6239 (12.5)	21 673 (16.1)	55 371 (12.9)	14 060 (15.2)	21 073 (11.7)	8281 (14.7)	28 210 (18.3)	71 624 (14.8)

Data are number (%). ICD, International Classification of Diseases; y, years. *Source*: Research Data Centers of the Federal Bureau of Statistics and the statistical offices of the federal states, DRG-statistics 2005, 2007, and 2009, own calculations.
*$P < 0.001$ vs. previous time point.

CLI (*Table 1*). Hypertension was present in >60% of PAD cases with a continuous increase in prevalence over time.

Concomitant chronic renal failure (=GFR < 60 mL/min) among PAD patients rose from 16.2% among claudicants and 28% among CLI patients in 2005 to 22.4 and 37.4% in 2009, respectively (a relative increase of 38 and 34%, respectively). Coronary artery disease (CAD), however, remained constant, affecting 30% of Fontaine class IV and 37% of claudicants. In contrast, chronic heart failure among all hospitalized PAD patients increased from 10.4% in 2005 to 14.8% in 2009. The increase in the prevalence of chronic heart failure was more pronounced among Fontaine IV patients (from 12.7 to 18.3%) than in claudicants (from 8.9 to 11.7%).

Revascularization procedures and amputations

The detailed numbers and trends of endovascular and surgical revascularization procedures as well as the numbers of major and minor amputations for each Fontaine class are illustrated in *Table 2*.

From 2005 to 2009, there was an increase of 46% in overall in-hospital EVR procedures. The highest increase over time in EVR was observed in Fontaine IV subset (+73%) followed by the claudicants (+39%) and Fontaine III (+35%), while the lowest increase was observed in Fontaine I/IIa (6%). During the same time period, the total number of thrombectomy/embolectomy, endarterectomy, and of patch plastic increased by 67, 42 and 21%, respectively, while the total number of peripheral bypasses decreased by 2%. Similarly to the endovascular procedures, the highest increase in the above-mentioned surgical procedures was observed in Fontaine IV, followed by claudicants and Fontaine III subgroup (*Table 2*).

In 2005, a total of 38 415 amputations (major+minor) were performed with a ratio of major to minor amputation of 48 to 52%, respectively. In 2009, the number increased to 41 458 with a major to minor ratio of 40–60%. Despite an increase of 8% in total amputation number, the percentage of major amputation decreased from 4.6 in 2005 to 3.5 in 2009 (relative decrease of 25%). Minor amputations increased during the same time period from 4.98 to 5.11% (relative increase of 2.8%). The most pronounced change occurred in Fontaine IV patients with a 31% decrease.

In-hospital and periprocedural mortality

The crude overall in-hospital mortality among hospitalized patients with PAD in 2005 was 2.2, 5.9, and 9.8% for claudicants, for cases with rest pain, and for those classified as Fontaine IV, respectively. In 2009, these figures slightly decreased to 2.2, 5.3, and 8.4%, respectively. In-hospital mortality rate was lower among patients undergoing EVR compared with those who did not have an EVR. Periprocedural mortality rate did not change over time (*Table 3*). As illustrated in *Figure 1*, the in-hospital mortality rates according to the Poisson model (*n*/1000 hospital residence days) were higher in patients with CLI compared with claudicants ($P < 0.001$) and remained unchanged over time, while mortality rates among claudicants significantly increased from 2005 to 2009 ($P < 0.01$). Women exhibited generally higher mortality across all PAD stages compared with men with the highest gender difference among CLI patients. As illustrated in *Table 3*, >50% of all in-hospital deaths among all PAD patients occurred in Fontaine IV patients. Major amputation was associated with 20% periprocedural mortality, while the rate among patients undergoing minor amputations was 2–5%, depending on the PAD stage.

In-hospital reimbursement costs

Detailed per case reimbursement costs for the different stages of PAD in 2007and 2009 are presented in *Table 4* (no reimbursement data available for 2005). The total reimbursement costs for the in-hospital treatment of PAD were €2.14 billion in 2007 and increased to €2.56 billion in 2009, an increase of 21% within 2 years. With regard to the proportion of these PAD-related costs to the costs due to all hospitalizations, there was also an increase from 4.52% in 2007 up to 4.84% in 2009. Although CLI patients represented only 43.5% of all PAD patients, the expenditures for CLI patients accounted for ~52% of all PAD reimbursement costs.

Discussion

The introduction of the G-DRG-system in Germany in 2003 allows now, for the first time, thorough exploration of the characteristics of PAD over time. The current analysis of PAD characteristics in the entire German healthcare system particularly highlights two important aspects of PAD.

Firstly, the medical aspect: the number of hospitalizations with PAD is disproportionately increasing with a dramatic rise among CLI patients, particularly those categorized as Fontaine IV. These patients have substantially higher degree of morbidity and higher in-hospital mortality compared with asymptomatics and claudicants (*Tables 1–3*). Although the tendency of reduction in major amputations and the periprocedural and in-hospital mortality rate is encouraging, the yearly figures of 18 000 major and 24 000 minor amputations in Germany with an increasing tendency in the latter one is alarming and warrant every effort to reduce these numbers. An in-hospital death rate of 2.2% among claudicants and particularly the 9% death rate among CLI patients during the same hospital stay underscore the malign prognosis associated with PAD and the need for further improvement of existing therapeutic strategies.

The second aspect that is highlighted by this analysis is the economic burden that is impeding by PAD to the German healthcare system: the total reimbursement costs for the in-hospital treatment of patients with PAD were €2.6 billion in 2009, representing an increase of 21% compared with 2007. Although CLI patients represented only 43.5% of all hospitalized PAD patients, the corresponding expenditures for this subset accounted for ~52% of all PAD reimbursement costs.

Although the PAD population burden (defined by the absolute number of all individuals in a society suffering from PAD) to a healthcare system has been demonstrated to be higher for women than for men,[10] our data show that among all PAD-related hospitalizations only 30% among claudicants and 40% among CLI patients were women, indicating a gender disparity in that women suffering from PAD receive hospitalized care to a lesser degree than their male counterparts. Gender-related differences in PAD treatment have already been described previously.[11] However, elaboration of the underlying causes for this disparity was beyond the scope of the current analysis. This aspect has to be further investigated in prospective, population-based studies.

Table 2 **Revascularization and amputation procedures of hospitalized patients with prevalence of peripheral arterial disease in 2005, 2007, and 2009**

Year	2005					2007					2009				
ICD-10 codes	I70.20	I70.21	I70.22	I70.23 + I70.24	Total	I70.20	I70.21	I70.22	I70.23 + I70.24	Total	I70.20	I70.21	I70.22	I70.23 + I70.24	Total
Hospitalizations with PAD, *n* (%)	82 651 (20.6)	155 371 (38.8)	46 045 (11.5)	116 861 (29.1)	400 928 (100)	77 864 (18.1)	168 262 (39.1)	49 986 (11.6)	134 271 (31.2)	430 383 (100)	92 550 (19.1)	180 792 (37.4)	56 206 (11.6)	154 413 (31.9)	483 961 (100)
EVR, *n* (%)	2233 (2.7)	36 149 (23.3)	8608 (18.7)	17 559 (15.0)	64 549 (16.1)	1911 (2.5)	43 131 (25.6)	9943 (19.9)	22 830 (17.0)	77 815 (18.1)	2378 (2.6)	50 180 (27.8)	11 704 (20.8)	30 407 (19.7)	94 669 (19.6)
Embolectomy, thrombectomy, *n* (%)	898 (1.1)	5711 (3.7)	6913 (15.0)	5974 (5.1)	19 496 (4.9)	755 (1.0)	7641 (4.5)	8748 (17.5)	8 050 (6.0)	25 194 (5.9)	909 (1.0)	9621 (5.3)	11 383 (20.3)	10 759 (7.0)	32 672 (6.8)
Endarterectomy, *n* (%)	374 (0.5)	14 757 (9.5)	6237 (13.5)	9001 (7.7)	30 369 (7.6)	314 (0.4)	18 078 (10.7)	7613 (15.2)	10 917 (8.1)	36 922 (8.6)	334 (0.4)	20 948 (11.6)	8 727 (15.5)	13 211 (8.6)	43 220 (8.9)
Bypasses, *n* (%)	448 (0.5)	13 574 (8.7)	7977 (17.3)	16 629 (14.2)	38 628 (9.6)	294 (0.4)	13 393 (8.0)	7960 (15.9)	16 943 (12.6)	38 590 (9.0)	264 (0.3)	12 375 (6.8)	7 868 (14.0)	17 421 (11.3)	37 928 (7.8)
Patch plastic, *n* (%)	220 (0.3)	5160 (3.3)	2846 (6.2)	3527 (3.0)	11 753 (2.9)	145 (0.2)	5 588 (3.3)	3061 (6.0)	3 988 (3.0)	12 782 (3.0)	149 (0.2)	6375 (3.5)	3 346 (6.0)	4395 (2.8)	14 265 (2.9)
Major amputation, *n* (%)	315 (0.4)	244 (0.2)	970 (2.1)	16 955 (14.5)	18 494 (4.6)	226 (0.3)	216 (0.1)	837 (1.7)	16 322 (12.2)	17 601 (4.1)	196 (0.2)	203 (0.1)	813 (1.4)	15 512 (10.0)	16 724 (3.5)
Minor amputation, *n* (%)	493 (0.6)	342 (0.2)	223 (0.5)	18 873 (16.1)	19 931 (5.0)	371 (0.5)	330 (0.2)	201 (0.4)	20 870 (15.5)	21 772 (5.1)	371 (0.4)	314 (0.2)	190 (0.3)	23 859 (15.5)	24 734 (5.1)

ICD, International Classification of Diseases; EVR, endovascular revascularization; n.a., no data available.

Table 3 In-hospital mortality of hospitalized patients with prevalence of peripheral arterial disease in 2005, 2007, and 2009

Year	2005					2007					2009				
ICD-10 codes	I70.20	I70.21	I70.22	I70.23 + I70.24	Total	I70.20	I70.21	I70.22	I70.23 + I70.24	Total	I70.20	I70.21	I70.22	I70.23 + I70.24	Total
Hospitalizations with PAD, *n* (%)	82 651 (20.6)	155 371 (38.8)	46 045 (11.5)	116 861 (29.1)	400 928 (100)	77 864 (18.1)	168 262 (39.1)	49 986 (11.6)	134 271 (31.2)	430 383 (100)	92 550 (19.1)	180 792 (37.4)	56 206 (11.6)	154 413 (31.9)	483 961 (100)
In-hospital death, *n* (%)	4422 (5.4)	3480 (2.2)	2735 (5.9)	11 487 (9.8)	22 124 (5.5)	3840 (4.9)	3601 (2.1)	2 877 (5.8)	12 064 (9.0)	22 382 (5.2)	4641 (5.0)	3995 (2.2)	2981 (5.3)	12 978 (8.4)	24 595 (5.1)
Death in women, *n* (%)	1499 (5.2)	1102 (2.3)	1.187 (6.7)	5179 (10.8)	8967 (6.3)	1347 (5.1)	1153 (2.2)	1165 (6.1)	5341 (9.9)	9006 (5.9)	1629 (5.1)	1255 (2.2)	1242 (5.7)	5629 (9.3)	9755 (5.7)
Death in men, *n* (%)	2923 (5.4)	2378 (2.2)	1548 (5.5)	6308 (9.2)	13 157 (5.1)	2493 (4.9)	2448 (2.1)	1712 (5.6)	6723 (8.4)	13 376 (4.8)	3012 (5.0)	2739 (2.2)	1739 (5.0)	7347 (7.8)	14 837 (4.7)
Death after EVR, *n* (%)	46 (2.1)	113 (0.3)	193 (2.2)	905 (5.2)	1257 (1.9)	49 (2.6)	124 (0.3)	213 (2.1)	1123 (4.9)	1509 (1.9)	68 (2.9)	170 (0.3)	228 (1.9)	1344 (4.4)	1810 (1.9)
Death without EVR, *n* (%)	4376 (5.4)	3 367 (2.8)	2542 (6.8)	10 582 (10.7)	20 867 (6.2)	3791 (5.0)	3477 (2.8)	2664 (6.7)	10 941 (9.8)	20 873 (5.9)	4573 (5.1)	3825 (2.9)	2753 (6.2)	11 634 (9.4)	22 785 (5.9)
Death after major amputation, *n* (%)	68 (21.6)	42 (17.2)	197 (20.3)	3376 (19.9)	3683 (19.9)	61 (27.0)	39 (18.1)	206 (24.6)	3192 (19.6)	3498 (19.9)	50 (25.5)	46 (22.7)	168 (20.7)	2841 (18.3)	3105 (18.6)
Death after minor amputation, *n* (%)	20 (4.1)	6 (1.8)	8 (3.6)	1029 (5.5)	1063 (5.3)	10 (2.7)	n.a.	10 (5.0)	1033 (4.9)	1053 (4.8)	n.a.	6 (1.9)	n.a.	1128 (4.7)	1134 (4.6)

ICD, International Classification of Diseases; EVR, endovascular revascularization; n.a., no data available.

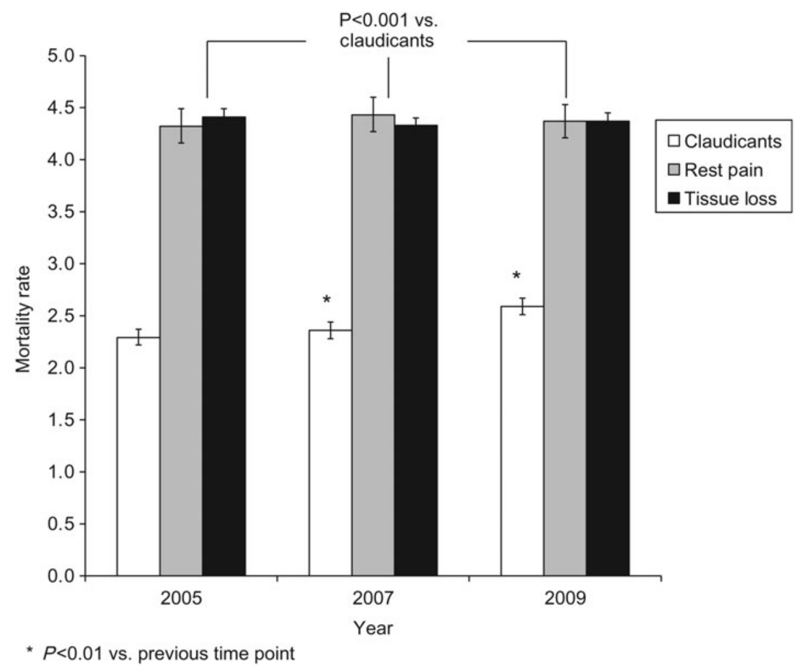

Figure 1 Mortality rates (*n*/1000 residence days/year, Poisson's regression model) among claudicants (white bars), patients with rest pain (grey bars) and those with tissue loss, i.e. Fontaine class IV (dark bars) for 2005, 2007, and 2009. Source: Research Data Centers of the Federal Bureau of Statistics and the statistical offices of the federal states, DRG-statistics 2005, 2007, and 2009, own calculations.

The 46% increase in EVR procedures between 2005 and 2009 in our analysis is a trend that has been observed consistently in all contemporary PAD-related studies and analyses.[11–13] Likewise, the slight decrease in peripheral bypass surgery procedures as illustrated here mirrors the global shift from invasive surgical to endovascular-first therapeutic strategy, that is propagated by recent recommendations and guidelines.[14] However, the marked increase of EVR procedures in general PAD population, particularly in claudicants, is in a strong contrast to the number of revascularization in the subset of PAD population that is in desperate need of revascularization, i.e. patients with CLI. Considering the fact that revascularization is the therapy of choice for limb salvage in CLI patients,[14,15] the proportion of EVR is lower in Fontaine IV cases (15% in 2005, 19.7% in 2009) compared with claudicants (23.3% in 2005, 27.8% in 2009). The rate of peripheral bypasses even decreasing from 14.2% in 2005 to 11.3% 2009. However, irrespective of the remarkable increase in EVR procedures our data do not allow any causal link or any quantification of the contribution of increased EVR procedures to the observed trends in decrease of mortality and major amputation rates.

Reimbursement characteristics among in-hospital PAD subgroups have not been investigated yet. When comparing costs among diverse vascular fields (coronary, cerebrovascular, and peripheral), patients with PAD have been shown to have the highest hospitalization and total annual costs.[16–18] The higher costs in CLI patients compared with claudicants can be attributed to the extensive therapeutic measures in this subset: as illustrated by this analysis, CLI patients require prolonged hospitalization and a higher rate of costly amputation procedures compared with claudicants and asymptomatic PAD patients. However, our data alongside with previously published data from Medicare databases demonstrate that even patients with asymptomatic PAD create a significant health economic burden, which has been shown to be mainly due to myocardial and cerebral ischaemic events. Margolis *et al.*[19] calculated from a healthcare database (1999–2003) in a US population a total averaged annualized costs of PAD-related care of $5955 per PAD patient per year. This amount per PAD patient per year is very close to the costs provided by our analysis (*Table 4*). Economic analysis of the REACH registry also revealed higher hospitalization rates, higher revascularization procedures and consequently higher costs for treatment of PAD compared with CAD and CVD.[17] Our data close the existing gap in knowledge of PAD stage-specific costs among different PAD subgroups in that the reimbursement costs are related to the severity of PAD in terms of clinical stage according to Fontaine classification. Compared with an asymptomatic or claudicant patient, a Fontaine IV patient causes 52% higher costs for the in-hospital treatment.

It has to be pointed out that the figures provided here are just the in-hospital costs. In addition to the direct costs for in-hospital treatment, there are secondary costs such as for rehabilitation, nursing home, and the value of lost work capacity due to PAD and amputation-related functional impairment. Therefore, the *de facto* PAD-related economic burden to the national healthcare systems is higher than mirrored only in the hospitalization costs. Nevertheless, the in-hospital PAD-related costs provided by our analysis may serve as potential inputs into health economic models aimed at examining the long-term cost implications and cost-effectiveness of different therapeutic strategies.

Table 4 Reimbursement costs of hospitalized prevalence of peripheral arterial disease patients in 2005, 2007, and 2009

Year	2005				2007				2009			
ICD-10 codes-	I70.20	I70.21	I70.22	I70.23 + I70.24	I70.20	I70.21	I70.22	I70.23 + I70.24	I70.20	I70.21	I70.22	I70.23 + I70.24
Hospitalizations with PAD, *n* (%)	82 651 (20.6)	155 371 (38.8)	46 045 (11.5)	116 861 (29.1)	77 864 (18.1)	168 262 (39.1)	49 986 (11.6)	134 271 (31.2)	92 550 (19.1)	180 792 (37.4)	56 206 (11.6)	154 413 (31.9)
Reimbursement, mean (±1 SD), €	n.a.	n.a.	n.a.	n.a.	4245 (5761)	4212 (4612)	5008 (5270)	6 397 (5630)	4527 (6 558)	4506 (5 488)	5284 (6061)	6 791 (6783)
Total reimbursement (Million), €	n.a.	n.a.	n.a.	n.a.	329 238	707 727	249 899	855 150	417 777	813 783	296 498	1 036 442

Data are absolute number (%) or mean (SD). ICD, International Classification of Diseases; n.a., no data available.
Source: Research Data Centers of the Federal Bureau of Statistics and the statistical offices of the federal states, DRG-statistics 2005, 200 2007, and 2009, own calculations.

Strengths and limitations

Our study has several strengths. Since the data are derived from an entire healthcare system of an 80 million population adhering to the diversity with respect to age, gender, regional, and ethnic differences, it is highly representative for an industrialized nation. This extensive analysis also provides insight into the temporal changes regarding the distribution of different PAD classes indicating a shift towards increased prevalence in more advanced forms of PAD (i.e. CLI) as well as regarding the growing economic burden that is posed by PAD to the healthcare system. Such data might be helpful in design and implementation of clinical trials, for healthcare providers and health policymakers to face the upcoming economic challenge.

Apart from the above-mentioned strengths, there are several limitations that have to be addressed: First, the data presented here do not include the entire spectrum of PAD population (i.e. in- and out-patients) as the analysis was restricted only to hospitalized patient. Thus, the exact magnitude of out-patient (ambulatory) PAD population on the epidemiological characteristics and the economic impact remains unknown. However, it is conceivable, that out-patient population and particularly the PAD-related out-of-hospital costs considerably add to the *de facto* epidemiological and economic burden that is posed by PAD to the German healthcare system.

Secondly, the DRG coding system is not specifically designed to obtain all information that are relevant for scientific purposes. In this analysis, for instance, risk factors such as hypercholesterolaemia, smoking habits, and genetic backgrounds are not reported, because they apparently do not increase the complexity of the in-hospital treatment. Therefore, it is probable that due to lack of reimbursement motivation these secondary diagnoses are neglected and thereby constituting a bias.

Thirdly, the entire analysis was based on hospitalization cases and not on individual patients. The number and figures illustrated here reflect the stage-specific hospitalizations and trends. It does not allow the direct extrapolation from PAD cases to PAD patients, since some patients could be included more than once in the statistics.

Fourthly, as the vast majority of those having PAD in stage I and IIa is either completely asymptomatic or have only mild symptoms, therefore rarely hospitalized primarily for PAD, their exact number might be underestimated. Likewise, the true increase in overall number and trend of EVR may be underestimated by our analysis, since more and more EVR are performed in an out-patient setting.

Fifthly, the uniformly nationwide implementation of such a complex coding system is usually subjected to a 'learning curve'. There might be some inaccuracy in the first year regarding the correct coding, especially PAD as a secondary diagnosis. Last but not least, enhanced perception of the importance of PAD among the general population as well as among healthcare providers might have partly contributed to the observed increase in PAD diagnoses and subsequent treatment.

In conclusion, despite all measures to optimize the public awareness for PAD and to implement primary and secondary preventive measures to optimize the underlying atherosclerotic risk factors, PAD-related hospitalizations and related costs are dramatically increasing. Despite some positive trends in outcome measures such as decreasing major amputation and mortality rates, PAD population remains a subset with extensive high burden of morbidity and mortality, particularly those patients with CLI.

Acknowledgements

We are indebted to the excellent assistance of Mrs. Susanne Schüler. We also like to thank the staff of the Research Data Centers of the Federal Bureau of Statistics and the statistical offices of the federal states for providing the data and the technical support during the analysis.

Funding

Holger Reinecke has received speaker honoraria from B.R.A.H.M.S., Bristol-Myers Squibb, Cordis, Daiichi-Sankyo, Medtronic, The Medicine Company, Novartis and Sanofi-Aventis; he has received research grants from the German Federal Ministry for Education and Research (BMBF).

Conflict of interest: none declared.

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