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ORIGINAL RESEARCH

Trends in Use of Cardioprotective Medication in Peripheral Artery Disease: A Nationwide Study

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BACKGROUND: Guideline-based cardioprotective medical therapy is intended to reduce the burden of adverse cardiovascular and limb outcomes in patients with peripheral artery disease (PAD). However, contemporary data describing trends in use of medication remains limited. The present study, therefore, aims to investigate changes in use of cardioprotective medication in PAD.

METHODS AND RESULTS: By using Danish national healthcare registries, we identified all patients with first-time diagnosis of PAD (1997–2016) and classified them into two groups: (1) PAD+ that includes all patients with PAD with a history of cardiovascular disease, ie, myocardial infarction, atrial fibrillation, and stroke (n=162 627); and (2) PAD (n=87 935) that comprise patients without a history of cardiovascular disease. We determined the use of medication in the first 12 months after the incident diagnosis of PAD and estimated age standardized 1-year mortality rates. Our results showed increase in use of cardioprotective medication throughout the study period in both groups. However, PAD+ had a higher use of medication (acetylsalicylic acid, 3.5%–48.4%; Clopidogrel, 0%–17.6%; vitamin K antagonists, 0.9%–7.8%; new oral anticoagulants, 0.0%–10.1%; Statins, 1.9%–58.1%; angiotensin-converting enzyme inhibitors, 1.2%–20.6%), compared with PAD (acetylsalicylic acid, 2.9%–54.4%; Clopidogrel, 0%–11.9%; vitamin K antagonists, 0.9%–2.4%; new oral anticoagulants, 0.0%–3.4%; Statins, 1.5%–56.9%; angiotensin-converting enzyme, 0.9%–17.2%), respectively. Furthermore, 1-year mortality rates in PAD declined with increased use of medications during study.

CONCLUSIONS: In this nationwide study, use of cardioprotective medication increased considerably with time, but compared to patients with other atherosclerotic diseases, there remains an underuse of guideline-based medical therapy in patients with PAD.

Key Words: atrial fibrillation ■ myocardial infarction ■ peripheral artery disease ■ stroke ■ temporal trends

Peripheral artery disease (PAD) is a progressive atherosclerotic disease characterized by occlusion of the arteries outside the heart and brain.[1] PAD is highly prevalent and recognized as a major contributor to cardiovascular health burden.[2] Indeed, patients with PAD are at an increased risk of adverse cardiovascular events and experience substantial impairment in quality of life, as well as increased morbidity rates.[3] Studies have reported that patients with PAD, compared to those with other coronary artery diseases, confer a greater economic burden in terms of the prevention and treatment of ischaemic complications and the management of lower limb-related symptoms.[4] Current US and European guidelines recommend a comprehensive programme with lifestyle modification and guideline-based medical therapy for all individuals with symptomatic PAD, which is intended to reduce the risk of adverse cardiovascular events

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CLINICAL PERSPECTIVE

What Is New?

- In this nationwide cohort study of 162 627 patients with first-time diagnoses of peripheral artery disease (PAD), we observed a noticeable increase in use of guideline-based medical therapy throughout the study period (1997–2016).
- Despite an overall increasing trend in medication use, PAD patients were undertreated and compared to PAD patients with a history of cardiovascular disease (myocardial infarction or stroke), the use of these medications was significantly lower.
- In addition, the age-standardized 1-year mortality rates in patients with PAD appeared to decline as the use of medical therapy increased over the study period.

What Are the Clinical Implications?

- Current US and European guidelines recommend cardioprotective medical therapy for all individuals with PAD intended to reduce the burden associated with adverse cardiovascular events.
- Despite the several sets of guidelines there remain an evident underuse of the guideline-based medical therapy in patients with PAD.
- Results from the present study underscores the urgent need to assist clinicians in translating the recommendations to clinical practice and to subsequently increase adherence to the PAD treatment guidelines.

Nonstandard Abbreviations and Acronyms

ASA	acetylsalicylic acid
ATC	anatomical therapeutic chemical
IR	incidence rates per 1000 person-years
NOACs	new oral anticoagulants
VKA	vitamin K antagonists

and to prevent the progression of the atherosclerotic process.[5–9] This guideline-based medical therapy includes cardioprotective medication (ie, antithrombotic therapy [antiplatelet and anticoagulant therapy], cholesterol lowering agents, and anti-hypertensive therapy [preferably angiotensin-converting enzyme inhibitors (ACEIs)]).[5–9] A few studies have demonstrated improved survival rates and a reduced risk of morbidity associated with cardioprotective medication in PAD patients.[10–12] However, despite the accumulating evidence on the high risk of cardiovascular mortality and morbidity and the improved outcomes associated with medical therapy, contemporary data describing the patterns of medication use in patients with PAD remain scarce.[13–15] We, therefore, used Danish national healthcare registers to determine time trends in the use of cardioprotective medication and mortality rates, between 1997 and 2016, in patients with incident diagnoses of PAD. We hypothesized that despite the well-established increased risk of cardiovascular morbidity and mortality, the recommended secondary preventive drugs are underused amongst PAD patients.

METHODS

The data underlying this study were provided by "Danmark Statistik" under licence/by permission. Data can be shared on request with permission of Danmark Statistik.

Data Sources

The nationwide healthcare registers in Denmark provide an exceptional opportunity for conducting large-scale epidemiological studies with a minimum loss to follow-up. All Danish inhabitants are assigned with a unique civil registration number at birth or immigration. This enables cross-linkage of data on an individual level across several national registers.[16–18] In the present study, we used Danish National Patient Registry to retrieve information on comorbidities, prior to the PAD diagnosis date.[17] This register holds information on all in-patient and out-patient treatments (recorded as *International Classification of Diseases* [*ICD*] codes). Information on concomitant pharmacotherapy was obtained from the Danish Register of Medicinal Product Statistics (National Prescription Register) that holds data on all medicines [recorded according to the International Anatomical Therapeutic Chemical (ATC) classification system] prescribed and dispensed since 1995.[16,17] The Danish National Cause of Death Registry (established since 1970) was used to retrieve information on vital status. These registers have previously been shown to be complete and accurate with a wide range of well-validated diagnoses and procedure codes.[16,17,19–22]

Study Population

The study population comprised all Danish citizens aged ≥18 years, with a first-time diagnosis of PAD (in-patient and out-patient) starting from January 1, 1997 until December 31, 2016. PAD was defined in accord with the ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases (2017) and comprised all arterial diseases (*ICD-10* codes: DI70, DI701, DI702, DI708, DI709, DI738, DI739, DI742, DI743, DI744, DI745, DI748, DI749) except the atherosclerotic

disease of the coronary arteries, aorta, and intracranial arteries. The study population was mainly divided into two categories, ie, PAD+ (all patients with a first-time incident diagnosis of PAD) and PAD (PAD patients with a history of AF, MI, and stroke were excluded). To capture the change in treatment patterns in concurrent cardiovascular disease, the study population was further subdivided into three more categories, namely PAD AF (PAD patients with a history of stroke and myocardial infarction [MI] were excluded), PAD stroke (PAD patients with a history of AF and MI were excluded), and finally PAD MI (patients with PAD with a history of AF and stroke were excluded). In addition, the study subjects were censored on death, migration, and end of the study period (December 31, 2016).

Outcome

The primary outcome of interest was annual change over time in use of cardioprotective medication. In addition, age-standardized mortality rate within 12 months after the incident diagnosis of PAD was also estimated.

Pharmacotherapy and Comorbidity

The cardioprotective medication included: acetylsalicylic acid (ASA), clopidogrel, vitamin-K antagonist, non-vitamin-K oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban), cholesterol lowering agents (statins), and ACEIs. To determine the consumption at baseline, we assessed use of medication over a 6-month period (3 months before and 3 months after the PAD diagnosis). Comorbidities were established based on *ICD* diagnostic codes recorded within 10 years of the incident diagnosis of PAD. Hypertension was identified by hospital diagnoses for hypertension or if patient was treated with at least two of the following anti-hypertensive agents inside a 90-day period after receiving the diagnosis: alpha-adrenergic blockers, non-loop diuretics, vasodilators, beta-blockers, calcium channel blockers, and renin-angiotensin system inhibitors.[23] The respective *ICD* and ATC-codes for all the examined comorbidities and pharmacotherapy are presented in Table S1.

Statistical Analysis

Baseline characteristics were presented as frequencies and percentages for categorial variables and as means for continuous variables. Differences between groups were analysed using Kruskal Wallis tests and χ^2-tests, as appropriate. Test of trend was performed with Cochran-Armitage test. Time trends in use of medical treatment were presented as proportion of patients claiming at least one prescription within 12 months after incident PAD diagnosis. The level of statistical significance was set as $P<0.05$. An additional analysis was performed to determine trends in use of medication 3 months prior to and 3 months after the incident PAD diagnosis. Furthermore, age-adjusted trends in mortality were estimated as incidence rates (IR) per 1000 person-years. Age was categorized in following age-groups (years): 18 to 49, 50 to 59, 60 to 69, and >70, respectively.

All statistical analyses were performed with SAS statistical software version 9.4 (SAS Institute Inc., Cary, NC), and R Core Team (2020),[24] and Joinpoint regression program (4.2.0.1 May 2015, National Cancer Institute, https://surveillance.cancer.gov/joinpoint/).

Ethics Statement

For retrospective register-based studies in Denmark, approval from an ethics committee is not required. The present study (ref. 2007-58-0015, int. ref: GEH-2014-018), was approved by The Danish Data Protection Agency and data were made available in a way that individuals could not be identified. The study was conducted and reported in accordance with the recommendation of Strengthening the Reporting of Observational Studies in Epidemiology (STROBE).[25]

RESULTS

A total of 160 364 individuals (53.8% male; mean age 70.2 [IQR 62–79] years) were identified with a first-time diagnosis of PAD between January 1, 1997 and December 31, 2016. After exclusion of patients with a history of AF, stroke, and/or MI, there were 85 500 patients with a diagnosis of PAD. Baseline characteristics stratified by the subgroups (PAD+, PAD, PAD MI, PAD stroke, and PAD AF) are presented in Table 1. Patients in PAD+ groups had an over-all higher frequency of comorbidities compared with PAD at baseline. Medication use at baseline (3 months prior to incident diagnosis of PAD) is described in Table S2.

Annual time trends of cardioprotective medication within 12 months after incident diagnosis of PAD are illustrated on Figure 1 and indicate a significant increase in use of medication in all groups across study period. Of note, use of statins increased from 2.0% in 1997 to 60.0% in 2016. Use of any-antiplatelet medication increased from 3.5% to 61.0%, with the greatest increase in ASA (3.5%–50.0%) and use of ACEIs increased from 1.2% to 21.3% during the study period. *P* values for trends were <0.0001 for all medications across all groups.

Table 2 shows use of cardioprotective medication within 12 months after incident diagnosis of PAD for all groups (a subgroup analysis is attached as Figure S1). The PAD group had the lowest use

Table 1. Baseline Characteristics of Study Population

	PAD+ (n=160.364)	PAD (n=85.500)	PAD MI (n=14.208)	PAD Stroke (n=20.145)	PAD AF (n=19.076)	*P* Value
Patient characteristics						
Age, y mean (IQR)	70.2 (62–79)	68.2 (59–77)	70.0 (62–78)	70.9 (63–79)	74.9 (68–82)	<0.0001
Male (%)	53.8 (86.400)	51.2 (43.753)	60.5 (8.600)	55.4 (11.153)	54.4 (10.382)	<0.0001
Comorbidities						
Heart failure (%)	13.1 (20.992)	7.7 (6.560)	19.9 (2.832)	8.3 (1.674)	23.7 (4.521)	<0.0001
Hypertension (%)	28.2 (45.236)	20.5 (17.517)	33.7 (4.791)	33.9 (6.828)	34.8 (6.651)	<0.0001
Chronic kidney disease (%)	6.8 (10.968)	5.1 (4.361)	9.1 (1.287)	6.7 (1.344)	8.9 (1.715)	<0.0001
DVT (%)	3.3 (5.339)	3.4 (2.924)	2.4 (338)	3.1 (641)	3.8 (727)	<0.0001
COPD (%)	11.2 (17.892)	9.7 (8.283)	11.6 (1.645)	9.8 (1.974)	15.8 (3.027)	<0.0001
Pulmonary embolism (%)	1.3 (2.113)	1.2 (1.006)	1.1 (161)	1.1 (214)	1.9 (365)	<0.0001
Cancer (%)	11.0 (17.639)	10.9 (9.329)	9.5 (1.349)	10.8 (2.165)	12.6 (2.409)	<0.0001
Bleeding (%)	12.6 (20.193)	9.9 (8.517)	12.9 (1.838)	14.4 (2.907)	16.0 (3.049)	<0.0001
GI bleeding (%)	5.6 (8.960)	4.4 (3.772)	5.8 (821)	5.9 (1.195)	7.4 (1.412)	<0.0001
IC bleeding (%)	1.1 (1.756)	0.7 (608)	0.7 (100)	2.4 (477)	0.8 (151)	<0.0001
Diabetes mellitus (%)	18.4 (29.463)	15.3 (13.069)	24.2 (3.442)	20.0 (4.017)	19.5 (3.717)	<0.0001
Concomitant medication						
Heparin (%)	0.3 (529)	0.3 (221)	0.2 (34)	0.3 (60)	0.6 (123)	<0.0001
Persantin (%)	4.1 (6.504)	1.0 (870)	1.4 (200)	16.1 (3.233)	1.1 (216)	<0.0001
NSAID (%)	21.1 (33.804)	21.9 (18.747)	20.6 (2.933)	21.3 (4.286)	19.8 (3.768)	<0.0001
Diuretics (%)	31.7 (50.791)	29.2 (24.945)	31.9 (4.538)	32.4 (6.622)	37.4 (7.128)	<0.0001
Beta-blockers (%)	25.5 (40.931)	16.9 (14.425)	41.3 (5.865)	20.8 (4.184)	37.4 (7.136)	<0.0001
CC-blockers (%)	25.1 (40.176)	21.9 (18.746)	28.5 (4.055)	27.0 (5.445)	27.9 (5.327)	<0.0001
Loop diuretics (%)	25.1 (40.180)	19.3 (16.477)	29.5 (4.184)	20.4 (4.100)	39.1 (7.451)	<0.0001
Proton pump inhibitor (%)	23.2 (37.228)	20.7 (17.732)	26.0 (3.696)	24.2 (4.884)	25.2 (4.797)	<0.0001
Glucose lowering agents (%)	17.6 (28.278)	15.4 (13.153)	23.4 (3.331)	18.4 (3.713)	17.9 (3.431)	<0.0001

AF indicates atrial fibrillation; CC-blockers, calcium channel blockers; COPD, chronic obstructive pulmonary disorder; DVT, deep venous thrombosis; GI, gastrointestinal; IC, intracranial; IQR, interquartile range; MI, myocardial infarction; NSAID, non-steroid anti-inflammatory drugs; and PAD, peripheral artery disease.

of any cardioprotective medication throughout the study period compared with patients with PAD with AF, stroke, and MI. The highest proportion of patients treated with were found in the PAD MI group (76.7% in 2016) followed by the PAD stroke group (67.5% in 2016). Same trend was observed in treatment with ACEIs and anti-coagulants medications. The highest increase in use of any cardioprotective medication was observed in patients with PAD with a history of MI and stroke. Furthermore, in the supplementary analysis we determined temporal trends in use of cardioprotective medication at baseline and observed a significant increase in use of all agents across each group following the incident PAD diagnosis (Table S2).

The age-standardized mortality rates (Figure 2) showed decreasing trends from IR 19.26 (1997) to IR 13.92 (2016). The estimated annual percent change (APC) for the entire study period (1997–2016) decreased by 1.7% (95% CI 1.3–2.1, *P*<0.0001). Furthermore, the absolute risk of death was 15.4% (95% CI 14.8–16.0) in 1997 and 12.6% (95% CI 11.9–13.4) in 2016, respectively. All trends were statistically significant with a *P* value below 0.05.

DISCUSSION

In this nationwide cohort of patients with incident PAD, we examined 20 years of trend data on the use of cardioprotective medication. The results demonstrated remarkable improvements in the use of all examined medications over time. However, these medicines remained underutilized in patients with PAD compared with patients with PAD with concurrent conditions, in particular MI or stroke. Moreover, age-adjusted 1-year mortality incidence rates appear to decrease as the use of medical therapy increased over the study period.

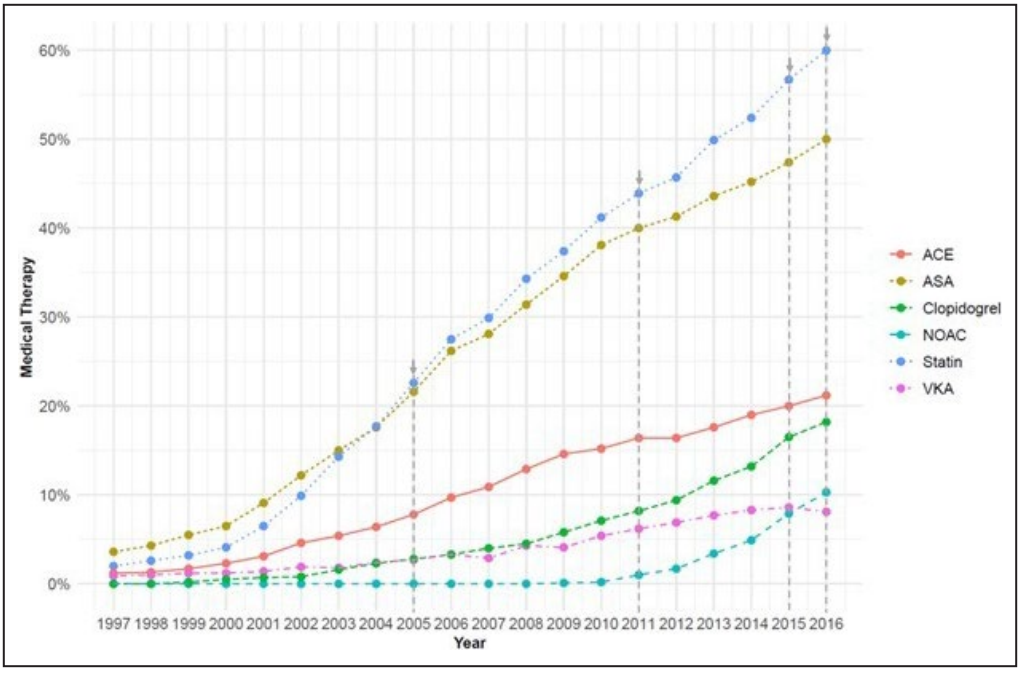

Figure 1. Temporal change in use of medication from 1997 to 2016 for PAD+ patients.
The arrows indicate changes in guideline recommendations over time. ACE indicates angiotensin-converting enzyme; ASA, acetylsalicylic acid; NOAC, new oral anticoagulant; and VKA, vitamin-K antagonist. For year 2005, 2011, and 2016 the arrow (↓) represents AHA/ACC 2005, 2011, and 2016 treatment guidelines for PAD, respectively. For year 2015 the arrow (↓) represents Society of Vascular Surgery (SVS) 2015 treatment guidelines for PAD.

Medical therapeutic strategies in PAD management are intended to reduce the burden of adverse cardiovascular outcomes and limb events and primarily involve risk factor modification and secondary prevention pharmacotherapy.[10–12] Several studies have reported that the use of medical therapy intended for secondary prevention in patients with PAD improves survival but lags significantly behind the medical treatment of patients with coronary artery disease.[11,26] The suboptimal use of medical therapies could contribute to impaired cardiovascular health and an increased risk of adverse outcomes. To gain an improved understanding of poor outcomes amongst PAD patients, contemporary data describing the use patterns of medication for secondary prevention in patients with PAD is needed. We have therefore employed nationwide Danish healthcare registers to investigate time trends in the use of cardioprotective medication in patients with incident PAD.

Noticeable changes over the course of study period from 1997 to 2016 included many-fold increases in proportions of PAD patients using statins (2.0%–60.0%) and ASA (3.5%–50.0%), as shown in Figure 1. Even though these results indicate steady progress, it appears that patients with PAD may not be prescribed medication to mitigate cardiovascular risk at the same rate as for other atherosclerotic conditions (Table 2). Indeed, PAD patients with MI were treated far better

Table 2. Use of Medical Therapy (in Percentage) in the First 12 Months After Incident PAD Diagnosis From 1997 to 2016

	PAD+	PAD	PAD MI	PAD Stroke	PAD AF
ASA	3.5–50.0	2.9–56.9	3.4–78.8	4.3–35.9	4.9–23.1
CLOP	0–18.1	0–12.7	0–21.8	0–57.5	0–6.3
VKA	0.9–8.1	0.8–2.6	0.4–5.3	1.0–2.9	1.4–29.9
NOAC	0–10.3	0–3.7	0–2.7	0–5.3	0–38.0
STATIN	2.0–60.0	1.5–59.7	2.6–76.8	2.3–67.5	2.5–46.0
ACE	1.2–21.3	0.9–18.2	1.4–31.9	1.5–24.3	2.1–22.4
OtherAP	0–1.9	0–0.4	0–16.8	0–0.8	0–0.4

P value for trend <0.0001 for all medications. ACE indicates angiotensin-converting enzyme; ASA, acetylsalicylic acid; Clop, clopidogrel; NOAC, new oral anticoagulant; OtherAP, Brillique/Efient; and VKA, vitamin-K antagonist.

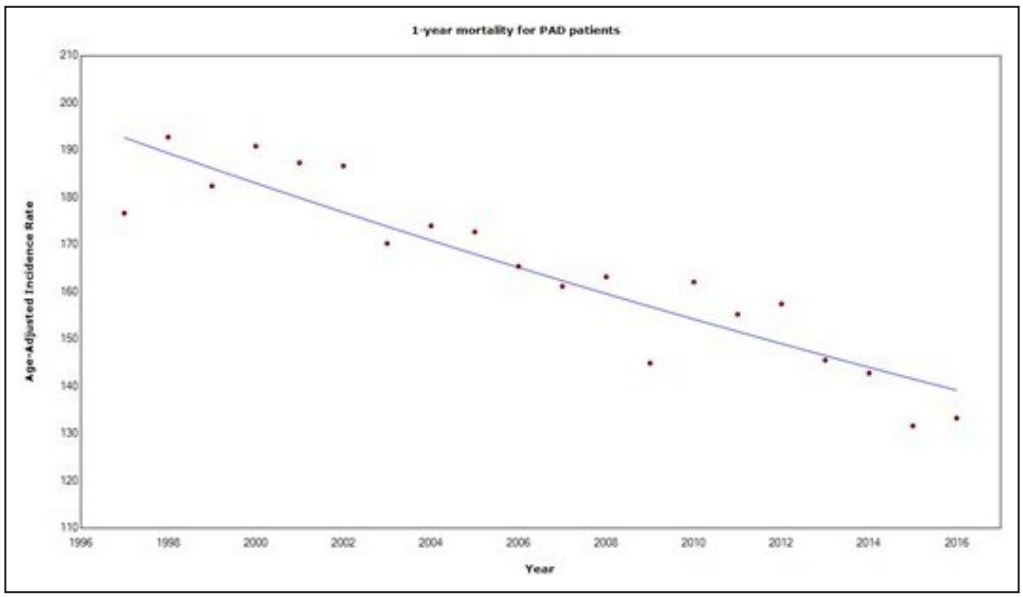

Figure 2. Age-standardized 1-year mortality rates per 1000 person-years for PAD+ patients (*y*-axis) from 1997 to 2016 (*x*-axis).

with all examined cardioprotective agents compared to patients with PAD. The same pattern was observed in patients with PAD with stroke, where the proportions of patients on statins (59.8% versus 67.5%), ACEIs (18.2% versus 24.5%), and clopidogrel (12.7% versus 57.5%) were higher compared with patients with PAD (Table 2).

The medical management of PAD has undergone many improvements in recent decades (Figure 1). Formalized guidelines on the medical management of PAD first established in 2005 by the American Heart Association (AHA) and the American College of Cardiology (ACC) endorsed ASA as a safe and effective antiplatelet agent with clopidogrel as an alternative therapy.[8] Furthermore, as already recognized for other atherosclerotic diseases, the guidelines also recommended adding statins and ACEIs into the cardiovascular risk preventive regimen for patients with PAD. In 2011 these recommendations were revised, and the possibility of either standalone or combined treatment with ASA and clopidogrel for the risk reduction of CV events in patients with PAD was proposed.[9] In 2015, the Society of Vascular Surgery (SVS) published guidelines with the same antithrombotic therapy recommendation for symptomatic PAD patients as the AHA/ACC guidelines, in addition to the decreased use of vitamin K antagonists for cardiovascular risk reduction in.[5]

These improvements in the guidelines are apparent in our results; we observed a greater uptake in the use of the recommended medications amongst patients with PAD following the publication of the guidelines in 2005. However, despite the temporal improvements overall, the proportion of PAD patients using cardioprotective medication remained modest, even at the end of the study period, when just about half of PAD patients were using statins, and only 18% received ACEIs. In addition, the use of ASA was estimated to be under 60% in patients with PAD.

The most recent guidelines on medical management (AHA/ACC 2016 and ESC 2017) prefer clopidogrel as an antiplatelet for symptomatic PAD, since the data has suggested that clopidogrel (compared with ASA) provides a more effective prophylaxis in PAD.[1,6,7] However, our results indicate that amongst the patients diagnosed with incident PAD in 2016, only 13% were using clopidogrel following the implementation of new guidelines. Moreover, these patients were more likely to receive ASA (56.9%) as an antiplatelet therapy. This underscores the urgent need to assist clinicians in translating the recommendations to clinical practice and to subsequently increase adherence to the guidelines.

The therapeutic management of patients with MI and stroke also includes ASA, clopidogrel, and statins, since these agents have been shown to induce a clinically meaningful reduction in cardiovascular and cerebrovascular events.[27,28] On the other hand, studies have suggested that PAD is associated with higher rates of adverse cardiovascular outcomes compared with coronary artery disease.[29,30] Despite this, throughout the study period, we observed that patients with PAD with a history of cardiovascular disease (prior MI or stroke) received guideline-based medical therapy more often than patients with PAD. Nearly 80% of patients with PAD with MI used ASA, in comparison with 56.9% in the PAD group. Similarly, 57% of patients with PAD with stroke used clopidogrel compared with 13% in the

PAD group (Table 2). The same pattern was observed in the use of statins and ACEIs in both PAD patients with MI or stroke and patients with PAD. This trend likely reflects the greater immediate attention clinicians have placed on secondary prevention following the occurrence of hard outcomes such as MI and stroke. Moreover, this change also indicates that a more aggressive approach has been adopted by clinicians to prevent increased morbidity and mortality related to the increased occurrence of systemic atherosclerosis in PAD patients with concurrent MI or stroke compared with PAD. Nevertheless, the observed rates indicate the suboptimal use of all examined cardioprotective agents, despite the guideline recommendations for aggressive cardiovascular risk reduction in patients with PAD.

In a more recent large double-blind trial of patients with PAD who had undergone lower-extremity revascularisation, rivaroxaban (2.5 mg twice daily) combined with ASA was associated with a significantly lower incidence of the composite outcome of acute limb ischaemia, MI, stroke, and CV cardiovascular death than was ASA alone.[31] Likewise, another large, randomized trial showed that rivaroxaban plus ASA was associated with fewer major adverse cardiovascular and limb events in patients with stable atherosclerotic vascular disease (ie, both PAD and CAD) than was ASA or rivaroxaban alone.[32] These findings hold great importance for patients with PAD, since the correct use of low dose rivaroxaban and ASA may significantly improve quality of life by reducing the risk of adverse cardiovascular and limb events in this high-risk population. Strategies to improve adherence to these recommendations are therefore critical.

Interestingly, we also observed a decrease in the all-cause mortality rate in patients with PAD that appeared to correspond to the improved use of cardioprotective medication across the study period (Figure 2). These findings are consistent with previous studies identifying similar reductions in mortality trends for ischaemic heart disease and cardiovascular disease.[33–35] Effective treatment algorithms, including a markedly better use of cardioprotective medications, are likely to have contributed to the overall decrease in mortality rates in patients with PAD. Despite this reduction and the accumulating evidence on the benefits of cardioprotective medications, our results suggest that a large proportion of individuals with PAD are nonetheless not receiving optimal treatment.

At the end of the present study, most patients with concurrent PAD and AF were managed with either vitamin K antagonists (30.0%) or non-vitamin-K oral anticoagulants (37.9%), whereas treatment with clopidogrel (6.3%) and ASA (23.1%) was low (Table 2). Although treatment with non-vitamin-K oral anticoagulants and vitamin K antagonists is in accordance with the guidelines on managing AF, the proportion of patients on these agents is markedly low. This could be due to a higher number of patients with a low risk (CHA2DS2-VASc score <1) who may not require anticoagulation. Also, anticoagulation could be nephrologically contraindicated for some patients due to renal insufficiency (n=1715 in the PAD-AF group). Nevertheless, if compared with the treatment trends observed in other groups examined in this study, the lower numbers may, in part, be due to decreased compliance with guidelines amongst PAD patients. Taken together, our results demonstrate that although temporal improvements occurred, the use of the examined cardioprotective medications is suboptimal amongst patients with PAD and significantly lower than for PAD patients with concurrent MI or stroke. These findings suggest an ongoing need for operationalising quality improvement initiatives to ensure that patients with PAD receive adequate prevention to reduce adverse cardiovascular and limb events.

Strengths and Limitations

The most notable strength of the present study is its inclusion of a large number of unselected patients in a real-world setting with low loss to follow-up and the use of validated measures of exposure and outcomes. Furthermore, the Danish healthcare system is government financed and guarantees free and, in principle, equally accessible care for all inhabitants, which reduces confounding by variables associated with social class. Moreover, the registers employed in this study are known to be accurate and complete as demonstrated by several validation studies.[16,20–22]

Despite these strengths, several limitations must be acknowledged. Firstly, the observational nature of the study only enables the establishment of association and does not represent cause-and-effect relationships. Moreover, the subpopulation was identified using diagnoses from registers; although the data in Danish registers is generally known to be accurate, limitations may remain regarding PAD diagnoses, particularly since PAD is underreported due to the often-asymptomatic nature of the disease. Hence, patients with asymptomatic PAD with no healthcare records were not captured in this study. The findings in our study may be even more accentuated since the use of medications in patients with asymptomatic PAD is expected to be lower than amongst symptomatic PAD patients. Furthermore, we did a subgroup analysis by dividing subjects into strata of other atherosclerotic and cardiovascular diseases (PAD, PAD+, PAD-MI, PAD-AF, PAD-stroke) which may enable us to observe impact of these common cardiovascular diseases on use of cardioprotective medication in the study population. However, the risk of minute residual

confounding inherent to the observational nature of the study cannot be refuted entirely.

Notably, guideline-based cardioprotective medication for treatment of PAD includes ACEIs (or as an alternative angiotensin II receptor blockers) as the preferred choice of anti-hypertensive treatment.[6] However, the ATC codes for angiotensin II receptor blockers were not included in this study and the actual temporal change for ACEIs including angiotensin II receptor blockers may have been slightly higher.

Lastly, it is noteworthy that Danish guidelines for the treatment of PAD endorse global guidelines (AHA/ACC, ESC, SVS) and do not differ in any aspect.

CONCLUSIONS

In this nationwide study, use of cardioprotective medical therapy in PAD increased considerably over time and mortality rate appeared to decline accordingly. However, despite the several sets of guidelines providing recommendations regarding best possible therapeutic management of adverse cardiovascular events, there remains an evident underuse of these agents in patients with PAD.

ARTICLE INFORMATION

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None.

Supplementary Material

Tables S1–S2
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Overview of International Classification of Diseases (ICD) and Anatomical Therapeutic Chemical Classification System (ATC) Codes

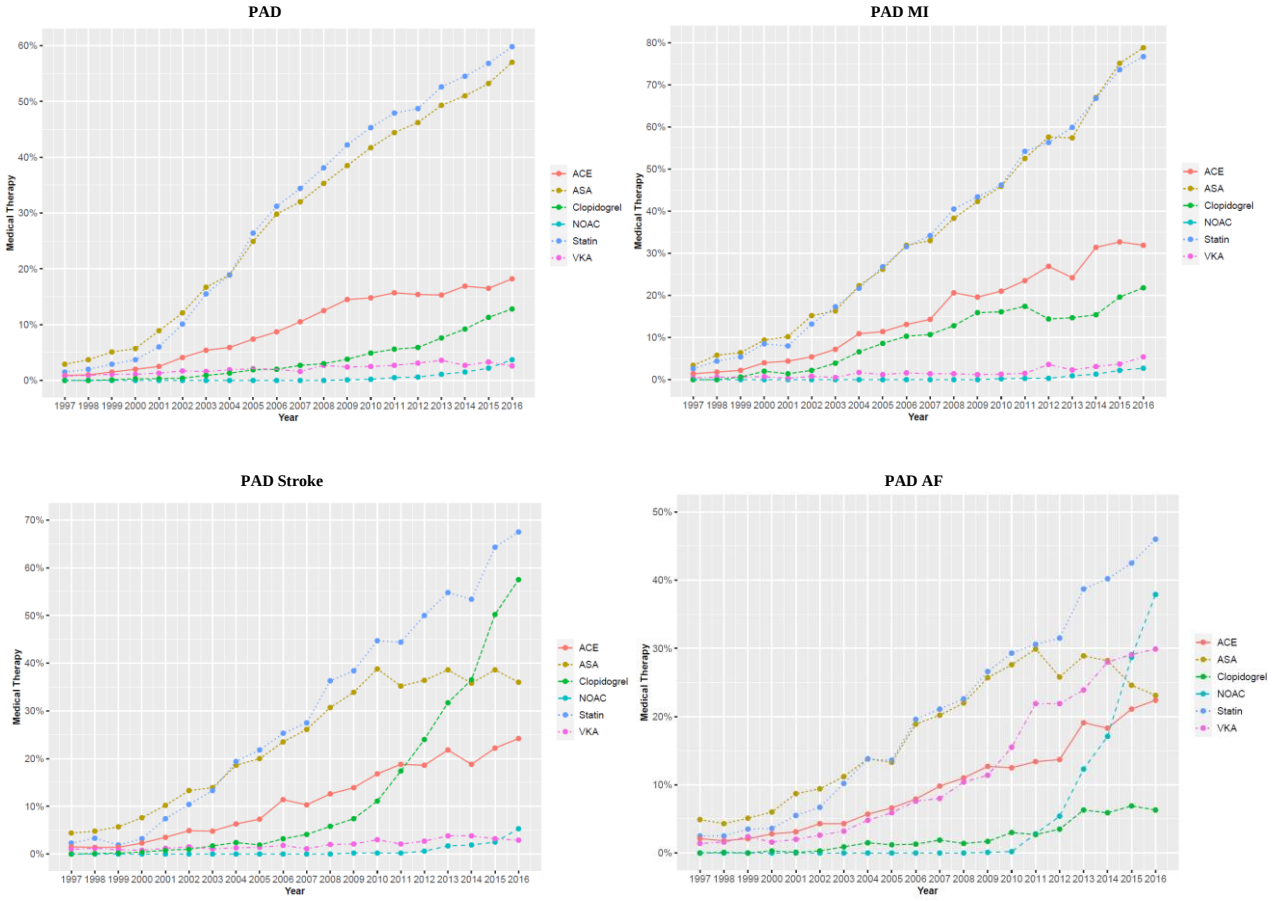
Pharmacological Treatments	**ATC**
Cholesterol-lowering drugs	C10AA
Glucose-lowering agents	A10
Acetylsalicylic acid	B01AC06, N02BA01
Clopidogrel	B01AC04
Vitamin K antagonists	B01AA
New Oral Anticoagulants	B01AF, B01AE
Non-steroid Anti-inflammatory Drugs	M01A
Brillique	B01AC24
Efient	B01AC22
Heparin	B01AB
Persantin	B01AC07
Hypertension	
Loop diuretics	C03C, C02A, C02B, C02C, C02DA, C02L,
Non-loop diuretics	C03A, C03B, C03D, C03E, C03X, C07A, C07B,
Beta blockers	C03C, C03EB, C07C, C07D, C08G, C09BA, C09DA,
Calcium channel blockers	C03EA, C09XA52, C07, C07F, C08, C02DB, C02DD,
Angiotensin converting enzyme inhibitors	C09AA
Comorbidity	**ICD-10**
Chronic Obstructive Pulmonary Disorder	J42 to J44
Heart failure	I42, I50, J81, I110
Pulmonary embolism	I26
Diabetes	E10 to E14
Deep venous thrombosis	I801 to I803, I808, I809, I821, I822, I823, I828, I829
Bleeding	D62, I60 to I62, N02, R31, R04, D500, H313, H356, H431, H450, I312, I850, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K661, K920 to K922, S064 to S066, J942, K228F, K298A, K638B, K638C, K838F, K868G, I864A, H052A, S368D, G951A
Gastro-intestinal bleeding	I850, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K290, K625, K661, K920 to K922, K228F, K298A, K638B, K638C, K838F, K868G,
Intra-cranial bleeding	I864A, S368D
Hypertension	I60 to I62, S064 to S066
Chronic kidney disease	I10 to I15
	N02 to N08, N11, N12, N14, N18, N19, N26, dq61, N158 to N164, N168, E102, E112, E132, E142, I120, M321B

Table S2. Use of medication 3 month prior and 3 months after incident PAD diagnosis from 1997 to 2016.

	PAD+ <3months	*PAD+ >3months*	*PAD <3months*	*PAD >3months*	*PAD MI <3months*	*PAD MI >3months*	*PAD AF <3months*	*PAD AF >3months*	*PAD Stroke <3months*	*PAD Stroke >3months*
*ASA**	1.9 – 30.8	2.3 – 37.7	1.5 – 32.8	1.9 – 42.7	1.8 – 56.4	2.5 – 58.7	2.6 – 16.0	3.1 – 18.0	2.3 – 26.8	2.5 – 28.5
*CLOP**	0 – 9.5	0 – 13.6	0 – 5.3	0 – 9.6	0 – 10.5	0 – 13.9	0 – 2.7	0 – 4.7	0 – 36.9	0 – 44.8
*VKA**	0.3 – 6.2	0.6 – 6.5	0.3 – 1.6	0.5 – 1.9	0.1 – 3.6	0.3 – 3.4	0.7 – 25.1	0.9 – 25.8	0.4 – 1.8	0.7 – 2.3
*NOAC**	0 – 6.1	0 – 7.5	0 – 1.5	0 – 2.4	0 – 2.1	0 – 1.7	0 – 25.4	0 – 29.4	0 – 2.4	0 – 3.0
STATIN	1.1 – 40.4	1.3 – 46.4	0.9 – 38.9	1.0 – 45.8	1.7 – 52.4	1.7 – 59.5	1.3 – 32.1	1.9 – 36.2	1.4 – 48.5	1.5 – 52.6
*ACE**	0.8 – 16.5	0.9 – 16.5	0.6 – 13.5	0.6 – 13.9	0.8 – 24.9	1.0 – 25.2	1.8 – 19.8	1.7 – 18.3	1.3 – 17.8	1.2 – 18.5
*OtherAP**	0 – 1.2	0 – 1.4	0 – 0.18	0 – 0.21	0 – 11.1	0 – 13.9	0	0 – 0.3	0 – 0.2	2.5 – 65.5

*(ACA)Acetylsalicylic Acid, *(Clop)Clopidogrel, *(VKA)Vitamin-K antagonist, *(NOAC)New Oral Anticoagulant, *(ACE)Angiotensin Converting Enzyme, *(OtherAP) Brillique/Efient.

Figure S1. Temporal change in use of medication from 1997 to 2016 for PAD, PAD MI, PAD Stroke, and PAD AF.



*(ASA)Acetylsalicylic Acid, *(VKA)Vitamin-K antagonist, *(NOAC)New Oral Anticoagulant, *(ACE)Angiotensin Converting Enzyme.
(PAD) Peripheral artery disease, (MI) Myocardial infarction, (AF) Atrial fibrillation