Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization

Birgitta Sigvant, MD, PhD,[a,b] Björn Kragsterman, MD, PhD,[c] Mårten Falkenberg, MD, PhD,[d] Pål Hasvold, MSc Pharm,[e] Saga Johansson, MD, PhD,[e] Marcus Thuresson, PhD,[f] and Joakim Nordanstig, MD, PhD,[g] *Karlstad, Stockholm, Uppsala, Gothenburg, and Mölndal, Sweden*

Objective: Peripheral artery disease (PAD) is common worldwide, and PAD patients are increasingly offered lower limb revascularization procedures. The aim of this population-based study was to describe the current risk for cardiovascular (CV) events and mortality and also to elucidate the current pharmacologic treatment patterns in revascularized lower limb PAD patients.

Methods: This observational, retrospective cohort study analyzed prospectively collected linked data retrieved from mandatory Swedish national health care registries. The Swedish National Registry for Vascular Surgery database was used to identify revascularized PAD patients. Current risk for CV events and death was analyzed, as were prescribed drugs aimed for secondary prevention. A Cox proportional hazard regression model was used to explore risk factors for suffering a CV event.

Results: Between May 2008 and December 2013, there were 18,742 revascularized PAD patients identified. Mean age was 70.0 years among patients with intermittent claudication (IC; n = 6959) and 76.8 years among patients with critical limb ischemia (CLI; n = 11,783). Antiplatelet therapy, statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and beta-blockers were used by 73%, 60%, 57%, and 49% at admission for revascularization. CV event rate (a composite of myocardial infarction, ischemic stroke, or CV death) at 12, 24, and 36 months was 5.1% (95% confidence interval [CI], 4.5-5.6), 9.5% (95% CI, 8.7-10.3), and 13.8% (95% CI, 12.8-14.8) in patients with IC and 16.8% (95% CI, 16.1-17.6), 25.9% (95% CI, 25.0-26.8), and 34.3% (95% CI, 33.2-35.4) in patients with CLI. Best medical treatment, defined as any antiplatelet or anticoagulant therapy along with statin treatment, was offered to 65% of IC patients and 45% of CLI patients with little change during the study period. Statin therapy was associated with reduced CV events (hazard ratio, 0.76; 95% CI, 0.71-0.81; $P < .001$), whereas treatment with low-dose aspirin was not.

Conclusions: Revascularized PAD patients are still at a high risk for CV events without a declining time trend. A large proportion of both IC and CLI patients were not offered best medical treatment. The most commonly used agent was aspirin, which was not associated with CV event reduction. This study calls for improved medical management and highlights an important and partly unmet medical need among revascularized PAD patients. (J Vasc Surg 2016;64:1009-17.)

Peripheral artery disease (PAD) represents a common health problem affecting millions of people worldwide.[1] The prevalence in Sweden is estimated to be nearly 20% among people older than 60 years.[2]

Because of the polyvascular nature of atherosclerotic disease, PAD patients have a high risk for cardiovascular (CV) events and premature death.[3-5] Treatment strategies in PAD are therefore targeted against risk factors for CV events in addition to limb symptoms. Despite several sets

of guidelines providing physicians with recommendations regarding best medical management, systemic vascular events are probably not optimally treated in this group of patients.[6-8] Current recommendations include antiplatelet therapy for any PAD patient (class I level) and on-demand treatment of statins and antihypertensive drugs to achieve the target values for serum lipids and blood pressure.[9-12] The recommendations are, however, largely based on data derived from subgroup analyses of trials performed

in populations with manifestations in other vascular territories.[13]

A large and increasing number of PAD patients are currently offered revascularization, mainly because of the rapid development and availability of modern, minimally invasive endovascular revascularization techniques.[5,14,15] In this defined population of patients, reliable modern data regarding the risk for short- and long-term CV events and associated risk factors for suffering such events are scarce. Also, information on how pharmacologic treatment actually provided to these patients influences CV risk constitutes an important piece of the puzzle in deciding on the best medical management for the individual PAD patient.[4]

This observational study aimed to describe the contemporary incidence and risk factors for CV events and mortality in a large cohort of revascularized PAD patients, retrieved from mandatory population-based registries in Sweden. It further aimed to describe the current secondary drug prevention treatment, and treatment persistence, in revascularized PAD patients in a population-based setting. The hypothesis was that CV event rates are still high in this group of patients and that recommended secondary preventive drugs are underused among PAD patients.

METHODS

Data sources

This observational cohort study analyzed prospectively collected data retrieved from mandatory Swedish national health care registries. The Swedish National Board of Health and Welfare performed data linkage by using the unique and mandatory personal identification numbers entailing full coverage of the Swedish health care system.

Swedish National Registry for Vascular Surgery. The Swedish Vascular Surgery Registry (Swedvasc)[15,16] is the world's oldest national vascular registry, launched in 1987, with full coverage of all centers performing vascular surgery in Sweden since 1994. The registry prospectively collects basic characteristics and periprocedural and follow-up data for all vascular procedures in Sweden, and data are entered into the registry by vascular surgeons and nurses. The registry has repeatedly been validated with high data accuracy.[17,18]

Data on PAD stage (ie, intermittent claudication [IC] and critical limb ischemia [CLI]), smoking status, and type of procedure (open and endovascular) were retrieved from this registry.

National Patient Register. The National Patient Register includes all primary and secondary diagnoses recorded within Swedish hospitals regarding inpatient care and in-hospital-based ambulatory care. Participation in the registry is mandatory for all county council caregivers. The International Classification of Diseases, Tenth Revision (ICD-10) has been used for coding of diagnoses since 1997. The National Patient Register is updated once a year and covers >99% of all hospital discharges.[19] From this registry, data on comorbidity and events were retrieved.

Cause of Death Register. The Cause of Death Register contains data on all deaths in Sweden since 1961. Data collected include time of death and underlying and contributing causes of death, in addition to about 30 other variables. The use of the Cause of Death Register, in combination with the National Patient Register, has previously been demonstrated to provide highly accurate data in studies performed on similar populations of patients.[20]

Prescribed Drug Register. The Prescribed Drug Register was launched July 1, 2005. The register provides data on dispensed item (substance and formulation), dispensed amount, data of dispensing, and prescriber and is updated monthly.[21] All drugs are classified according to the Anatomical Therapeutic Chemical classification system.

Data extraction and synthesis

Patient-level Swedvasc data were cross-referenced with the other studied data sources (National Patient Register, Cause of Death Register, and Prescribed Drug Register), based on the unique personal identification numbers, and the predefined study variables were subsequently extracted from the different data sources. After completion of the cross-referenced database, the personal identity numbers were exchanged to anonymous study numbers.

Study population

All individuals >50 years who had undergone lower limb revascularization for chronic PAD were eligible for study inclusion and were identified in a Swedvasc data set ranging from May 2008 to December 2013.

The date of the first recorded procedure code of lower limb revascularization during the specified time period (not necessarily the patient's first lower limb revascularization) was defined as the revascularized PAD index event. PAD stage (IC and CLI) was identified on the basis of the recorded indication for revascularization in the Swedvasc registry. Diagnoses before the index event were included in the baseline data (Supplementary Table I, online only). The baseline medication catchment period was defined as medications dispensed within 4 months prior and until the day before the index event. Patients concomitantly treated with statins in combination with antiplatelets or anticoagulants were considered to have received best medical treatment (BMT), and this proportion was calculated at baseline as well as within 3 months after the index event.

Outcomes

Event rate. The primary end point was defined as a composite of nonfatal myocardial infarction (ICD-10: I21), nonfatal ischemic stroke (ICD-10: I63-I64), or CV death (all primary causes of death diagnosed with ICD-10 codes I00-I99). If one patient had several end points, only the first was used in the time-to-event analysis. Separate analysis was performed for the individual components of the composite end point.

All-cause mortality was defined as death of any cause after the index date.

Medication persistence. Persistence to major drug classes (Supplementary Table II, online only) aimed for CV secondary prevention was described for the year before

Table I. Baseline demographic and clinical characteristics for intermittent claudication (*IC*) and critical limb ischemia (*CLI*) patients at admission for revascularization

	IC (n = 6959)	*CLI (n = 11,783)*	*Total (N = 18,742)*
Sex			
Male	3798 (54.6)	5806 (49.3)	9604 (51.2)
Female	3161 (45.4)	5977 (50.7)	9138 (48.8)
Age, years			
Mean (SD)	70.0 (8.3)	76.8 (9.6)	74.3 (9.7)
Median	70	78	74
Smoking status[a]			
Current smoker	433 (6.2)	1537 (13.0)	1970 (10.5)
Former smoker	1919 (27.6)	3077 (26.1)	4996 (26.6)
Never smoked	531 (7.6)	2229 (18.9)	2760 (14.7)
Missing data/unknown status	4076 (58.6)	4940 (41.9)	9016 (48.1)
Comorbidity[b]			
Hypertension	5650 (81.2)	10,111 (85.8)	15,761 (84.1)
Unstable angina/angina pectoris	2386 (34.3)	4114 (34.9)	6500 (34.7)
Myocardial infarction	1011 (14.5)	2386 (20.2)	3397 (18.1)
Heart failure	754 (10.8)	3473 (29.5)	4227 (22.6)
Atrial fibrillation	775 (11.1)	3124 (26.5)	3899 (20.8)
Ischemic stroke	523 (7.5)	1774 (15.1)	2297 (12.3)
TIA	387 (5.6)	837 (7.1)	1224 (6.5)
Diabetes	1957 (28.1)	5319 (45.1)	7276 (38.8)
Chronic obstructive pulmonary disease	867 (12.5)	1682 (14.3)	2549 (13.6)
Chronic renal insufficiency	183 (2.6)	730 (6.2)	913 (4.9)
Renal artery stenosis	105 (1.5)	142 (1.2)	247 (1.3)
Aortic aneurysm	448 (6.4)	489 (4.2)	937 (5.0)
Arterial embolism and thrombosis	69 (1.0)	150 (1.3)	219 (1.2)
Pulmonary embolism	82 (1.2)	245 (2.1)	
Major organ-specific bleedings	454 (6.5)	1452 (12.3)	1906 (10.2)
Cancer	1208 (17.4)	2467 (20.9)	3675 (19.6)
Dementia	28 (0.4)	339 (2.9)	367 (2.0)

SD, Standard deviation; *TIA*, transient ischemic attack.
Data are presented as number (%) unless otherwise indicated.
[a]Register data from Swedvasc.
[b]Data from National Patient Register.

and for the year after the index date using persistence plots. At each day, the proportion of patients taking each specific drug was calculated among the patients still in the study. The treatment duration of each dispense depended on the number of pills as well as the number of pills taken (dose) per day. If a patient had a treatment gap of >30 days, the patient was defined as a nonuser from the last calculated day with available drug. Furthermore, if the same drug was again dispensed to a patient with a treatment gap during follow-up, the patient was defined as a user from that actual date; and if a patient was switched to another type of drug within the same drug class after the revascularized PAD index event, the patient was defined as a user. For opioids, which are used more intermittently, the proportion of patients with any dispense within a specific 3-month interval was calculated.

Statistical analysis

Descriptive statistics are presented for demographic and baseline variables as mean ± standard deviation and absolute and relative frequencies. Time-to-event end points were analyzed using a Cox proportional hazards model comparing the two study groups with adjustment for type of procedure (open vs endovascular), sex, age, calendar year, prior CV disease (myocardial infarction, ischemic

stroke, or unstable angina pectoris), diabetes, and indication of BMT. In addition, univariate and multivariate Cox regression procedures were performed to explore factors related to the risk of the primary composite end point. The analysis was performed in three steps. At first, a series of univariate analyses were performed for each predefined risk factor. In a second step, factors with a *P* value < .2 were selected and entered into a multivariate analysis. In the third step, a backward stepwise procedure was applied in which the best model was defined as the model with the smallest Akaike information criterion value. The procedure was performed separately for each study group. Statistical programming and analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC) and R version 3.2.2.[22]

Ethical considerations

Ethical approval was obtained from the Regional Ethical Review Board at the University of Gothenburg (reference number 649-14). The data sets from the different national registers were received after a formal consent from the registry stakeholders (National Steering Committee of the Swedvasc and the Swedish National Board of Health and Welfare, respectively), according to the formal requirements of the registries.

Table II. Medication use for intermittent claudication (*IC*) and critical limb ischemia (*CLI*) patients at admission for revascularization

	IC (n = 6959)	CLI (n = 11,783)	Total (N = 18,742)
Low-dose acetylsalicylic acid[a]	5116 (73.5)	7245 (61.5)	12,361 (66.0)
Clopidogrel	527 (7.6)	827 (7.0)	1354 (7.2)
Warfarin	376 (5.4)	1250 (10.6)	1626 (8.7)
Heparin	272 (3.9)	924 (7.8)	1196 (6.4)
Cilostazol	131 (1.9)	60 (0.5)	191 (1.0)
Statins	5044 (72.5)	6172 (52.4)	11,216 (59.8)
Fibrates	73 (1.0)	54 (0.5)	127 (0.7)
Beta-blockers	3070 (44.1)	6018 (51.1)	9088 (48.5)
ACEIs	2299 (33.0)	4184 (35.5)	6483 (34.6)
ARBs	1674 (24.1)	2523 (21.4)	4197 (22.4)
Calcium channel blockers	2658 (38.2)	3708 (31.5)	6366 (34.0)
Diuretics	2000 (28.7)	6247 (53.0)	8247 (44.0)
Nitrates	1007 (14.5)	2412 (20.5)	3419 (18.2)
Oral antidiabetic drugs	1043 (15.0)	1972 (16.7)	3015 (16.1)
Insulin	895 (12.9)	3117 (26.5)	4012 (21.4)
Opioids	1193 (17.1)	7016 (59.5)	8209 (43.8)
Mild opioids	838 (12.0)	3625 (30.8)	4463 (23.8)
Strong opioids	479 (6.9)	4948 (42.0)	5427 (29.0)
BMT for PAD[b]	4524 (65.0)	5305 (45.0)	9829 (52.4)

ACEIs, Angiotensin-converting enzyme inhibitors; *ARBs*, angiotensin II receptor blockers; *BMT*, best medical treatment; *PAD*, peripheral artery disease.
Data from the Prescribed Drug Register. Data are presented as number (%).
[a]Dual antiplatelet treatment: n = 974 (IC and CLI, 5.4% and 5.1%).
[b]BMT was defined as treatment with any antiplatelet or anticoagulant and statin.

RESULTS

Baseline data and comorbidity. The final analyzed data set contained 18,742 patients, of whom 6959 (37%) had IC and 11,783 (63%) had CLI. Demographic data and previous medical history are given in Table I. Mean age at the index lower limb revascularization was 70.0 years for patients with IC and 76.8 years for patients with CLI. Age distribution in 5-year intervals for the two groups is presented in the Supplementary Fig (online only). Time interval between first PAD diagnosis and revascularization differed between PAD stages, as the median time between diagnosis and index revascularization was 193 (range, 0-5900) days in IC and 80 (range, 0-6063) days in CLI.

CV disease was common for both IC and CLI patients, and almost half of the CLI patients had diabetes (Table I).

Antiplatelets, statins, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs), and beta-blockers were used by 73%, 60%, 57%, and 49% of patients at admission for the index revascularization (Table II).

CV events and all-cause mortality. Event rate of the primary composite end point (nonfatal myocardial infarction, nonfatal ischemic stroke, or CV death) at 12, 24, and 36 months was 5.1%, 9.5%, and 13.8% for subjects with IC and 16.8%, 25.9%, and 34.3% for subjects with CLI (Fig 1).

Event rate of CV-related mortality at 12, 24, and 36 months was 1.9 (95% confidence interval [CI], 1.6-2.3), 3.5 (95% CI, 3.1-4.0), and 5.7 (95% CI, 5.0-6.3) for IC subjects and 11.7 (95% CI, 11.1-12.3), 18.3 (95% CI, 17.5-19.1), and 24.4 (95% CI, 23.4-25.3) for CLI subjects (Fig 1). Event rates for all-cause and

CV-related mortality, myocardial infarction, and stroke are displayed in Fig 1. No trends for changes in event rates were found for myocardial infarction, stroke, and CV-related or all-cause mortality during the study period (data not shown).

Among all studied patients, cause of death was classified as CV related in 51.8%. Death due to neoplasms was tripled among IC patients compared with CLI patients (30.6% vs 10.9%). By contrast, endocrine and metabolic disease (diabetes mellitus) as underlying cause of death was tripled for CLI subjects (12.5% vs 4.9%; Supplementary Table III, online only).

The Cox multivariable proportional regression revealed similar risk factors for IC and CLI; previous myocardial infarction, ischemic stroke, and heart failure were associated with the highest risk for a new CV event. Renal failure was associated with the highest risk among CLI subjects. Concomitant medication with beta-blockers, calcium channel blockers, and strong opioids was associated with increased CV death event rate, whereas statin therapy was associated with decreased rates of CV death events in both IC and CLI patients. Treatment with low-dose acetylsalicylic acid (aspirin) did not relate to the risk of the primary composite end point in the multivariable Cox regression model (Table III). Unadjusted hazard ratios (HRs) for all variables explored in the Cox multivariable proportional regression are available in Supplementary Table IV (online only).

Medication. Among CLI patients, the use of aspirin increased from 62% at baseline to a maximum of 71% within 3 months after intervention (Table II; Fig 2). The use of clopidogrel and statins increased from 7% to 26% and
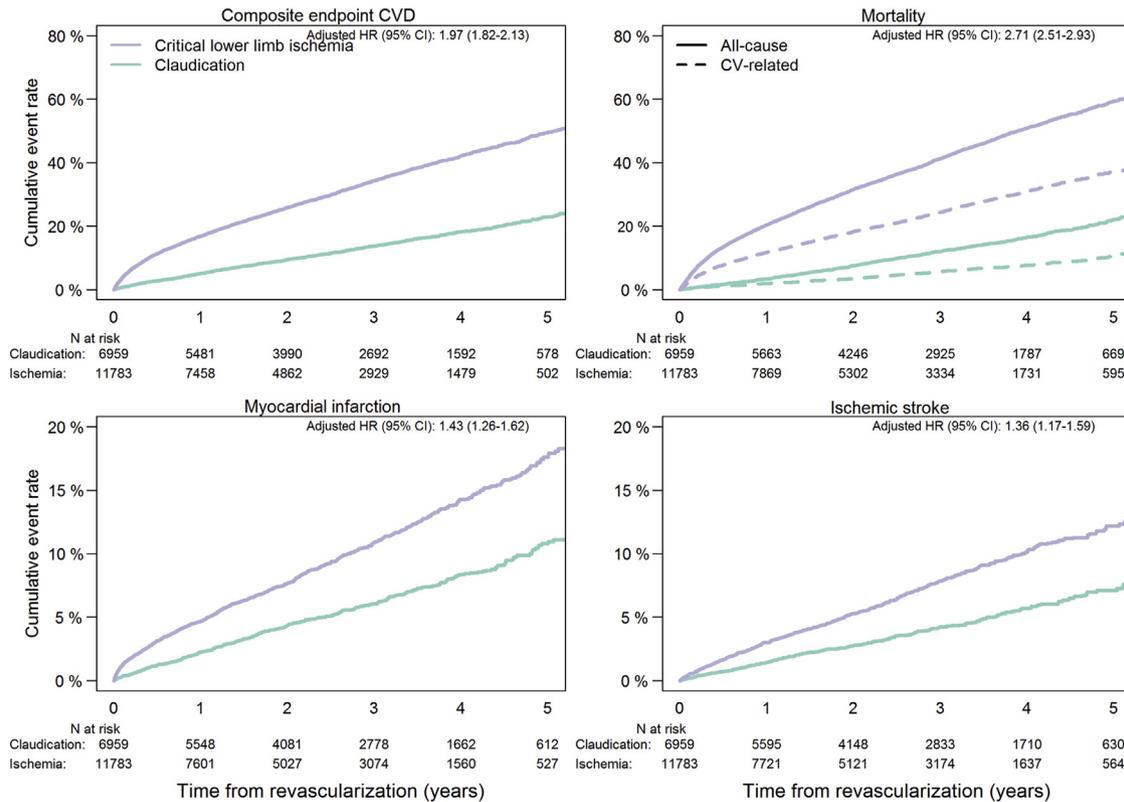
Fig 1. Kaplan-Meier estimates of the risk of the primary composite end point (myocardial infarction, ischemic stroke, or cardiovascular [*CV*] death), all-cause mortality, and myocardial infarction and ischemic stroke after revascularization, separated by peripheral artery disease (PAD) stage. *CI,* Confidence interval; *CVD,* cardiovascular disease; *HR,* hazard ratio.

52% to 61%, respectively. Corresponding figures for IC patients for aspirin, clopidogrel, and statins were 76% to 80%, 8% to 21%, and 73% to 77%, respectively. The index revascularization did not affect use of beta-blockers or ARBs and ACEIs in either of the subgroups.

BMT was offered to 4524 (65%) of all IC patients and to 5305 (45%) of all CLI patients (Table II). The proportion of patients receiving BMT after revascularization was relatively unchanged during the 5 years studied (Fig 3).

DISCUSSION

This population-based large cohort study on the risk of CV events and contemporary secondary preventive drug treatment patterns in revascularized PAD patients has four main findings. First, CV event rates and mortality rates for revascularized PAD patients are still high without trends of reduction during the study period. Second, concomitant morbidities with coronary disease, heart failure, and renal failure were significantly associated with CV events. Third, a large proportion of patients did not receive recommended secondary preventive drug treatment, and no improvement in the proportion of patients receiving BMT was observed during the study period.

Last, treatment with aspirin was not associated with CV event reduction in multivariable analysis. By contrast, statin use was highly protective.

The CV event rates at 12 and 36 months after the index revascularization procedure were 5% and 14% for patients with IC and 17% and 34% for patients with CLI, respectively. During past decades, the negative influence of concurrent risk factors for the PAD patients has become more recognized, and it could have been assumed that modern pharmacologic treatments should positively influence the CV event rate. The persistently high event rates might, at least partly, be explained by change in selection of patients for revascularization with new available minimally invasive techniques together with underuse or poor efficacy of available preventive drugs. Comorbidities with myocardial infarction, stroke, heart failure, and renal failure were highly associated with risk for new CV events after revascularization. This emphasizes the need for close monitoring before and after intervention to improve overall outcome for this group of patients. Diabetes mellitus, on the other hand, was associated with a lower risk than expected, particularly for patients with CLI (HR, 1.18; 95% CI, 1.10-1.26). All-cause mortality was in line with other similar recent surveys, and a diagnosis of IC was associated with improved overall

Table III. Final[a] Cox multivariable proportional regression model of risk factors for a composite end point event (myocardial infarction, stroke, or cardiovascular [CV] death)

	IC			CLI		
	HR	95% CI	P value	HR	95% CI	P value
Baseline						
Male gender	1.26	1.09-1.44	.001	1.14	1.06-1.23	<.001
Age (per year)	1.04	1.03-1.05	<.001	1.04	1.03-1.04	<.001
Comorbidity						
Myocardial infarction	1.40	1.17-1.66	<.001	1.50	1.38-1.63	<.001
Heart failure	1.56	1.30-1.88	<.001	1.50	1.38-1.62	<.001
Angina pectoris	1.15	0.99-1.34	.068	1.10	1.01-1.18	.023
Ischemic stroke	1.59	1.30-1.94	<.001	1.32	1.21-1.44	<.001
Transient ischemic attack	1.37	1.08-1.73	.008	1.14	1.01-1.28	.037
Diabetes mellitus	1.33	1.15-1.53	<.001	1.18	1.10-1.26	<.001
Respiratory insufficiency	1.19	0.99-1.45	.070	1.11	1.01-1.23	.030
Renal failure				1.57	1.37-1.79	<.001
Bleeding	1.29	1.03-1.63	.027	1.16	1.05-1.28	.003
Medication						
Warfarin				0.84	0.75-0.94	.002
Statins	0.70	0.61-0.81	<.001	0.76	0.70-0.81	<.001
Beta-blockers	1.18	1.02-1.37	.022	1.17	1.08-1.26	<.001
Calcium channel blockers	1.18	1.03-1.35	.019			

CI, Confidence interval; *CLI*, critical limb ischemia; *HR*, hazard ratio; *IC*, intermittent claudication.
[a]Remaining variables contributing to the model after the final backward stepwise procedure. Factors with *P* value < .20 in univariable analysis were considered for inclusion in multivariable analysis.

survival compared with CLI (12-month mortality of 3% vs 20%; Fig 1).[23] Strikingly, our reported mortality data were also similar to a previous Swedish study preformed in 1970 to 1994.[24] By contrast, coronary heart disease mortality in Sweden decreased by 67.4% in men and 65.1% in women between 1987 and 2009.[25]

Only 45% of CLI and 65% of IC patients were offered BMT preoperatively (Table II). One month after revascularization, antiplatelets, statins, ACEIs/ARBs, and beta-blockers were used by 81%, 77%, 57%, and 46% of the IC patients and by 71%, 61%, 57%, and 52% of the CLI patients (Fig 2). These treatment patterns for intervened PAD patients are consistent with data from the United States.[26] However, the corresponding numbers after coronary revascularization in Sweden in 2014 were 90%, 92%, 81%, and 86%.[27] A reason that patients with PAD are less intensively treated compared with heart patients may be the lack of data to support pharmacologic treatment for this population. Another reason is possibly that PAD patients are not being recognized as a high-risk group among cardiologists and primary care physicians. Last, cardiologists may be more active in commencing pharmacologic treatment compared with vascular surgeons, who are largely responsible for the care of PAD patients in Sweden. This calls for increased awareness and improved pharmacologic management in this group of largely overlooked patients. Few changes were seen with regard to the use of beta-blockers and ACEIs/ARBs in the perioperative period. Antiplatelet therapy and statins were, on the other hand, prescribed with increasing frequency at the time of hospitalization, which indicates that this treatment

is mostly initiated by hospital-based vascular surgeons. Our data also show that revascularized patients seem to adhere to hospital-initiated treatment at 1 year.

Treatment with aspirin was not associated with a reduction in CV events in our cohort. This is in accordance with a meta-analysis performed by Berger et al, in which treatment with antiplatelets alone or in combination with dipyridamole did not significantly decrease CV events.[28] Despite the lack of compelling evidence for reduction of CV events in a PAD setting, aspirin was the most frequently used drug in our cohort, as it is worldwide.[28] Aspirin is also the only drug with a level I recommendation in available guidelines for PAD management.[9-12] There may be several reasons that the atherosclerosis in limbs, contrary to other vascular territories, is less responsive to antiplatelet therapy, such as inherent platelet activation, extensive atherosclerosis, and high inflammatory burden.[29-31] Further studies with the aim of investigating the effects of newer and more potent antiplatelets in PAD populations are warranted.

The use of beta-blockers in the perioperative phase of noncardiac surgery is controversial. A newly published analysis showed no impact on patients with few risk factors.[32] In our data set, the use of beta-blockers was even slightly negatively associated with CV outcome.

Evidence suggests that the use of ACEIs/ARBs may offer protection against CV events beyond what would be expected from blood pressure lowering only.[33,34] The Heart Outcomes Prevention Evaluation (HOPE) study demonstrated that the CV events were reduced by 14% to 19%, depending on ankle-brachial index level.[35] However, our data do not support these findings, as
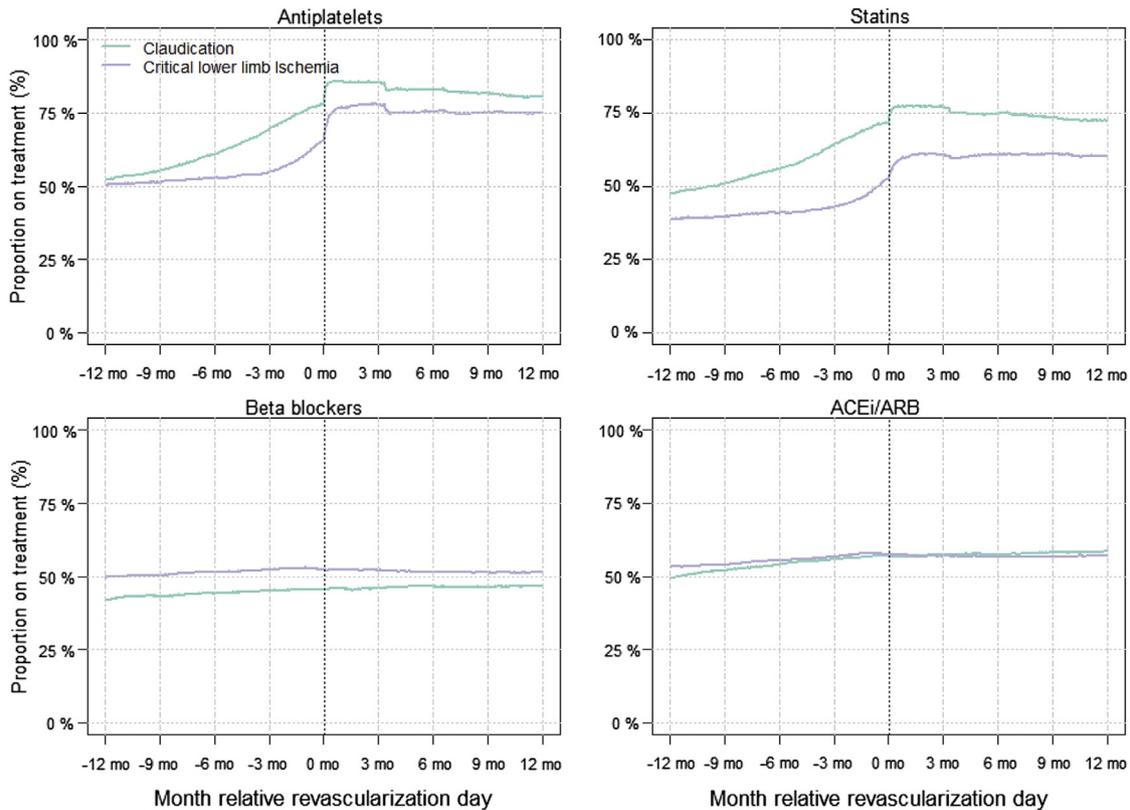
Fig 2. Persistence to preventive drug treatment for intermittent claudication (IC) and critical limb ischemia (CLI). *ACEi,* Angiotensin-converting enzyme inhibitor; *ARB,* angiotensin receptor blocker.

treatment with ACEIs/ARBs did not show a reduced risk for CV events in our model. This finding could be due to selection of patients; ACEIs/ARBs could be more frequently used by patients with a higher atherosclerotic burden and therefore at higher risk for CV events.

Statins were the only drug in this survey that was markedly associated with a reduction in CV events (HR, 0.76; 95% CI, 0.71-0.81; $P < .001$). Similar cardioprotective effects in PAD patients and, in addition, plausible effects on leg symptoms in IC have previously been demonstrated.[36,37] Overall, <60% of patients were offered statins preoperatively (Table II) in our cohort, with only a small change postoperatively, particularly among patients with CLI. The gap between international guideline recommendations and "real-world" clinical implementation needs to be addressed, and a way forward may be to recommend statin treatment for all PAD patients, regardless of plasma cholesterol levels.

Efforts should be made for a holistic management, including both the reduction of adverse CV events and the improvement of leg symptoms. As for leg symptoms, very few claudicants were offered cilostazol (2%) despite available randomized data on improvement of walking distance[38] and health-related quality of life.[39] A recent systematic review concluded that both naftidrofuryl oxalate
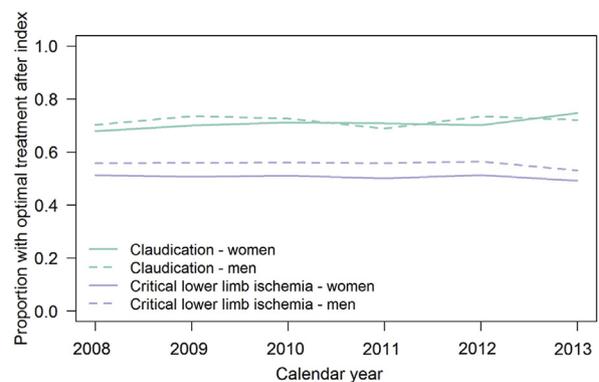
Fig 3. Time trends for best medical treatment (BMT; antiplatelet or anticoagulant therapy and statin treatment) 1 month after revascularization of claudication and critical lower limb ischemia patients.

and cilostazol are effective treatment options in IC.[40] An increased use of such vasoactive drugs in IC may reduce the proportion of patients ultimately requiring invasive interventions.

This study comprises a contemporary national audit of revascularized PAD patients. The use of large and

population-based registries in combination with unique identification numbers facilitates tracking of each patient through the health care system, with highly accurate data from the Swedish mandatory national registries. Limitations include the incomplete data on smoking habits (48% missing data in the Swedvasc registry), and as for all observational registry studies, the inherent design of our study has limitations. However, all analyzed data were prospectively collected in large population-based registries, and we therefore would argue that the presented results reasonably mirror current real-world CV outcomes and pharmacologic treatment patterns for revascularized PAD patients, at least in Sweden.

CONCLUSIONS

Revascularized PAD patients are still at a high risk for CV events and mortality, without a declining time trend during the observation period. One in three CLI patients experienced a CV event within 3 years after revascularization. Comorbidity in other vascular territories was associated with high risk for CV events after revascularization. Use of statins was associated with reduced CV events but was offered only to just more than half of patients with PAD. Aspirin was the most commonly used drug but was not associated with CV event reduction in multivariable analyses. Thus, there is an urgent need for a more effective implementation of currently recommended medications as well as for a continued search after more effective pharmacologic treatment options in PAD.

AUTHOR CONTRIBUTIONS

Conception and design: BS, BK, MF, PH, SJ, MT, JN
Analysis and interpretation: BS, BK, MF, PH, SJ, MT, JN
Data collection: JN
Writing the article: BS, PH, MT, JN
Critical revision of the article: BS, BK, MF, PH, SJ, MT, JN
Final approval of the article: BS, BK, MF, PH, SJ, MT, JN
Statistical analysis: MT
Obtained funding: Not applicable
Overall responsibility: JN

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Additional material for this article may be found online at www.jvascsurg.org.

Supplementary Table I (online only). Diagnostic codes and identifiers used in the extraction of baseline data

Disease group	ICD-10	Treatment
Renal artery stenosis	I70.1	
Aortic aneurysm	I71	
Arterial embolism and thrombosis	I74.0-2	
Pulmonary embolism	I26	
Diabetes	E10-E14	A10
Hypertension	I10	C02C, C09C, C09D, C09A, C09B, C08C, C03A, C03EA01
Myocardial infarction	I21-I22	
Unstable angina	I20.0	
Angina pectoris	I20.1, I20.8, I20.9	
Ischemic stroke	I63-I64	
Transient ischemic attack	G45.0-3, 8-9	
Heart failure	I50	
Atrial fibrillation	I48	
Major organ-specific bleedings	D62.9, I60-62, I85.0, K22.6 K25.0, K25.2, K25.4, K25.6 K26.0, K26.2, K26.4, K26.6 K27.0, K27.2, K27.4, K27.6 K28.0, K28.2, K28.4, K28.6 K29.0, K62.5, K92.0-K92.2	
Chronic renal insufficiency	I15.0, I15.1, N03, N04, N05, N11, N18.4, N18.5, Q60, Q61, Z49.1, Z99.2	
Pulmonary insufficiency	J44	
Cancer	C00-C99	
Dementia	F00-02, F03.9	

ICD-10, International Classification of Diseases, Tenth Revision.

Supplementary Table II (online only). Medication of interest in the study

Medication group	High-level ATC	Medication subgroup	Lower level ATC
Antiplatelets	B01AC	Clopidogrel	B01AC04
		Prasugrel	B01AC22
		Ticagrelor	B01AC24
		Low-dose aspirin	B01AC06
		Cilostazol	B01AC
Dual antiplatelets		Low-dose aspirin + any of clopidogrel, prasugrel, or ticagrelor	
Anticoagulants	B01AA B01AE B01AF	Warfarin	B01AA03
Antidyslipidemics	C10A	Statins	C10AA
		Fibrates	C10AB
Antihypertensives		Beta-blockers	C07
		ACEIs	C09A, C09B
		ARBs	C09C, C09D
		Calcium channel blockers	C08
		Diuretics	C03
Antidiabetics	A10	NIAD	A10B
		Insulin	A10A
Analgesics	N02	Opioids	N02A
		Strong opioids	N02A excluding N02AA59 and N02AX02
Other			
		Nitrates	C01
		Low-molecular-weight heparin	B01AB

ACEIs, Angiotensin-converting enzyme inhibitors; *ARBs,* angiotensin receptor blockers; *ATC,* Anatomical Therapeutic Chemical classification system; *NIAD,* non-insulin antidiabetic drug.

**Supplementary Table III (online only).** Primary cause of death

	IC, No. (%)	CLI, No. (%)	Total, No. (%)
Circulatory system	385 (45.94)	2437 (52.8)	2822 (51.80)
Neoplasms	256 (30.55)	500 (10.85)	756 (13.88)
Endocrine and metabolic diseases	41 (4.89)	576 (12.49)	617 (11.33)
Diseases of respiratory system	48 (5.73)	294 (6.38)	342 (6.28)
Diseases of the digestive system	27 (3.22)	159 (3.45)	186 (3.41)
Infectious disease	16 (1.91)	151 (3.28)	167 (3.07)
Abnormal clinical and laboratory findings	18 (2.15)	116 (2.52)	134 (2.46)
Diseases of the genitourinary system	7 (0.84)	97 (2.10)	104 (1.91)
Mental disorders	6 (0.72)	66 (1.43)	72 (1.32)
Diseases of the skin and musculoskeletal system	2 (0.24)	61 (1.32)	63 (1.16)
Other causes	32 (3.82)	153 (3.32)	185 (3.40)

CLI, Critical limb ischemia; *IC*, intermittent claudication.

Supplementary Table IV (online only). Univariate analysis of primary composite cardiovascular (CV) end point

	Claudication			Critical lower limb ischemia		
Variable	HR	95% CI	Covariate P value	HR	95% CI	Covariate P value
Open vs endovascular	1.01	0.86-1.19	.891	0.85	0.78-0.92	<.001
Male gender	1.29	1.13-1.48	<.001	1.09	1.02-1.16	.013
Age (per year	1.05	1.04-1.06	<.001	1.04	1.04-1.05	<.001
Previous smokers vs nonsmokers	0.76	0.59-0.97	.068	0.86	0.78-0.95	<.001
Current smokers vs nonsmokers	0.91	0.65-1.26		0.68	0.60-0.78	
Diabetes	1.50	1.31-1.72	<.001	1.18	1.10-1.26	<.001
Hypertension	1.67	1.37-2.03	<.001	1.47	1.32-1.64	<.001
Myocardial infarction	2.00	1.71-2.34	<.001	2.01	1.87-2.17	<.001
Unstable angina pectoris	1.74	1.45-2.10	<.001	1.36	1.22-1.51	<.001
Angina pectoris	1.65	1.44-1.89	<.001	1.56	1.45-1.67	<.001
Ischemic stroke	2.17	1.79-2.63	<.001	1.57	1.44-1.71	<.001
Transient ischemic attack	1.88	1.50-2.36	<.001	1.45	1.29-1.63	<.001
Heart failure	2.59	2.21-3.04	<.001	2.29	2.13-2.45	<.001
Atrial fibrillation	2.05	1.74-2.43	<.001	2.05	1.91-2.20	<.001
Major organ-specific bleedings	1.74	1.39-2.17	<.001	1.39	1.26-1.53	<.001
Liver disease	1.26	0.41-3.92	.686	1.45	0.99-2.14	.056
Renal disease	1.80	1.27-2.54	.001	1.73	1.52-1.97	<.001
Respiratory insufficiency	1.39	1.15-1.67	.001	1.17	1.07-1.29	.001
Cancer	0.99	0.83-1.19	.916	1.17	1.08-1.27	<.001
Aspirin	0.79	0.69-0.91	.001	0.95	0.89-1.02	.139
Warfarin	1.83	1.45-2.31	<.001	1.32	1.19-1.46	<.001
Statins	0.76	0.66-0.88	<.001	0.72	0.67-0.77	<.001
Beta-blockers	1.60	1.40-1.82	<.001	1.54	1.44-1.64	<.001
ACEIs	1.21	1.06-1.39	.006	1.12	1.05-1.20	.001
ARBs	1.04	0.90-1.22	.587	0.97	0.89-1.05	.472
Calcium channel blockers	1.27	1.11-1.44	<.001	0.98	0.91-1.05	.504
Strong opioids	1.52	1.21-1.90	<.001	1.38	1.28-1.47	<.001
Heparin	1.62	1.22-2.14	.001	1.04	0.92-1.18	.505

ACEIs, Angiotensin-converting enzyme inhibitors; *ARBs*, angiotensin receptor blockers; *CI*, confidence interval; *HR*, hazard ratio.
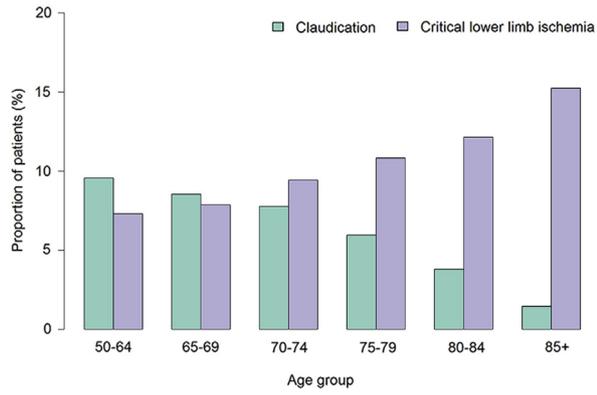
Supplementary Fig (online only). Age distribution for claudication and critical lower limb ischemia patients at admission for revascularization.