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*Published in:*
European Journal of Vascular and Endovascular Surgery

*DOI (link to publication from Publisher):*
10.1016/j.ejvs.2024.02.002



*Publication date:*
2024

*Document Version*
Publisher's PDF, also known as Version of record

Eur J Vasc Endovasc Surg (2024) 67, 948—957



ORIGINAL ARTICLE

# Adherence and Persistence to Antiplatelet Therapy in Lower Extremity Peripheral Arterial Disease: A Danish Population Based Cohort Study

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**WHAT THIS PAPER ADDS**

This population based nationwide cohort study investigated adherence to antiplatelet therapies in patients with lower extremity peripheral arterial disease (PAD). Among 39 687 individuals with an inpatient or outpatient diagnosis of symptomatic PAD, $<$ 60% claimed a guideline directed prescription for any aspirin or clopidogrel agent within 90 days of diagnosis. Adherence to antiplatelet therapy was moderate during the first year after diagnosis. Overall, 13.0% had discontinued treatment at one year follow up, and 31.5% at three year follow up. These novel findings emphasise the need to enhance initiation and monitor adherence to medical prescriptions during structured follow up.

**Objective:** Adherence to antiplatelet therapy is recommended but unexplored in patients with symptomatic lower extremity peripheral arterial disease (PAD). Therefore, this study aimed to determine adherence and persistence to antiplatelet therapy in patients with PAD, defined as intermittent claudication and chronic limb threatening ischaemia.

**Design:** Population based nationwide cohort study.

**Methods:** This study included all Danish citizens aged $\geq$ 40 years with a first inpatient or outpatient diagnosis of symptomatic PAD between 2010 — 2017, and who had at least one prescription claim for aspirin and/or clopidogrel within 90 days after diagnosis. Adherence was determined by the proportion of days covered (PDC) during the first year after diagnosis. Persistence was defined as no treatment gap $\geq$ 30 days between prescription renewals over three year follow up.

**Results:** A total of 39 687 patients were eligible for inclusion, of whom 23 279 (58.7%) claimed a prescription for aspirin and/or clopidogrel within 90 days of diagnosis. Among these, 12 898 (55.4%) were *prevalent users*, while the remainder comprised *new users* who initiated the therapy after the index PAD diagnosis. The mean PDC was 74.5% (SD 35.0%) for prevalent users and 60.5% (SD 30.5%) for new users. Adherence increased with age and number of concomitant drugs. The overall one year cumulative incidence treatment discontinuation was 13.0% (95% CI 12.5 — 13.4%) overall, 17.2% (CI 16.6 — 17.9%) for prevalent users, and 7.9% (CI 7.4 — 8.4%) for new users. At three year follow up, the cumulative incidence of discontinuation was 31.5% (CI 30.9 — 32.2%) overall, 44.6% (CI 43.7 — 45.4%) for prevalent users, and 14.6% (CI 13.9 — 15.3) for new users.

**Conclusion:** Less than 60% of patients with newly diagnosed symptomatic PAD claimed a prescription for antiplatelet therapy within 90 days of diagnosis, and both adherence and persistence were moderate during the first year after diagnosis. These findings underscore the importance of efforts to improve the initiation and continuation of antiplatelet therapy in patients with PAD.

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https://doi.org/10.1016/j.ejvs.2024.02.002

Keywords: Adherence, Antiplatelet therapy, Peripheral artery disease, Persistence, Secondary prevention
Article history: Received 8 September 2023, Accepted 2 February 2024, Available online 8 February 2024


## INTRODUCTION

Lower extremity peripheral arterial disease (PAD) is a severe and progressive atherosclerotic vascular disorder currently affecting approximately 237 million people worldwide and half of all people with diabetes during their lifetime.[1,2] Within five years of diagnosis, 9 — 48% of individuals with intermittent claudication and 25 — 88% of those with chronic limb threatening ischaemia will be amputated or die.[3–5] In addition to lower limb disease deterioration, PAD is also associated with an increased risk of myocardial infarction and ischaemic stroke.[6,7]

To address these risks, current guidelines recommend lifelong secondary prevention with antithrombotic therapy and statins (or other lipid-modifying drugs) for all patients with symptomatic PAD, combined with risk factor management to halt progression and minimise risks of major limb and cardiovascular events.[8–12] Despite well established guidelines with strong evidence and high risk of adverse outcomes associated with PAD, studies have consistently reported suboptimal use of secondary preventive therapies in this patient group.[13–18] Estimates indicate that a substantial proportion of patients with symptomatic PAD, ranging 35.7 — 90%, do not receive the recommended preventive therapy.[13–17] However, many of these studies have determined antiplatelet therapy use based on a single prescription claim[14,15,17,19–22] or self reported use,[13,16] potentially leading to an overestimation of antiplatelet use.[23] Adherence (taking drugs as prescribed[24]) and persistence (continuation without interruption or discontinuation[25]) to secondary prevention treatment in patients with PAD have not been well investigated.[26–28] This is a concern, since inadequate adherence and persistence to antiplatelet therapy may compromise the overall efficacy of preventive and invasive treatment, leading to avoidable morbidity and mortality.[29,30] Therefore, this study aimed to investigate adherence and persistence with antiplatelet therapy in a large Danish nationwide cohort of patients with an incident diagnosis of symptomatic PAD.

## METHODS

This registry based nationwide cohort study examined the Danish population aged $\geq$ 40 years and with an incident PAD diagnosis between 1 January 2010 and 31 December 2017.

### *Setting and data source*

The Danish healthcare system provides universal, nationwide, tax supported healthcare, guaranteeing unfettered access to general practitioners and hospitals.[31] Using national administrative health registries, the study identified patients diagnosed with symptomatic PAD. Specifically, it linked the following registries: 1) the Danish Civil Registration System, which holds information on sex, date of birth, vital and emigration status;[32] 2) the National Patient Registry, which holds information on dates of admission and discharge diagnoses classified according to the Danish modification of the International Classification of Diseases (ICD);[31] 3) the Danish National Prescription Registry containing information on purchase date, Anatomical Therapeutic Chemical (ATC) classification codes, and package size for all prescriptions since 1994;[33] 4) the Danish Education Registers holding information on highest completed education;[34] and 5) the Income Statistics Registry with information on household income to adjust for socioeconomic confounders.[35] All information obtained from the registries was linked using the personal identification number provided to all permanent residents of Denmark at birth or migration.[36]

### *Study population*

All Danish individuals aged $\geq$ 40 years with an incident inpatient or outpatient diagnosis of symptomatic PAD (ICD-10: I702, I739A, I739C, and I74) during the study period were identified. Patients aged $\leq$ 40 years were excluded, as ischaemia in younger individuals is often due to trauma or iatrogenic injury, and unrelated to PAD. The cohort was then restricted to patients who had at least one prescription claim of antiplatelet therapy (aspirin or clopidogrel) within 90 days after diagnosis, requiring patients to survive this 90 day period. Given the focus on adherence and persistence, patients with indications for oral anticoagulant therapy (atrial fibrillation, venous thromboembolism, mitral stenosis, and mechanical heart valve) were excluded. The patients were categorised as *prevalent users* and *new users* based on their established use of antiplatelet therapy at the time of index diagnosis. Prevalent users were defined as patients with prescription claims for antiplatelet therapy in the year before diagnosis; the date of incident PAD diagnosis was applied as the index date. New users were defined as patients with no antiplatelet therapy use in the year before diagnosis; the index date was defined as the date of the first antiplatelet therapy prescription claim following diagnosis.

### *Baseline covariables and follow up*

The following baseline factors were assessed: demographic factors (dichotomised sex and age); socioeconomic factors, defined by cohabiting status (living together or living alone); education level (>/< 12 years of education); available household income (continuous variable of household income/year in tertile of the study population); level of peripheral vascular morbidity (intermittent claudication, chronic limb threatening ischaemia, or acute limb ischaemia); other comorbidities; and concurrent medication

use, defined as redeeming each drug, differentiated by the fifth level of the ATC code (the chemical substance), at least twice within the previous 12 months. The ATC groups that were considered were the following: A (alimentary tract and metabolism), B (blood and blood forming organs), C (cardiovascular system), H (systemic hormonal preparations, except reproductive hormones and insulin), M (musculoskeletal system), and R (respiratory system). Patients' adherence to antiplatelet therapy was ascertained within one year after the index date, based on data on prescription frequency, package size, and the defined daily dose. For assessment of persistence, patients were followed for up to three years after the index date, until outcome, death, or administrative censoring on 31 December 2018, whichever came first.

### Adherence

Adherence to antiplatelet therapy was estimated by the proportion of days covered (PDC), defined as the total number of days with one tablet of antiplatelet therapy available in the year following the index date. The calculation of the PDC accounted for the package size for each prescription claim, assuming an intake of one tablet per day according to the package label. For patients who died within the first year of diagnosis, the PDC was measured until the date of death. For prevalent users, pre-supply of antiplatelet therapy was included in the calculation. Carry-over was also granted for early refills of the same drug in both prevalent and new users, but not for switching between aspirin and clopidogrel. Information on in hospital medication dispensing was not available and not accounted for. Good adherence to antiplatelet therapy was defined as a PDC $>$ 80%, moderate as 50 $-$ 80%, and poor as $<$ 50%, as in previous studies.[26,37] A gap day was defined as any day when antiplatelet therapy would be unavailable according to prescription claims and calculated tablets available.

### Persistence

Persistence with antiplatelet therapy was defined as the duration of time from the first prescription claim after PAD diagnosis to treatment discontinuation within a period of up to three years following the index date. Non-persistence was defined as a prescription gap of $>$ 30 days after the estimated last day covered by the cumulative acquired tablets of the prescribed medication. To calculate the length of the period covered by medication, all tablets carried over from early prescription claims were considered. Like the adherence analysis, the availability of one tablet of antiplatelet therapy (aspirin or clopidogrel) per day was used to calculate persistence. The start of non-persistence was defined as the first day after the end of the period covered by the prescribed medication to indicate discontinuation.

### Statistical analysis

Baseline characteristics of prevalent and new users were described using frequencies and percentages for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables. Adherence was assessed by calculation of the PDC in the first year after PAD diagnosis, overall, and within strata of sex, living status, age group, education level, level of peripheral vascular morbidity, baseline use of statins and other lipid modifying drugs, and baseline number of concomitant drugs. Persistence was assessed as the cumulative incidence and 95% CI of non-persistence using the Aalen—Johansen estimator, considering death as a competing event. The risk of non-persistence was depicted by the cumulative incidence function over the three year follow up period. Mortality was assessed using the Aalen—Johansen estimator and depicted by the cumulative incidence function over the three year follow up period.

To explore the impact of the 90 day threshold for classifying use of antiplatelet therapy after diagnosis, an analysis was conducted allowing patients up to 365 days to claim a prescription of antiplatelet therapy following diagnosis. Additionally, to examine the effect change in treatment indication, a sensitivity analysis was performed assessing the cumulative incidence of discontinuation, censoring patients who initiated oral anticoagulant therapy during follow up. A sensitivity analysis was also performed to evaluate adherence allowing a prescription gap of 30 days. Lastly, a sensitivity analysis was performed allowing for varying prescription gaps of 0 and 60 days when estimating antiplatelet therapy treatment periods in the persistence analysis. All analyses were conducted using STATA version 17.0 (StataCorp LP, College Station, TX, USA).

### Ethical approval and data availability

This study was based on data from Statistics Denmark and conducted in compliance with the General Data Protection Regulation through institutional registration (record number 2017-509-00006), which does not require ethical approval according to Danish law.[36] Owing to data protection rules, individual level data are unable to be shared. Researchers who fulfil the requirements set by the data providers could obtain similar data.

## RESULTS

Among 39 687 Danish patients with an incident symptomatic lower extremity PAD diagnosis, 23 279 patients (58.7%) had a prescription claim for antiplatelet therapy within 90 days after the diagnosis. Among patients with antiplatelet therapy prescription claims, 12 898 patients (55.4%) were prevalent users who already used antiplatelet therapy at diagnosis, while 10 381 patients (44.6%) were classified as new users who initiated antiplatelet therapy after index diagnosis (Fig. 1). Based on the initial prescription claim after diagnosis, aspirin was the predominant antiplatelet drug prescribed, although use of clopidogrel increased over time (Supplementary Figure S1). Table 1 shows baseline characteristics according to antiplatelet history. Prevalent users had a median age of 72 years (IQR 65, 79), and 42.0% were female. The median age for new users was 68 years (IQR 60, 75), and 46.3% were female. Diabetes and

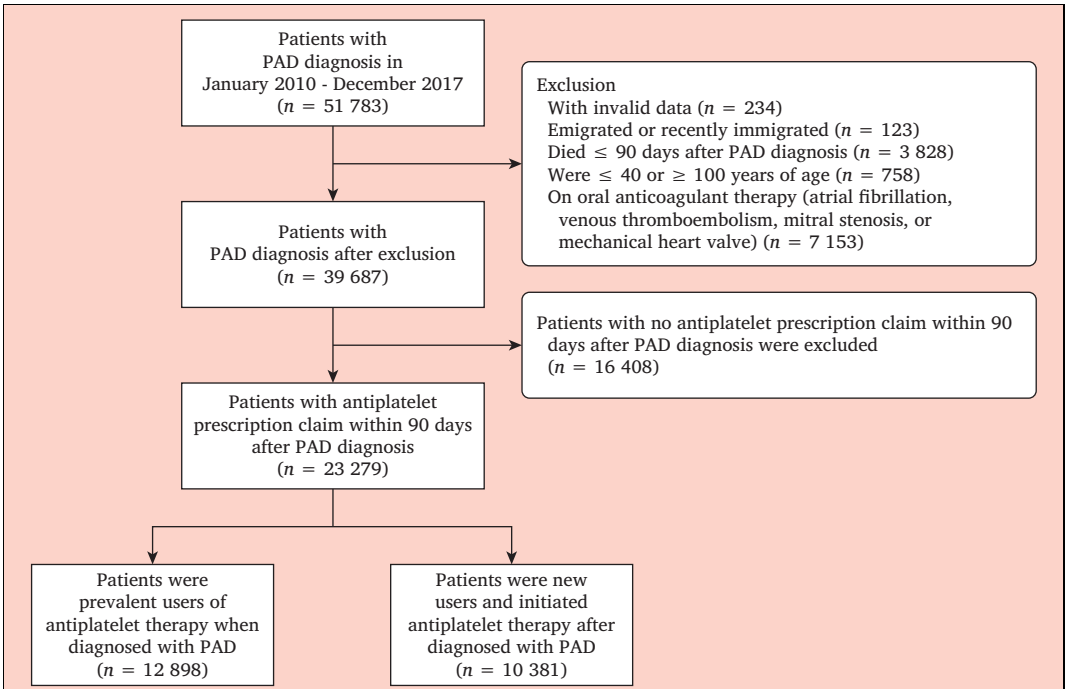


**Figure 1.** Identification of patients with lower extremity peripheral arterial disease (PAD) for analyses of adherence and persistence with antiplatelet therapy. PAD = peripheral arterial disease.

cardiovascular diseases were more often diagnosed in prevalent users, for example: diabetes (26.3% of prevalent users *vs.* 11.4% of new users), hypertension (70.9 *vs.* 41.5%), ischaemic heart disease (43.0 *vs.* 8.2%), and stroke (22.6 *vs.* 4.6%) (Table 1). Medication history in the 365 days before the index date was more common in prevalent users, with a median of five drugs (IQR 3, 7) compared with two (IQR 0, 4) for new users. At baseline, 76.1% of prevalent users and 29.0% of new users were treated with statins or other lipid modifying drugs.

### *Adherence to antiplatelet therapy*

The overall one year adherence to antiplatelet therapy, as estimated by the mean PDC, was 67.5% (SD 32.5) among all users. When stratified by antiplatelet history, it was 74.5% (SD 35.0) for prevalent users, and 60.5% (SD 30.5) for new users. This level of adherence changed little over time (Fig. 2). Table 2 presents adherence according to different subgroups. Mean adherence was higher in women than in men (70.0 *vs.* 66.5%) and increased with age (59.5 in patients aged 40 – 59 years *vs.* 73.5% in patients aged ≥ 80 years) and number of concomitant drugs (61.5 in patients with ≤ 3 concomitant drugs *vs.* 79.5% in patients with ≥ 7 concomitant drugs). Across all strata, adherence was higher in prevalent users than among new users who initiated antiplatelet therapy following PAD diagnosis.

### *Persistence with antiplatelet therapy*

The one year cumulative incidence of discontinuation with antiplatelet therapy after PAD diagnosis was 13.0% (CI 12.5 – 13.4%) for all users, 17.2% (CI 16.6 – 17.9%) for prevalent users, and 7.9% (CI 7.4 – 8.4%) for new users. Figure 3 shows the cumulative incidence function for discontinuation in prevalent and new users of antiplatelet therapy. The incidence of treatment discontinuation varied little across patient subgroups, but discontinuation was more frequent among males, patients in the youngest age group, with high education, and with intermittent claudication (Table 3). Conversely, persistence increased with the increasing number of concomitant drugs. Across all strata, the incidence of discontinuation was higher in prevalent users compared with new users of antiplatelet therapy.

At three year follow up, the overall cumulative incidence of non-persistence with antiplatelet therapy was 31.5% (CI 30.9 – 32.2%). Among prevalent users, the cumulative incidence was 44.6% (CI 43.7 – 45.4%), while it was 14.6% (CI 13.9 – 15.3%) among new users. Supplementary Table S1 shows the three year cumulative incidence of discontinuation across subgroups.

### *Mortality*

The overall one year cumulative mortality was 6.1% (CI 5.8 – 6.4%), 7.2% (CI 6.7 – 7.6%) among prevalent users, and 4.7% (CI 4.3 – 5.1%) among new users. At three year follow up, the overall cumulative mortality was 17.3% (CI 16.8 – 17.8%), 20.2% (CI 19.4 – 20.9%) among prevalent users, and 13.8% (CI 13.1 – 14.5%) among new users (Supplementary Fig. S2).

### *Supplementary and sensitivity analyses*

Supplementary and sensitivity analyses yielded results consistent with the main analyses. Extending the time to initiation of antiplatelet therapy beyond 90 days after PAD

**Table 1. Baseline patient characteristics according to antiplatelet therapy use at lower extremity peripheral arterial disease (PAD) diagnosis**

| Patient characteristics | Prevalent users ($n$ = 12 898) | New users ($n$ = 10 381) |
|---|---|---|
| *Demographic factors* | | |
| Sex − female | 42.0 (5 416) | 46.3 (4 803) |
| Age − years | 72.0 (65.0, 79.0) | 68.0 (60.0, 75.0) |
| *Age group − years* | | |
| 40–59 | 12.0 (1 552) | 23.2 (2 404) |
| 60–79 | 65.9 (8 504) | 63.4 (6 579) |
| ≥ 80 | 22.0 (2 842) | 13.5 (1 398) |
| *Socioeconomic factors and social history* | | |
| *Living status* | | |
| Cohabiting | 53.1 (6 849) | 50.2 (5 215) |
| *Education level* | | |
| Low | 84.9 (10 944) | 84.0 (8 715) |
| High | 11.9 (1 537) | 13.2 (1 368) |
| Unknown | 3.2 (417) | 2.9 (298) |
| *Available household income/year* | | |
| Lowest tertile | 25.1 (3 237) | 24.4 (2 531) |
| Middle tertile | 40.6 (5 238) | 35.1 (3 641) |
| Highest tertile | 34.3 (4 423) | 40.5 (4 209) |
| *Vascular morbidity* | | |
| Intermittent claudication | 59.1 (7 619) | 59.3 (6 157) |
| Chronic limb threatening ischaemia* | 37.1 (4 791) | 33.0 (3 422) |
| Acute limb ischaemia | 3.8 (488) | 7.7 (802) |
| *Medical history and comorbidities* | | |
| Diabetes | 26.3 (3 389) | 11.4 (1 186) |
| Hyperlipidaemia | 28.9 (3 722) | 6.4 (669) |
| Hypertension | 70.9 (9 142) | 41.5 (4 313) |
| Heart failure | 24.2 (3 127) | 6.6 (690) |
| Ischaemic heart disease | 43.0 (5 544) | 8.2 (856) |
| Stroke | 22.6 (2 914) | 4.6 (482) |
| Chronic obstructive pulmonary disease | 14.1 (1 822) | 10.8 (1 123) |
| Chronic kidney disease | 8.6 (1 106) | 3.3 (345) |
| Cancer | 12.3 (1 581) | 11.6 (1 207) |
| Any bleeding | 20.7 (2 666) | 13.8 (1 432) |
| Dementia | 1.8 (231) | 0.6 (64) |
| Psychiatric diseases† | 4.3 (561) | 3.1 (321) |
| Obesity | 7.2 (923) | 3.4 (350) |
| *Medication history* | | |
| Statins and other lipid modifying drugs | 76.1 (9 816) | 29.0 (3 008) |
| Renin–angiotensin inhibitor (ARB or ACE inhibitor) | 64.6 (8 327) | 38.6 (4 012) |
| Beta blocker | 43.2 (5 574) | 15.7 (1 625) |
| Calcium channel blocker | 40.7 (5 247) | 25.6 (2 653) |
| Loop diuretics | 23.6 (3 041) | 8.4 (871) |
| Non-loop diuretics | 46.5 (5 998) | 30.8 (3 197) |
| Non-steroidal anti-inflammatory drug | 24.8 (3 197) | 29.3 (3 039) |
| *Number of drugs* | 5 (3, 7) | 2 (0, 4) |
| ≤ 3 types of medication | 31.7 (4 091) | 72.9 (7 571) |
| 4–6 types of medication | 38.8 (5 000) | 20.0 (2 076) |
| ≥ 7 types of medication | 29.5 (3 807) | 7.1 (734) |

Data are shown as % ($n$) or median (IQR). ACE = angiotensin converting enzyme; ARB = angiotensin receptor blockers; IQR = interquartile range.

* Chronic limb threatening ischaemia includes ischaemic rest pain, ulcer, and gangrene.

† Psychiatric diseases include schizophrenia, depression, and personality disorder.

diagnosis did not materially change the proportion of patients not initiating treatment (Supplementary Fig. S3).

Censoring patients if they initiated oral anticoagulant therapy resulted in a slightly lower cumulative incidence of discontinuation. At three year follow up, the overall cumulative incidence of antiplatelet therapy discontinuation was 29.9% (CI 29.3 − 30.5%), with an cumulative incidence of 41.8% (CI 40.9 − 42.74%) among prevalent users and 14.8% (CI 14.1 − 15.5) among new users.

Allowing a 30 day gap in the analyses of one year adherence showed a similar conclusion as the main analyses, with higher levels of adherence observed with an increasing number of gap days (e.g., overall mean PDC of 85.5% (SD 24.0), 92.5% among prevalent users, and 78.5%

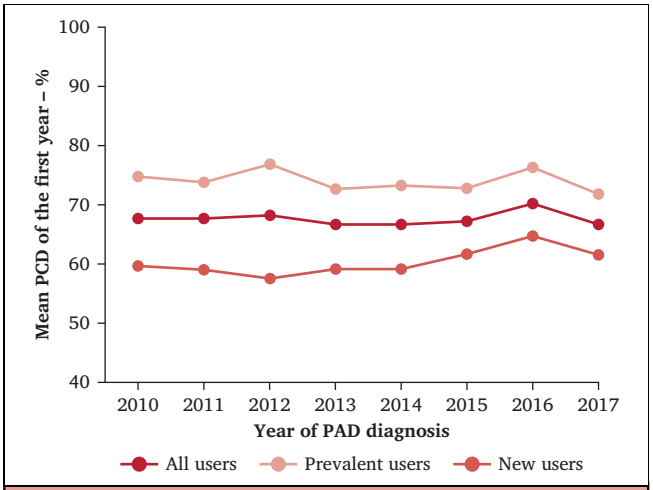


**Figure 2.** Temporal changes in mean proportion of days covered (PDC) the first year after diagnosis of lower extremity peripheral arterial disease (PAD) overall and according to antiplatelet therapy use at the time of diagnosis.

among new users), indicating good one year adherence (Supplementary Table S2).

Sensitivity analyses considering different prescription gaps when estimating non-persistence were also consistent with the main analyses (Supplementary Tables S3 and S4), demonstrating an expected increase in non-persistence with shorter prescription gaps and a decrease with longer gaps. The three year cumulative incidence of non-persistence ranged 27.1 — 41.0%, depending on the allowed prescription gap (Supplementary Table S4).

## DISCUSSION

This population based nationwide cohort study of patients with incident symptomatic PAD in a highly centralised Western European country found that < 60% claimed a prescription for antiplatelet therapy within 90 days after their index diagnosis. This emphasises suboptimal initiation of secondary prevention in a vulnerable population with multiple comorbidities. Moreover, among patients who initiated guideline directed antiplatelet therapy, adherence was modest across all subgroups. Thereby, prevalent users had higher adherence than new users. Overall, 13.0% discontinued antiplatelet therapy within the first year following diagnosis, which increased to 31.5% at three year follow up.

### *Comparison with previous studies*

The finding that six of 10 patients claimed a prescription of antiplatelet following PAD diagnosis is consistent with previous studies reporting estimates of antiplatelet therapy ranging 35.7 — 90%.[13—18,38—41] Recent studies examining temporal changes in the use of secondary preventive therapy

**Table 2. One year mean proportion of days covered (PDC) according to antiplatelet therapy use at lower extremity peripheral arterial disease (PAD) diagnosis**

| | All users ($n$ = 23 279) | Prevalent users ($n$ = 12 898) | New users ($n$ = 10 381) |
|---|---|---|---|
| Total | 67.5 (32.5) | 74.5 (35.0) | 60.5 (30.5) |
| *Sex* | | | |
| Female | 70.0 (33.0) | 76.5 (35.5) | 63.5 (30.5) |
| Male | 66.5 (34.0) | 73.0 (34.0) | 58.0 (30.5) |
| *Age group — years* | | | |
| 40—59 | 59.5 (33.0) | 67.0 (37.0) | 55.0 (30.0) |
| 60—79 | 68.5 (33.5) | 74.5 (34.5) | 62.0 (30.5) |
| ≥ 80 | 73.5 (33.0) | 78.5 (33.5) | 64.0 (30.0) |
| *Living status* | | | |
| Living together | 67.5 (33.5) | 74.0 (35.0) | 60.0 (30.5) |
| Living alone | 68.5 (33.5) | 75.0 (35.0) | 61.5 (30.5) |
| *Education level* | | | |
| Low | 68.5 (33.5) | 74.5 (34.5) | 61.0 (30.5) |
| High | 65.0 (34.0) | 72.0 (35.5) | 58.0 (30.5) |
| Unknown | 70.0 (33.5) | 76.5 (34.5) | 62.0 (30.5) |
| *Vascular morbidity* | | | |
| Intermittent claudication | 67.0 (33.5) | 74.0 (35.0) | 59.5 (30.5) |
| Chronic limb threatening ischaemia* | 70.0 (33.5) | 75.5 (35.0) | 63.0 (30.0) |
| Acute limb ischaemia | 65.0 (33.0) | 71.0 (35.0) | 61.5 (31.0) |
| *Statins and other lipid modifying drugs at baseline* | | | |
| Yes | 71.0 (34.0) | 75.0 (34.5) | 60.5 (30.5) |
| No | 64.5 (32.5) | 73.0 (35.5) | 61.0 (30.5) |
| *Number of drugs at baseline* | | | |
| ≤ 3 types of medication | 61.5 (33.0) | 67.5 (36.5) | 58.5 (30.5) |
| 4—6 types of medication | 71.5 (34.0) | 74.5 (35.0) | 65.5 (30.0) |
| ≥ 7 types of medication | 79.5 (32.5) | 81.5 (31.5) | 70.0 (29.5) |

Data are shown as mean % (standard deviation). PDC = proportion of days covered.
* Chronic limb threatening ischaemia includes ischaemic rest pain, ulcer, and gangrene.

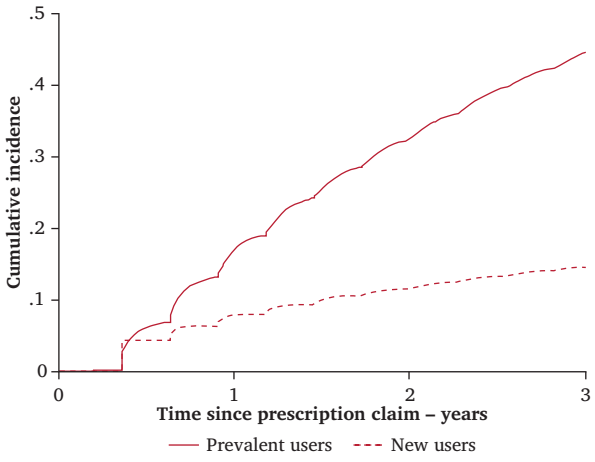


**Figure 3.** Cumulative incidence of non-persistence in prevalent and new users of antiplatelet therapy after lower extremity peripheral arterial disease (PAD) diagnosis.

for PAD have reported improvements over time.[19–22,42] In Denmark, the use of antiplatelet therapy in patients with PAD increased from 3.5% in 1997 to 61.0% in 2016.[20] Another Danish study including patients with PAD undergoing vascular interventions reported an increase from 57.3% in 2000 – 2004 to 64.3% in 2013 – 2016.[42] Moreover, a study in Scotland found that 84% of patients hospitalised for a cardiovascular event initiated antiplatelet therapy. Notably, initiation rates varied across types of vascular events, with patients with PAD having the lowest initiation rate at 68% (compared with 94% following a myocardial infarction and 83% following an ischaemic stroke).[43] As such, the implementation of secondary medical prevention in patients with PAD remains modest, leaving a substantial proportion of patients with potential for optimised medical treatment.

Two previous studies have investigated adherence as measured by the PDC in patients with PAD. The first study was based on data from a Danish vascular screening trial involving 65 – 74 year old men, and reported that 60% of new users initiated antiplatelet therapy within 120 days after screening.[28] Consistent with the current findings, adherence was higher among prevalent users at baseline compared with new users: 58% of new users and 89% of prevalent users had good adherence in the following five years.[28] The second study examined adherence to antiplatelet therapy in a cohort of 9 178 Slovakian patients with PAD and aged > 65 years. This study reported a mean PDC of 89.6% over the following five years.[26] The high level of adherence in this study might have been related to the older population, as the current findings indicate higher adherence with increasing age. In comparison, the one year adherence to antiplatelet therapy in other cardiovascular diseases have been reported to range from 46 – 84% among patients with myocardial infarction.[44–46] Another study found that 60% of patients admitted with a cardiovascular event remained adherent to antiplatelet therapy one year after admission.[47]

Few studies have investigated persistence with antiplatelet therapy in patients with PAD. A study reported that 33% of Slovakian patients with PAD were non-persistent after five years.[27] This is lower than observed in the current study but may be attributable to differences in treatment gaps. Patients were considered non-persistent if they had a treatment gap > 30 days in the current study, while the Slovakian study accepted gaps of up to six months before defining patients as non-persistent. The Danish vascular screening study also investigated persistence, reporting that 21% of prevalent users and 33% of new users had discontinued antiplatelet therapy at five year follow up.[28] The current study observed a higher level of discontinuation in prevalent users than new users: prevalent users had a higher burden of comorbidities than new users, which to some extent may have been associated with treatment discontinuation.

Taken together, the limited available evidence suggests suboptimal adherence and persistence with antiplatelet therapy in patients with PAD, probably for multifactorial reasons. Treatment initiation and adherence as well as lifestyle modification are also highly influenced by the patient's individual understanding of their condition and associated cardiovascular risks. Studies have shown that patients with PAD often underestimate risks of cardiovascular disease, limb thrombosis, and amputation associated with PAD.[48,49] Previous studies have demonstrated that patients diagnosed with PAD are less likely to fulfil a prescription for antiplatelet therapy after diagnosis compared with patients with coronary artery disease,[19] aortic aneurysms,[28] myocardial infarction,[38] or PAD in combination with other cardiovascular diseases.[20] This might reflect clinicians' focus on immediate secondary prevention following severe cardiovascular events or deficiencies in physician knowledge and attitudes toward the importance of atherosclerotic risk factor treatment.[50,51] However, it is important to acknowledge that adherence and persistence to antiplatelet therapy can be influenced by various factors, including patient demographics, comorbidities, and medication side effects.

### *Clinical implications*

These findings may have clinical implications and generate important hypotheses. It is well established that antiplatelet therapy reduces morbidity, mortality, and limb related outcomes in patients with PAD.[8–10,52] However, despite some improvements in the use of secondary prevention over the past decade, the current findings indicate that medical treatment remains suboptimal among patients with PAD, contributing to impaired cardiovascular health and increased risk of adverse outcomes.[20] The current study further underscores the need for clinical follow up to ensure appropriate medication use and monitor adherence to prescribed drugs, as also emphasised by the recent European Society for Vascular Surgery (ESVS) clinical practice guideline.[12] Special attention should be given to antiplatelet therapy naive patients, as the current study found low initiation and modest adherence.

**Table 3. Estimated one year cumulative incidence of non-persistence with antiplatelet therapy according to antiplatelet therapy use at lower extremity peripheral arterial disease (PAD) diagnosis**

| | All users ($n$ = 23 279) | Prevalent users ($n$ = 12 898) | New users ($n$ = 10 381) |
|---|---|---|---|
| Total | 13.0 (12.5–13.4) | 17.2 (16.6–17.9) | 7.9 (7.4–8.4) |
| *Sex* | | | |
| Female | 11.9 (11.3–12.5) | 16.2 (15.2–17.2) | 7.1 (6.4–7.9) |
| Male | 13.8 (13.2–14.4) | 18.0 (17.1–18.9) | 8.5 (7.8–9.3) |
| *Age group – years* | | | |
| 40–59 | 15.5 (14.4–16.7) | 24.8 (22.6–27.0) | 9.8 (8.7–11.1) |
| 60–79 | 12.7 (12.1–13.2) | 16.7 (15.9–17.6) | 7.6 (7.0–8.3) |
| ≥ 80 | 11.6 (10.7–12.6) | 14.6 (13.3–16.0) | 5.7 (4.6–7.0) |
| *Living status* | | | |
| Living together | 13.4 (12.8–14.1) | 17.4 (16.5–18.3) | 8.4 (7.6–9.2) |
| Living alone | 12.5 (11.9–13.1) | 17.0 (16.1–18.0) | 7.3 (6.7–8.1) |
| *Education level* | | | |
| Low | 12.7 (12.3–13.2) | 16.9 (16.2–17.6) | 7.7 (7.2–8.3) |
| High | 15.3 (14.0–16.6) | 20.9 (18.8–23.0) | 9.2 (7.8–10.8) |
| Unknown | 10.4 (8.3–12.8) | 13.4 (10.3–16.9) | 6.4 (4.0–9.6) |
| *Vascular morbidity* | | | |
| Intermittent claudication | 14.4 (13.8–14.9) | 18.0 (17.1–18.9) | 10.0 (9.3–10.8) |
| Chronic limb threatening ischaemia* | 10.7 (10.1–11.4) | 15.5 (14.5–16.6) | 4.3 (3.7–5.0) |
| Acute limb threatening ischaemia | 12.3 (10.6–14.2) | 21.7 (18.1–25.5) | 6.7 (5.1–8.6) |
| *Statins and other lipid modifying drugs at baseline* | | | |
| Yes | 14.2 (13.5–14.8) | 16.7 (16.0–17.5) | 6.0 (5.2–6.9) |
| No | 11.5 (10.9–12.2) | 18.9 (17.5–20.3) | 8.6 (8.0–9.3) |
| *Number of drugs at baseline* | | | |
| ≤ 3 types of medication | 14.1 (13.4–14.7) | 23.5 (22.2–24.9) | 9.2 (8.5–9.8 |
| 4–6 types of medication | 12.4 (11.7–13.2) | 15.8 (14.8–16.8) | 4.7 (3.8–5.6) |
| ≥ 7 types of medication | 11.0 (10.1–12.0) | 12.5 (11.5–13.6) | 3.4 (2.3–4.9) |

Data are shown as % (95% confidence interval).
* Chronic limb threatening ischaemia includes ischaemic rest pain, ulcer, and gangrene.

### *Strengths and limitations*

This study was strengthened by the large national sample of patients with PAD with detailed and precise data on drug dispensing and comorbid conditions. It also had limitations that should be acknowledged when interpreting the results. The use of administrative health registries has inherent limitations, as identification of patients with PAD relies on accurate coding. A validation study indicated a positive predictive value of PAD diagnoses in the Danish National Patient Registry of 69.4%,[53] but the actual positive predictive value may be higher, as the main reason for rejected diagnoses was lack of clinical information in the medical records to confirm the diagnosis. While misclassification or inclusion of patients with asymptomatic PAD cannot be ruled out, relying on PAD diagnoses from a hospital setting emphasised that patients sought medical attention due to symptomatic experiences, as asymptomatic PAD cases are not typically referred to hospitals in Denmark. Prescription data were used to estimate medical adherence and persistence. Although aspirin is available over the counter in Denmark, most low dose (75 – 150 mg) aspirin purchases (92% in 2012) are dispensed by prescription, and patients are reimbursed.[54] Moreover, the calculation of adherence may have been affected by the packaging size of antiplatelet therapy, typically available in packages of 100 tablets. Additionally, the use of national health registries did not allow determination of whether patients took their medications as prescribed, and the reasons for discontinuation could not be identified nor could who decided to discontinue the treatment (i.e., the patient or the physician) be differentiated. However, censoring patients who initiated oral anticoagulant therapy had minimal impact on the cumulative incidence of discontinuation, arguing against that a change in treatment indication could explain the high incidence of discontinuation. Finally, the analyses only assessed the first discontinuation and did not account for whether patients subsequently re-initiated therapy.

### *Conclusion*

This Danish nationwide cohort study of patients diagnosed with PAD demonstrated that < 60% of patients claimed a prescription for antiplatelet therapy following diagnosis. Among treated patients, treatment adherence was modest in the year following diagnosis, particularly among new users. At three years, one third had discontinued antiplatelet therapy. These findings underscore the importance of efforts to improve the initiation and continuation of antiplatelet therapy to prevent progression and adverse cardiovascular events in this high risk population.

### SOURCE OF FUNDING

This study was partly funded by Karen Elise Jensens Foundation. The foundation had no role in the design or conduction of the study.

## DISCLOSURES

PBN has received fees for speaking engagements from SERVIER and BMS/Pfizer, fees for consulting from Bayer and Daiichi-Sankyo, and grant support from Bayer and Daiichi-Sankyo Europe. NE has served as an investigator for Bayer and has received fees for speaking engagements from Bayer and AstraZeneca. AAH reports research grants from The Danish Heart Foundation and The Novo Nordisk Foundation, consulting fees from Bayer and The Bristol-Myers Squibb-Pfizer Alliance, speaker bureaus from Bayer, The Bristol-Myers Squibb-Pfizer Alliance, and Merck Sharp & Dohme, and role as vice chair of special interest group venous thromboembolism of Danish Nurses' Council. All other authors declare no conflicts of interest.

## APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2024.02.002.

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