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ORIGINAL ARTICLE

Long-term cardiovascular outcome, use of resources, and healthcare costs in patients with peripheral artery disease: results from a nationwide Swedish study

Pål Hasvold[1,2]*, Joakim Nordanstig[3,4], Björn Kragsterman[5], Thomas Kristensen[1], Mårten Falkenberg[6], Saga Johansson[7], Marcus Thuresson[8], and Birgitta Sigvant[9,10]

[1]AstraZeneca Nordic-Baltic, Medical department, Astraallén, Södertälje 151 85, Sweden; [2]The Faculty of Medicine, University of Oslo, P.O box 1078, Blindern, 0316 Oslo, Norway; [3]Department of Vascular Surgery, Sahlgrenska University Hospital, Blå Stråket 5, Gothenburg 41345, Sweden; [4]Institute of Medicine, Department of Molecular and Clinical Medicine, The Sahlgrenska Academy, Gothenburg University, Blå Stråket 5B Wallenberglab/SU, Gothenburg 405 30, Sweden; [5]Department of Surgical Sciences, Vascular Surgery, Uppsala University, Uppsala 751 85 , Sweden; [6]Department of Radiology, Institute of Clinical Sciences, Sahlgrenska Academy, Gothenburg 413 45, Sweden; [7]AstraZeneca Gothenburg, AstraZeneca R&D, Pepparedsleden 1, Mölndal 431 53, Sweden; [8]Statisticon AB, Östra Ågatan 31, Uppsala 753 22, Sweden; [9]Department of Vascular Surgery, Karlstad Central Hospital, Rosenborgsgatan 2, Karlstad 652 30, Sweden; and [10]Department of Clinical Science and Education, Södersjukhuset, Karolinska Institute, Solnavägen 1, Stockholm 171 77, Sweden

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Aims: Data on long-term healthcare costs of patients with peripheral artery disease (PAD) is limited, and the aim of this study was to investigate healthcare costs for PAD patients at a nationwide level.

Methods and results: A cohort study including all incident patients diagnosed with PAD in the Swedish National Patient Register between 2006-2014, and linked to cause of death- and prescribed drug registers. Mean per-patient annual healthcare costs (2015 Euros [€]) (hospitalisations and out-patient visits) were divided into cardiovascular (CV), lower limb and non-CV related cost. Results were stratified by high and low CV risk.

The study included 66,189 patients, with 221,953 observation-years. Mean total healthcare costs were €6,577, of which 26% was CV-related (€1,710), during the year prior to the PAD diagnosis. First year after PAD diagnosis, healthcare costs were €12,549, of which €3,824 (30%) was CV-related and €3,201 (26%) lower limb related. High-risk CV patients had a higher annual total healthcare and CV related costs compared to low risk CV patients during follow-up (€7,439 and €1,442 versus €4,063 and €838). Annual lower limb procedure costs were €728 in the PAD population, with lower limb revascularisations as key cost driver (€474).

Conclusion: Non-CV related hospitalizations and outpatient visits were the largest cost contributors for PAD patients. There is a substantial increase in healthcare costs in the first year after being diagnosed with PAD, driven by PAD follow-up and lower limb related procedures. Among the CV-related costs, hospitalisations and outpatient visits related to PAD represented the largest costs.

Keywords Nationwide register data • peripheral artery disease • healthcare resource use • healthcare costs

* Corresponding author. Tel: +0047 21006400, Fax: +0047 21006401, Email: paal.hasvold@astrazeneca.com

Introduction

Peripheral artery disease (PAD) has been recognized as a major contributor to the cardiovascular (CV) health burden.[1,2] Peripheral artery disease is a highly prevalent atherosclerotic syndrome affecting approximately 20% of people over 60 years of age in Sweden, and estimates [assessed using the ankle-brachial index (ABI)] have shown a recent increase in prevalence worldwide (of 23% during the last decade).[3,4]

Peripheral artery disease patients are at high risk of experiencing major CV events (MACE), which are associated with substantial impairment in quality of life and increased morbidity rates.[5–8] Thus, PAD is associated with a substantial economic burden both in terms of prevention and treatment of MACE and when managing lower limb-related symptoms and procedures.[2]

Previous studies have found that PAD patients are even more costly than patients with coronary artery disease (CAD) or cerebrovascular disease (CVD), having a 2-year cumulative cost of nearly USD 12 000, where half of the hospitalization costs are limb-related and half are due to treatment of MACE.[2] Despite the high prevalence of PAD, very few studies have investigated the long-term use of resources and costs after diagnosis. In addition, the relationship between costs related to PAD and total healthcare costs requires clarification.

As PAD is associated with high risk of MACE and mortality, with an increasing trend over time, the costs to healthcare in the long-term should also be acknowledged. In this observational study, we investigated CV outcome and long-term CV resource use and total healthcare costs for patients, before and after diagnosis of PAD in a Swedish nationwide setting.

Methods

Overview

In this observational cohort study, we retrieved data from three mandatory Swedish nationwide registries: the Swedish National Patient Register (NPR), the Swedish Prescribed Drug Register (SPDR), and the Swedish Cause of Death Register. The Swedish NPR covers more than 99% of all somatic and psychiatric hospital discharges, with inpatient admission and discharge dates, and also main and secondary diagnoses according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision [ICD-10].[8] The SPDR has data on all prescription medications dispensed by all pharmacies in Sweden.[9] Individual patient-level data from the registers were linked using the mandatory and unique Swedish personal identification numbers, which were subsequently replaced with study identification numbers before further data processing.

The study protocol was reviewed and approved by the regional ethics committee of the University of Gothenburg, Sweden (reference number: 649-14). Linkage of data was performed by the Swedish National Board of Health and Welfare. The linked database was managed by the Institute of Medicine at the Sahlgrenska Academy, Gothenburg, Sweden.

Population

All patients with a first time primary or secondary diagnosis of PAD in a hospital setting (as inpatient or outpatient) [ICD-10 I70.0 (atherosclerosis of aorta), I70.2 (atherosclerosis of arteries of extremities), or I73.9 (claudicatio intermittens)] between 2006 and 2013 were included. The index date was defined as the date of the first recorded PAD diagnosis during the specified observation period. Follow-up ended when a patient died or at the end of the observational period (January 2014). In Sweden, the diagnosis of PAD in a hospital setting is normally based on the medical history and on results of a clinical vascular examination including the ABI test.

Baseline characteristics and data on medication use were retrieved from the NPR and SPDR registers.

The population was stratified by age and risk profile at index date:

- Patients aged <65 years
- Patients aged 65–75 years
- Patients aged >75 years
- Patients with none of the following comorbidities in their previous medical history were defined as low-risk patients: diabetes mellitus, myocardial infarction (MI), stroke, heart failure, and chronic renal dysfunction.
- Patients with one or more of the following comorbidities were defined as high-risk patients: diabetes mellitus, MI, stroke, heart failure, or chronic renal dysfunction.

Clinical outcomes

The primary endpoint of MACEs was a composite of hospitalization with a main diagnosis of non-fatal MI (ICD-10: I21), non-fatal IS (ICD-0: I63-I64), or CV death (ICD-10 codes I00–I99). Lower limb revascularization was defined as an open or endovascular procedure as captured in NPR based on procedure codes (see Supplementary Material online).

Resource use

Data on hospitalizations and outpatient care visits were collected from the NPR. In cases where a subsequent hospitalization occurred without a calendar day between the discharge date and the new admission date, a single episode of hospitalization was recorded. When a patient had both a primary and a secondary diagnosis, the primary diagnosis defined the event type.

Resource use associated with CV disease included hospitalizations, outpatient care visits, and drug use. All non-procedural lower limb-related events were included in the category 'CV events'. Lower limb procedures included only invasive procedures for treatment of PAD. Non-CV-related care included all hospitalizations, outpatient care visits, and drug use that were not related to a diagnosis of CV as defined in ICD-10.

The Prescribed Drug Register included data on dispensed, prescribed drugs in terms of substance, formulation, dose, and date of administration. Cardiovascular drugs included drugs in the ATC class C: anti-platelets, warfarin, statins, NOACs, nitrates, and anti-hypertensives. Non-CV drugs were defined as all drugs not included in the ATC class C.

The major items of resource use and unit costs are listed in Supplementary material online, *Table S4a–d*.

Unit costs

Each recorded hospitalization and outpatient care visit was assigned a 2015 diagnosis-related group (DRG) weight, which was multiplied by the most recent 2015 cost per weight.[11] In cases of missing DRG codes in the 2015 DRG catalogue, older DRG catalogues were used to apply the correct weight. If DRG codes recorded before 2015 had been stratified into several DRG codes in the 2015 DRG catalogue, a weighted average of these weights was applied. Irrespective of the year in which the DRG code was recorded, all costs were multiplied by the most recent cost per weight.

The daily cost of a drug was calculated by multiplying the average dose by the most recent retail price available.[12]

All costs were converted to euros using an average 2015 exchange rate, according to the European Central Bank: 1 euro (EUR) = 9.35 Swedish crowns (SEK).

Analysis

Baseline characteristics are presented as mean and standard deviation for continuous variables and absolute and relative frequencies for categorical variables. Follow-up data were collected from the time of the index diagnosis of PAD until death or the end of follow-up. The frequency and proportion of patients with the primary composite endpoint were assessed and a Kaplan–Meier analysis was performed to estimate the cumulative probability of the primary composite endpoint during study follow-up. If one patient had several events, only the first was used in the survival model. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs).

Resource use was calculated for each year, i.e. 1 year before initial PAD diagnosis, the year after being diagnosed with PAD (starting from the hospital admission date, or the date recorded for the outpatient visit when the PAD diagnosis was established), and the 5 years that followed. Patients contributed to a particular year of analysis if they died during the year or had a full year of exposure. Thus, a patient dying after 1.5 years of follow-up contributed to Year 2 whereas patients who were censored at 1.5 years due to no more follow-up time did not.

Mean healthcare costs per patient per year were estimated by applying unit costs to the corresponding resource use items. If a patient had both a PAD CV-related diagnosis and a lower limb procedure performed at the same visit, the costs were reported as being lower limb-related. Costs were differentiated into CV-related, non-CV-related, and lower limb-related and presented as subgroups stratified by a combination of risk profile and age.

Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and R version 3.2.3.

Results

Overall, 141 266 patients with a diagnosis of PAD were identified, 66 189 of whom had their first PAD diagnosis established during the observation period and were included in the study. Peripheral artery disease was mainly diagnosed at hospital outpatient visits (71%), and was the main reason for hospital contact in 77% of the patients. Mean length of follow-up was 2.8 years, with a maximum of 8 years, resulting in a total of 184 614 patient-years of follow-up.

The youngest and oldest patient groups with a high risk of CV had different profiles. Compared with subjects over 75 years of age, a higher proportion of subjects less than 65 years old were men (69% vs. 50%), had diabetes (71% vs. 53%), and had renal insufficiency (11% vs. 4%), whereas cancer (9% vs. 23%) and stroke (16% vs. 29%) were more prevalent in older patients. Statin use was more common in the youngest patients than in the oldest (75% vs. 39%), who in turn used more analgesics (49% vs. 70%, Table 1). A higher proportion of older women (over 75 years old) were categorized as being low-risk (61%) than women aged 75 years or younger (47%).

Table 1 Description of analysis population after being diagnosed with peripheral artery disease

	Age <65 high-risk *n* = 5050	Age <65 low-risk *n* = 5752	Age 65–75 high-risk *n* = 10 733	Age 65–75 low-risk *n* = 9908	Age 75+ high-risk *n* = 21 068	Age 75+ low-risk *n* = 13 678	Total *n* = 66 189
Age (SD)	59.5 (3.8)	59.3 (3.9)	70.4 (3.1)	70.1 (3.1)	84.0 (5.2)	83.4 (5.3)	75.6 (10.3)
Gender (Female)	1567 (31.0)	2510 (43.6)	3719 (34.7)	4914 (49.6)	10 595 (50.3)	8297 (60.7)	31 602 (47.7)
Aorta aneurysm	163 (3.2)	258 (4.5)	712 (6.6)	708 (7.1)	951 (4.5)	629 (4.6)	3421 (5.2)
Diabetes	3594 (71.2)	0 (0.0)	6977 (65.0)	0 (0.0)	9840 (46.7)	0 (0.0)	20 411 (30.8)
Hypertension	4284 (84.8)	2708 (47.1)	9585 (89.3)	6326 (63.8)	18 086 (85.8)	9397 (68.7)	50 386 (76.1)
Myocardial infarction	1409 (27.9)	0 (0.0)	3189 (29.7)	0 (0.0)	6391 (30.3)	0 (0.0)	10 989 (16.6)
Angina pectoris	1553 (30.8)	474 (8.2)	3700 (34.5)	1129 (11.4)	6754 (32.1)	1913 (14.0)	15 523 (23.5)
Ischaemic stroke	794 (15.7)	0 (0.0)	2433 (22.7)	0 (0.0)	6040 (28.7)	0 (0.0)	9267 (14.0)
Heart failure	1141 (22.6)	0 (0.0)	3303 (30.8)	0 (0.0)	10 464 (49.7)	0 (0.0)	14 908 (22.5)
Atrial fibrillation	636 (12.6)	205 (3.6)	2495 (23.2)	808 (8.2)	8823 (41.9)	2256 (16.5)	15 223 (23.0)
Major organ specific bleedings	433 (8.6)	231 (4.0)	1088 (10.1)	553 (5.6)	2941 (14.0)	1161 (8.5)	6407 (9.7)
Chronic renal insufficiency	548 (10.9)	0 (0.0)	862 (8.0)	0 (0.0)	951 (4.5)	0 (0.0)	2361 (3.6)
Chronic obstructive pulmonary disease	428 (8.5)	325 (5.7)	1448 (13.5)	961 (9.7)	2310 (11.0)	1027 (7.5)	6499 (9.8)
Cancer	449 (8.9)	563 (9.8)	1822 (17.0)	1750 (17.7)	4883 (23.2)	3013 (22.0)	12 480 (18.9)
Anti-platelets	3711 (73.5)	3689 (64.1)	7974 (74.3)	6767 (68.3)	14 893 (70.7)	8677 (63.4)	45 711 (69.1)
Clopidogrel	731 (14.5)	333 (5.8)	1463 (13.6)	638 (6.4)	2166 (10.3)	769 (5.6)	6100 (9.2)
Low dose aspirin	3525 (69.8)	3564 (62.0)	7455 (69.5)	6453 (65.1)	13 856 (65.8)	8233 (60.2)	43 086 (65.1)
Warfarin	479 (9.5)	243 (4.2)	1694 (15.8)	608 (6.1)	3843 (18.2)	1169 (8.5)	8036 (12.1)
Statins	3793 (75.1)	3383 (58.8)	7816 (72.8)	6168 (62.3)	8985 (42.6)	5301 (38.8)	35 446 (53.6)
Anti-hypertensives	4429 (87.7)	3095 (53.8)	9938 (92.6)	7007 (70.7)	19 842 (94.2)	10 908 (79.7)	55 219 (83.4)
Anti-diabetics	3263 (64.6)	17 (0.3)	6159 (57.4)	19 (0.2)	7915 (37.6)	20 (0.1)	17 393 (26.3)
Analgesics	2478 (49.1)	2124 (36.9)	5742 (53.5)	3957 (39.9)	14 851 (70.5)	8017 (58.6)	37 169 (56.2)

All data are *n* (%) unless stated otherwise.
SD, standard derivation.

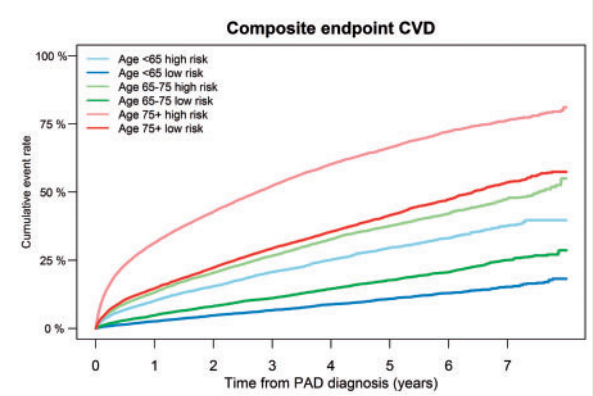

Figure 1 Kaplan–Meier estimate of the risk of the composite primary endpoint (myocardial infarction, ischaemic stroke, or cardiovascular death) in different age and risk categories.

The overall 1-year cumulative incidence rates of the primary composite CV endpoint (MI, stroke, or CV death) and all-cause death were 16.6% and 21.1%, respectively.

In patients who were 75 years old or younger, the 1-year cumulative incidence rate for the primary composite endpoint was 12.2% in high-CV-risk patients and 4.0% in low-CV-risk patients. Corresponding figures for patients over 75 years of age were 31.4% in high-CV-risk patients and 14.7% in low-CV-risk patients (*Figure 1*).

Procedures performed

In total, 23 481 lower limb revascularization procedures were performed during the study period. The cumulative incidence rate of lower limb revascularization procedures for the full study population was 23.2 (95% CI 22.9–23.5) at 1 year after being diagnosed with PAD. The cumulative probability of lower limb revascularization was 20.1 (95% CI 19.8–20.4) at 6 months and 27.6 (27.2–27.9) at 3 years (see Supplementary material online, *Table S2*). A larger proportion of high-risk patients underwent amputations, whereas the proportion of patients who underwent lower limb revascularizations was more similar across the low- and high-CV-risk populations and age categories (see Supplementary material online, *Table S5*).

Pattern of resource use

One year before diagnosis of PAD, the mean total number of contacts per patient (i.e. hospitalization and outpatient care visits) was 4.05, with outpatient visits being the main reason for contact (mean number: 3.21) (Table *2*). In the year following diagnosis of PAD, the mean total number of contacts increased to 6.36, with outpatient visits being the main reason for contact (mean number: 4.99). During the year after diagnosis of PAD, the mean number of CV-related hospitalizations and outpatient visits was 2.30, with PAD being the main reason for contact. The mean number of lower limb procedure contacts was 0.38 in the year after diagnosis of PAD, which became reduced to 0.04 in the subsequent years.

For the CV-related long-term drug therapy [such as low-dose aspirin, angiotensin-converting enzyme (ACE) inhibitors, and statins], the average number of days on drug continued to be higher from the second year after the year of being diagnosed with PAD compared with the year before the PAD diagnosis.

Healthcare costs

The mean annual total cost of healthcare in the year before the diagnosis of PAD was €6577, of which €1710 (26%) were CV event-related hospitalization costs and outpatient visits and €3748 (57%) were non-CV-related hospitalization costs and outpatient visits. Drug therapy was responsible for 17% of the total.

During the year after PAD diagnosis, there was a 90% increase in the mean total costs for all patient age and risk groups, totalling €12 549. Thirty per cent of this was attributed to CV-related hospitalizations and outpatient visits (€3824), with PAD-related follow-up being the main reason for hospital attendance (Table *2*). Also, the number of lower limb-related invasive procedures increased during this year, with a total mean cost of €3201. Non-CV-related costs were not substantially different from those in the year before the diagnosis of PAD.

The mean total healthcare cost decreased from the second year after diagnosis of PAD and onwards, with lower mean total annual costs (€5750) than the year before PAD diagnosis. However, lower limb-related procedure costs remained higher throughout the study period, with a mean total annual cost of €728. The mean annual CV-related cost was €1140 after the first year of being diagnosed with PAD.

High-risk CV patients had higher total healthcare costs than low-risk CV patients after diagnosis of PAD, the mean annual costs being €7439 and €4063, respectively. Also, the mean CV-related hospitalization cost was higher in the high-CV-risk group than in the low-risk CV group: €1442 as opposed to €838.

After patients were diagnosed with PAD, CV drug treatment contributed least to healthcare costs in all the years studied (mean annual cost: €200). Both CV drugs and non-CV drugs showed a similar trend, with a higher observed cost in high-risk patients.

High-risk patients had higher costs associated with lower limb-related procedures (mean total: £3952) than low-risk patients (mean total: €2605)-and for amputation in particular (€1703 vs. €629) (*Figure 3*). The selected CV-related costs were high in all risk groups and age categories, with a mean for all groups of €2071. In all patients, PAD-related costs (not including limb-related procedures) were the greatest costs within the selected CV category (52%), with coronary events and stroke (32%), and heart failure (13%) being observed as the other major CV cost drivers. Also, in the years that followed, total PAD-related costs remained the most important cost contributor among the different CV-related costs, although there was a shift in PAD costs to a larger proportion of limb procedure-related costs over time (*Figure 4*).

After being diagnosed with PAD, lower limb procedure-related costs were an annual major cost driver in the study population over time (mean: €728), with lower limb revascularizations being the main cost contributor (mean: €474) (*Figure 4*). The difference in lower limb procedure costs in high-risk and low-risk patients was mainly caused by the fact that there were more amputations in the high-risk CV population (*Figure 3* and see Supplementary material online, *Table S5*).

Table 2 Resource use pattern over time, year 1 being first year after peripheral artery disease diagnosis

	1 year prior to PAD diagnosis	Year after diagnosis					
		1	2	3	4	5	6
Number of patients	66,189	53,024	42,032	32,547	24,338	17,610	11.938
Hospitalizations							
CV related care	0,27	0,47	0,18	0,17	0,15	0,15	0,14
Lower limb procedures	0,03	0,35	0,07	0,05	0,04	0,04	0,04
Non-CV related care	0,54	0,55	0,4	0,38	0,37	0,35	0,35
Outpatient care visits							
CV related care	0,32	1,83	0,53	0,4	0,36	0,35	0,35
Lower limb procedures	0	0,03	0,01	0	0	0	0
Non-CV related care	2,89	3,13	2,58	2,41	2,37	2,34	2,28
Pharmaceuticals							
Anti-platelets	169	245	238	238	239	237	235
Clopidogrel	14	30	24	24	24	25	26
Low dose ASA	155	226	220	219	220	218	215
Anticoagulants	20	23	24	24	24	24	26
Statins	105	183	179	182	184	186	184
Anti-hypertensives	270	281	281	282	282	283	284
Anti-diabetics	77	79	79	79	79	79	77
Analgesics	79	101	87	83	81	80	80

CV related care, lower limb procedures and non-CV related care resource utilization are reported in mean numbers of contacts for hospitalisations and outpatient care visits. Drug usage are reported in mean number of days (DDD).

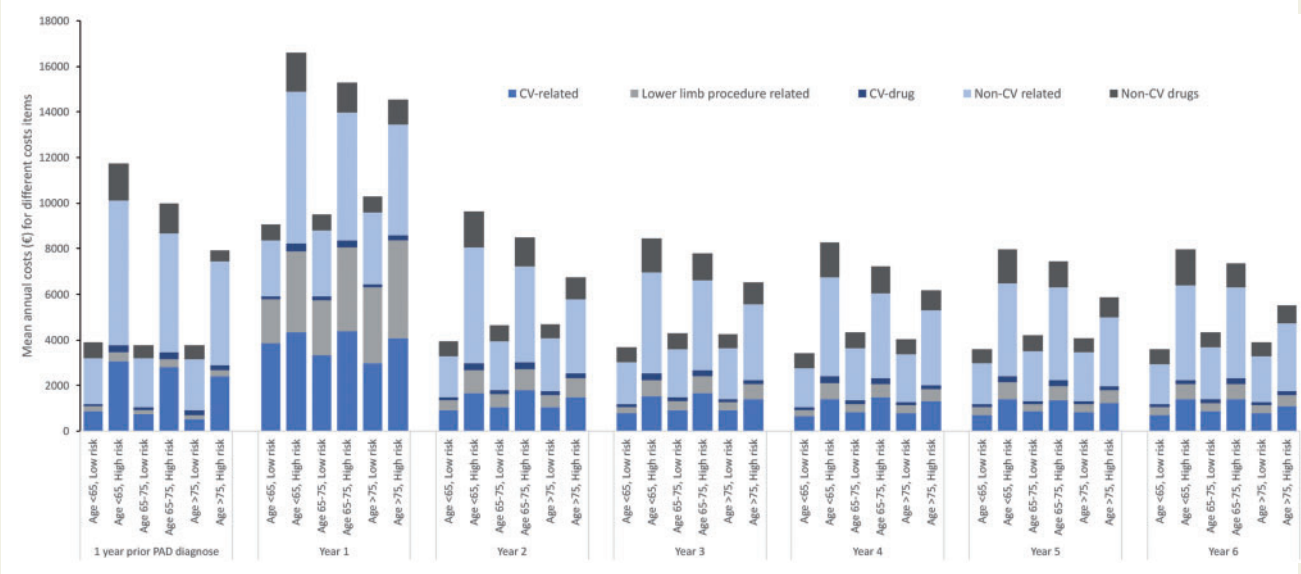

Figure 2 Annual costs per patient prior to and after peripheral artery disease (PAD), by cost category, age, and risk. cardiovascular (CV)-related: includes all ICD-10 CV 'I' diagnoses except PAD-related costs in combination with lower limb procedures. If a PAD patient had a hospitalization with a PAD diagnosis 'I' and a lower limb procedure, then the cost for this visit is reported as being lower limb procedure-related. Non-CV-related: all costs except costs related to CV (ICD-10 'I').

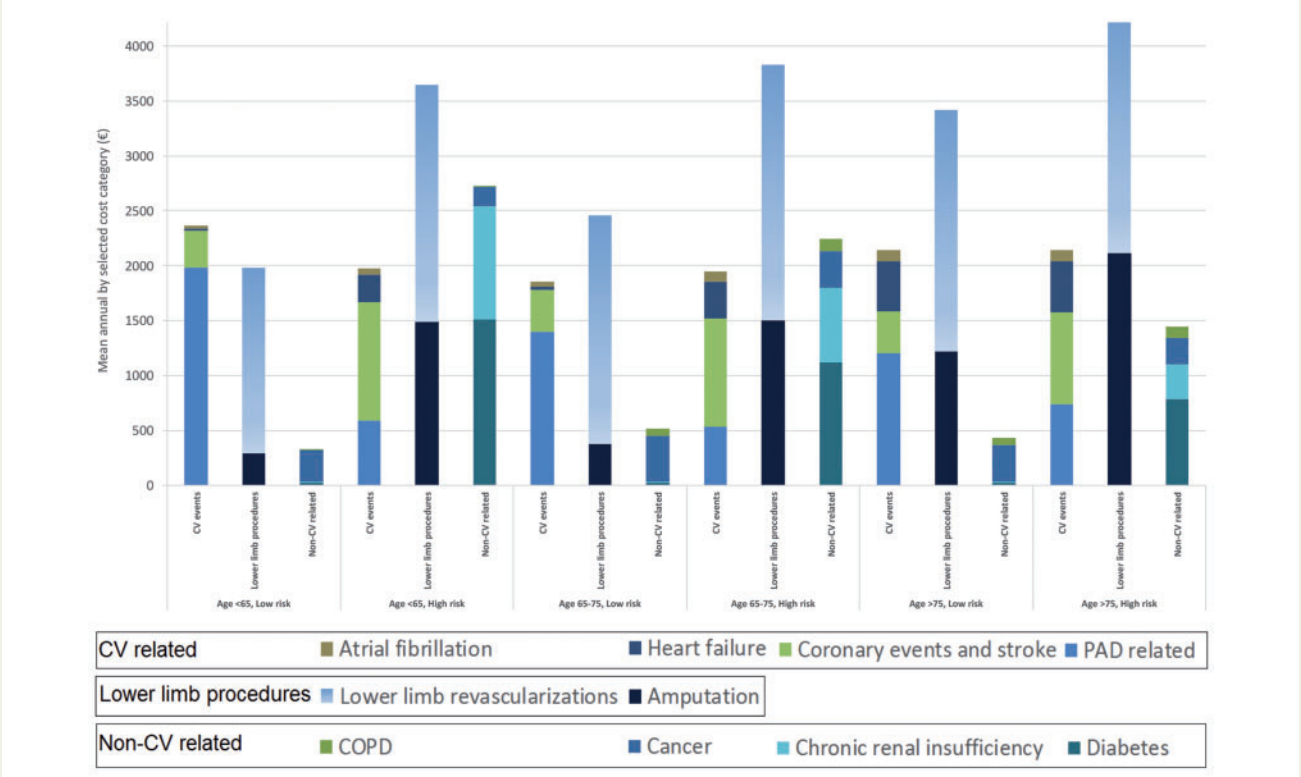

Figure 3 Mean costs per patient during the first year after diagnosis of peripheral artery disease, by selected cost category, age, and risk. Coronary events: myocardial infarction and unstable angina pectoris. PAD-related, peripheral arterial disease (follow-up, not including lower limb procedures); COPD, chronic obstructive pulmonary disease.

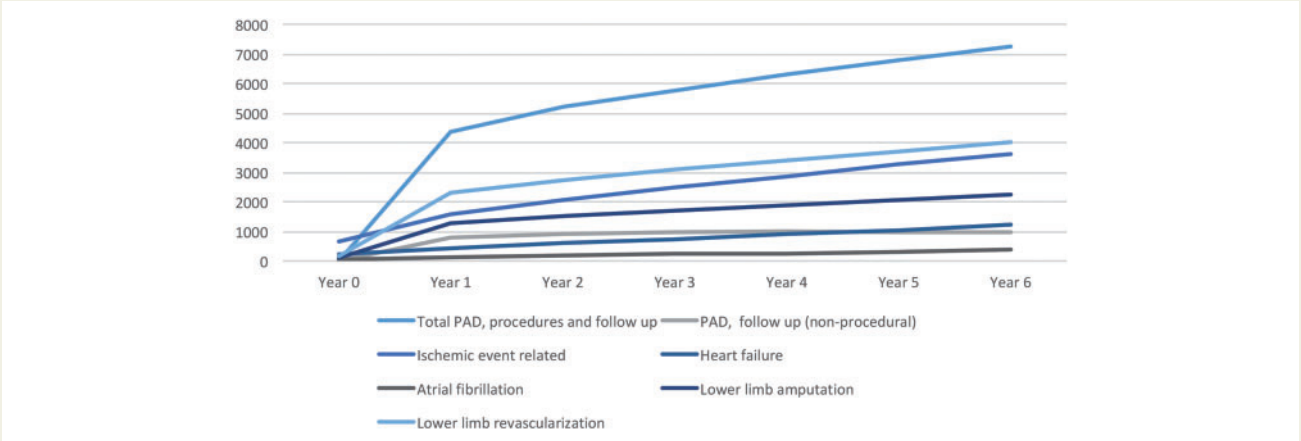

Figure 4 Cumulative cost during follow-up of selected diagnoses and procedures. Ischaemic event-related: myocardial infarction, unstable angina pectoris, and stroke. Peripheral arterial disease follow-up (non-procedural): follow-up of peripheral arterial disease, not including lower limb procedure.

Discussion

One-third of the PAD population was over 75 years of age and was categorized as high-risk, but even among patients aged less than 75 years, more than 50% could be classified as high-risk, with diabetes and a history of coronary events being the most prevalent comorbidities. Within a year after diagnosis of PAD, more than one in five patients died and one in six experienced a MACE. Compared with

patients surviving an MI, PAD patients had a significantly higher 1-year mortality risk (21.1% vs. 13.2%) and showed a comparable CV risk (16.6% vs. 18.3%).[13,14]

In high-risk patients, the 1-year risk of CV events was increased three-fold for those less than 75 years old and doubled for those over 75 years, as compared with PAD patients without risk factors. The resource use and pattern of costs was associated with age and underlying risk, with the latter being the most important determinant of costs, as has also been observed in MI patients.[15] This study reports only hospitalization costs (including hospital-based outpatient visits), but other drivers of the total healthcare costs for these patients, as for example nursing home and primary healthcare costs were not included. Furthermore, wider data on community-care and patients' own costs and productivity impacts are not included.

Costs of hospitalizations and outpatient visits related to PAD were the greatest of the CV-related costs, particularly during the year after PAD was diagnosed. However, non-CV-related hospitalizations were the largest cost contributor overall, being approximately twice as frequent in Year 2 after PAD diagnosis, with five times as many outpatient care visits, as compared with CV-related visits. Interestingly, although the PAD population has a well-recognized high risk of CV, the major part of the hospitalization costs for PAD patients (including outpatient visits) is not related to CV diseases-with, for example, costs associated with diabetes and chronic renal insufficiency being larger cost contributors (*Figure 3*). It may not be relevant to focus only on CV-related risk prevention separately, but it is perhaps better to have a broader view when assessing risk and potential interventions for this patient population.

Despite generally having a higher CV baseline risk and more CV events than younger patients, patients over 75 years of age generally had lower CV-related costs. This might be explained by the fact that a lower proportion of elderly patients undergo expensive invasive heart related procedures as percutaneous coronary intervention or coronary artery bypass grafting in Sweden.[16] Also, the lower limb procedure-related costs, especially for amputations, and non-CV-related costs were substantially higher in the youngest age group (< 65 years), which may have been attributable to the high prevalence of diabetes (71%).

The total annual CV-related costs-excluding lower limb procedure costs-for PAD patients during long-term follow-up were higher than they are for MI patients, with mean of €1945 per patient as opposed to approximately €1700–1800 per patient,[15] an effect of the progressive, chronic nature of PAD.

Not surprisingly, the contributors to CV-associated costs are somewhat different in the MI and PAD populations. Myocardial infarction patients have more recurrent MIs, while PAD patients have more recurrent PAD manifestations with relatively fewer MIs. This is supported by the observation that the PAD-related costs due to hospitalizations and outpatient visits were the main contributors to CV-related costs for all patient categories, contributing to more than 50% of the CV-related costs in first year after diagnosis of PAD. In total, approximately 23 500 revascularizations were performed, and the majority within the first 6 months, which would explain the decline in PAD-related costs over time.

Lower limb-related procedure costs were a significant overall cost contributor at Year 1, both for low- and high-CV-risk patients (*Figures 2–4*), but they decreased over time to be comparable with other studies where PAD procedure-related costs constitute only a modest fraction.[1] However, costs associated with amputations are higher in the high-CV-risk groups than in low-CV-risk patients, whereas the costs of lower limb revascularization are more similar in the different patient groups. This might be related to the inherently worse limb prognosis in patients with PAD in combination with diabetes, cardiac failure, or kidney failure, even when successful lower limb revascularization procedures are undertaken, due to having more severe lesions.

It is difficult to compare healthcare costs due to differences in study design and healthcare systems, but our data on total costs for the combination of CV-related and lower limb-related procedures are comparable to what has been reported previously for PAD patients in France and Germany,[17] but they are lower than data from the USA.[2]

Cardiovascular-related drug costs contributed least among the cost categories investigated. This is partly explained by the fact that most drugs given in association with CV disease today are generic, and have a low acquisition cost. Another contributing factor may be the still uncommon use of cardioprotective medications in PAD.

The present study had some limitations. Firstly, we did not have access to data describing the extent and severity of PAD, which may have an impact on the cost of treatment. Furthermore, the resource use and costs were divided into CV-related and non-CV-related, with a rather narrow definition of CV-related hospitalizations and outpatient care visits. A hospitalization was assigned an ICD-10 circulatory system diagnosis as the primary diagnosis to be categorized as CV, excluding CV-related hospitalization costs when attributable as for example a secondary diagnosis. As a registry data-based analysis, the study relied on ICD-10 codes for morbidity data, so the possibility of coding errors cannot be completely ruled out.

These data, however, provide a comprehensive description of the outcome, use of healthcare resources, and costs over time for all patients with a hospital diagnosis of PAD in a longitudinal, nationwide setting. These results provide information that will be useful for future healthcare planning and allocation of resources.

Conclusions

Data from this nationwide study showed that almost 50% of PAD patients aged below 75 years who were diagnosed in a hospital setting had additional CV risk factors. One in five patients died within a year after PAD diagnosis. The presence of additional risk factors other than age was the main driver for both CV-related and non-CV-related costs. Peripheral artery disease-related costs including hospitalizations and outpatient care visits were the main contributory CV-related costs in the first year after diagnosis of PAD. Also, lower limb procedure-related costs were initially high, and remained so during subsequent follow-up of these patients. Although the PAD population has a well-recognized high-CV risk, the major proportion of hospitalization costs for PAD patients are not related to CV disease. Healthcare systems will need to consider preventive strategies and optimize costs of prevention in the growing PAD population.

Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

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References

1. Hirsch AT, Hartman L, Town RJ, Virnig BA. National health care costs of peripheral arterial disease in the Medicare population. *Vasc Med* 2008;**13**:209–215.
2. Mahoney EM, Wang K, Keo HH, Duval S, Smolderen KG, Cohen DJ, Steg G, Bhatt DL, Hirsch AT; Reduction of Atherothrombosis for Continued Health (REACH) Registry Investigators. Vascular hospitalization rates and costs in patients with peripheral artery disease in the United States. *Circ Cardiovasc Qual Outcomes* 2010;**3**:642–651.
3. Sigvant B, Wiberg-Hedman K, Bergqvist D, Rolandsson O, Andersson B, Persson E, Wahlberg E. A population-based study of peripheral arterial disease prevalence with special focus on critical limb ischemia and sex differences. *J Vasc Surg* 2007;**45**:1185–1191.
4. Fowkes FG, Rudan D, Rudan I, Aboyans V, Denenberg JO, McDermott MM, Norman PE, Sampson UK, Williams LJ, Mensah GA, Criqui MH. Comparison of global estimates of prevalence and risk factors for peripheral artery disease in 2000 and 2010: a systematic review and analysis. *Lancet* 2013;**382**:1329–1340.
5. Alberts MJ, Bhatt DL, Mas J-L, Ohman EM, Hirsch AT, Rother J, Salette G, Goto S, Smith SC, Liau C-S, Wilson PWF, Steg PG; REduction of Atherothrombosis for Continued Health Registry Investigators. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. *Eur Heart J* 2009;**30**:2318–2326.
6. Sigvant B, Kragsterman B, Falkenberg M, Hasvold P, Johansson S, Thuresson M, Nordanstig J. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. *J Vasc Surg* 2016;**64**:1009–1017.
7. Regensteiner JG, Hiatt WR, Coll JR, Criqui MH, Treat-Jacobson D, McDermott MM, Hirsch AT. The impact of peripheral arterial disease on health-related quality of life in the Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival (PARTNERS) Program. *Vasc Med* 2008;**13**:15–24.
8. Sigvant B, Hasvold P, Kragsterman B, Falkenberg M, Johansson S, Thuresson M, Nordanstig J. Cardiovascular outcomes in patients with peripheral arterial disease as an initial or subsequent manifestation of atherosclerotic disease: results from a Swedish nationwide study. *J Vasc Surg* 2017;**66**:507–514.e1.
9. Ludvigsson JF, Andersson A, Ekbom A, Feychting M, Kim J-L, Reuterwall C, Heurgren M, Olausson PO. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;**11**:450.
10. Wallerstedt SM, Wettermark B, Hoffmann M. The First Decade with the Swedish Prescribed Drug Register - A Systematic Review of the Output in the Scientific Literature. *Basic Clin Pharmacol Toxicol* 2016;**5**:464–469.
11. Diagnosis related groups (DRG) system, Sweden. http://www.socialstyrelsen.se/klassificeringochkoder/norddrg/vikter (3 April 2017).
12. The Dental and Pharmaceutical Benefits agency (TLV) price data base. http://www.tlv.se/beslut/sok/lakemedel/ (3 April 2017).
13. Jemberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J* 2015;**36**:1163–1170.
14. Subherwal S, Patel MR, Kober L, Peterson ED, Bhatt DL, Gislason GH, Olsen AM, Jones WS, Torp-Pedersen C, Fosbol EL. Peripheral artery disease is a coronary heart disease risk equivalent among both men and women: results from a nationwide study. *Eur J Prev Cardiol* 2015;**22**:317–325.
15. Janzon M, Henriksson M, Hasvold P, Hjelm H, Thuresson M, Jernberg J. Long-term resource use patterns and healthcare costs after myocardial infarction in a clinical practice setting: results from a contemporary nationwide registry study. *Eur Heart J Qual Care Clin Outcomes* 2016;**2**:291–298.
16. Angerås O, Hasvold P, Thuresson M, Deleskog A, Braun O. Treatment pattern of contemporary dual antiplatelet therapies after acute coronary syndrome: a Swedish nationwide population-based cohort study. *Scand Cardiovasc J* 2016;**50**:99–107.
17. Smolderen KG, Wang K, de Pouv Ourville G, Brüggenjürgen B, Röther J, Zeymer U, Parhofer KG, Steg PG, Bhatt DL, Magnuson EA; REACH Registry Investigators. Two-year vascular hospitalisation rates and associated costs in patients at risk of atherothrombosis in France and Germany: highest burden for peripheral arterial disease. *Eur J Vasc Endovasc Surg* 2012;**43**:198–207.