Journal of the American Heart Association

ORIGINAL RESEARCH

Long-Term Effectiveness and Safety of Initiating Statin Therapy After Index Revascularization In Patients With Peripheral Arterial Occlusive Disease

Frederik Peters, MSc, PhD; Jenny Kuchenbecker, MSc; Thea Kreutzburg, MSc; Ursula Marschall, MD; E. Sebastian Debus, MD; Christian-Alexander Behrendt, MD

BACKGROUND: An increasing number of patients with a peripheral arterial occlusive disease were put on statins during the past years. This study assessed whether statin therapy was effective and safe for these new users.

METHODS AND RESULTS: Using health insurance claims data from Germany's second-largest insurance fund, BARMER, we identified patients with peripheral arterial occlusive disease who had index revascularization between 2008 and 2018 without prior statin therapy. We compared patients with and without statin therapy in addition to antithrombotics during the first quarter after discharge (new users versus nonusers). Outcomes were all-cause mortality, cardiovascular events, and incident major amputation for effectiveness and incident diabetes mellitus and incident myopathy for safety. Propensity score matching was used to balance the study groups. All analyses were stratified into patients with chronic limb-threatening ischemia and intermittent claudication. A total of 22 208 patients (mean age 71.1 years and 50.3% women) were included in the study. In 10 922 matched patients, statin initiation was associated with lower all-cause mortality (chronic limb-threatening ischemia: hazard ratio [HR], 0.75 [95% CI, 0.68–0.84]; intermittent claudication: HR, 0.80 [95% CI, 0.70–0.92]), lower risk of major amputation in patients with chronic limb-threatening ischemia (HR, 0.73; 95% CI, 0.58–0.93) and lower risk of cardiovascular events (hazard ratio, 0.80; 95% CI, 0.70–0.92) in patients with intermittent claudication during 5 years of follow-up. Safety outcomes did not differ among the study groups.

CONCLUSIONS: Initiating statin therapy in patients with peripheral arterial occlusive disease after index revascularization is efficient and safe with an effect size comparable to earlier studies. Awareness campaigns for evidence-based optimal pharmacological treatment among patients are recommended.

Key Words: chronic limb-threatening ischemia ■ intermittent claudication ■ peripheral arterial occlusive disease ■ statin-induced myopathy ■ statin therapy

During the past decades, various pharmacological therapies for vascular diseases became available, effectively preventing cardiovascular events.[1] Valid guidelines consistently emphasize the importance of the prescription of statins in patients with peripheral arterial occlusive disease (PAOD) irrespective of their concomitant risk profile as a cornerstone of secondary prevention.[2–7] Patients with PAOD are particularly dependent on optimal pharmacological treatment because of considerably elevated risks of cardiovascular events, acute limb ischemia, and amputation markedly impairing quality of life.[8–10] Yet, this subgroup exhibits particularly low utilization rates of statins as compared with patients with coronary artery disease or a history of stroke.[11,12]

Correspondence to: Christian-Alexander Behrendt, Department of Vascular Medicine, Research Group GermanVasc, University Medical Center Hamburg-Eppendorf, Hamburg, Germany. E-mail: behrendt@hamburg.de

Supplementary Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.120.018338

For Sources of Funding and Disclosures, see pages 11 and 12.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What is New?

- This is the first study assessing long-term benefits and harms of initiating statin therapy after lower limb revascularization for symptomatic peripheral arterial occlusive disease in a real-world setting.
- The proportion of patients initiating statin therapy doubled throughout the study period but is still substantially below societal guideline recommendations.
- Initiating statin therapy is effective and safe in patients with intermittent claudication or chronic limb-threatening ischemia.

What Are the Clinical Implications?

- Awareness campaigns emphasizing the importance of prescribing statins in the follow-up of patients should involve general practitioners and other medical specialist disciplines.
- The surveillance of patients after invasive revascularizations should comprise regular interviews for optimal pharmacological treatment and patient compliance.
- Health insurance claims can be used to automatically identify patients with potential for improvement in secondary prevention.

Nonstandard Abbreviations and Acronyms

ATC	Anatomical Therapeutic Chemical
CLTI	chronic limb-threatening ischemia
IC	intermittent claudication
ICD-10-GM	International Classification of Diseases, Tenth Revision, German Modification
PAOD	peripheral arterial occlusive disease

The underutilization of statin therapy has been predominantly ascribed to the lack of awareness about risks and therapy options among providers and patients[12,13] and concerns about adverse reactions such as myopathy and onset of diabetes mellitus.[14–16] Given the solid evidence of the benefits of statin therapy and, at the same time, the sharp increase in hospitalizations and costs related to PAOD, experts urge providers to push efficient secondary prevention more insistently.[17]

Recent observational studies confirmed that statins are effective and safe in both low- and high-risk patients with PAOD[18,19] and offer additional benefits at high-intensity doses.[18,20] Although these studies differed in study design and sample composition, they arrived at similar conclusions comparable to findings from randomized controlled trials.

Fueled by intensified guideline recommendations, statin utilization rates increased throughout the past decade among patients with PAOD.[21] In the current study, we determine the success of the expansion of statins in PAOD treatment and the impact on major outcomes in the longer term. This may contribute to the understanding of how effects measures in randomized controlled trials translate to the heterogenous real-world population and to what extent the benefit of the drug diminishes as prescription rates increase. This concept was recently discussed for other domains of health care.[22]

Our study employed a large nationwide database for quantifying the long-term effectiveness and safety of initiating statin therapy in symptomatic patients with PAOD after index revascularization. We aimed to quantify to what degree the initiation of statin therapy prolongs survival, reduces the risk for major amputation and cardiovascular events, and potentially increases the risk of the onset of diabetes mellitus or myopathy.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request. Our study complies with the Declaration of Helsinki 2013. Several review boards determined that using factual anonymized data from claims or national statistics retrospectively is not considered human subject research because deidentified data sets were used. All analyses were in accordance with the European Union's General Data Privacy Regulation, taking into account the theoretical concept of k-anonymity. Thus, patient informed consent was not obtained for this retrospective secondary data analysis. Our study is part of a larger project on outcomes of patients with PAOD after revascularization. Further details regarding this project can be found in the published study protocol (clinicaltrials.gov NCT03909022).[23]

Sample and Database

The longitudinal data of Germany's second-largest insurance fund, BARMER, includes the outpatient and inpatient medical care provided to ≈9.4 million German citizens (13.2% of Germany's population) involving >21 million hospitalizations between January 1, 2008, and December 31, 2018. The BARMER cohort is similar to Western European countries and has been widely used for research projects.[24,25] A regular random sample validation of internal and

external validity is performed by the Medical Service of the Health Funds in Germany, and various peer-reviewed validation studies have been previously published.[26,27]

The diagnoses and comorbidities routinely collected in health insurance claims data follow the commonly accepted international standard for reporting diseases and health conditions using World Health Organization *International Classification of Diseases, Tenth Revision, German Modification* (*ICD-10-GM*), operations and procedures codes, and the German version of the international Anatomical Therapeutic Chemical (ATC) classification.

In our analyses, we created separate cohorts for Fontaine stage II labeling intermittent claudication (IC) and Fontaine stages III to IV labeling chronic limb-threatening ischemia (CLTI) (for detailed coding see Table S1). We included patients with a primary diagnosis of IC (I70.22 until 2014 and I70.21-22 since 2015) and CLTI (I70.22-24 until 2014 and I70.23-25 since 2015) or IC and CLTI as a secondary diagnosis in combination with a primary diagnosis of diabetic foot syndrome (E10.50-51, E10.7, E11.50-51, E11.7), other peripheral vascular diseases (I73), arterial embolism and thrombosis (I74), cellulitis of the finger and toe including acute lymphangitis (L03.01-02, L03.11), or chronic ulcer of skin and gangrene (L98.4, R02) using the *ICD-10-GM*.

The index admission for symptomatic PAOD (denoted as index stay) was identified between January 1, 2008, and December 31, 2018, with follow-up until December 31, 2018. We used 3-year lookback in the BARMER data set[26] to create relevant comorbidities (available data going back to 2005) and to ensure index admission for symptomatic PAOD.

Statin-naive patients (statins: ATC coding C10AA, C10BA, or C10BX) without statin utilization for at least 3 years before index stay were selected for inclusion in our study. We further included only patients with at least 1 prescription for an antithrombotic agent (eg, acetylsalicylic acid, clopidogrel, or oral anticoagulation) during the first quarter after discharge to prevent selection bias caused by prevalent users.[5]

The following patients were excluded: patients aged <40 years, patients with prior major amputation or recorded myopathy (outpatient or inpatient), patients discharged without revascularization (amputation only or best medical treatment only) and death, patients with major amputation, and patients with cardiovascular events (myocardial infarction, stroke or transient ischemic attack) during the first quarter after discharge. Further, we excluded patients treated with other lipid-lowering drugs than statins or statin combinations during the first quarter after discharge to ensure that all patients were eligible for statin prescription. Few cases with missing information on age, sex, or follow-up (≈0.5%) were removed using complete case deletion.

Study Variables

We identified new users as patients filling at least 1 prescription for statins during the first quarter after index stay. Patients not filling a statin prescription during the quarter after index stay were denoted as nonusers.

The primary outcome was all-cause mortality during follow-up. In German claims data, the information about the death of the insured person is complete and validated.[27]

Secondary outcomes were incident major amputation and cardiovascular events (myocardial infarction, stroke, or transient ischemic attack), obtained from primary and secondary inpatient diagnoses.

Safety outcomes were incident diabetes mellitus and incident myopathy. Specifically, incidence was defined as first diagnosis after discharge from index stay. For assessing the risk of developing diabetes mellitus, we further excluded patients with diabetes mellitus during the 3 years before the index stay. For measuring incident outcomes, we evaluated both outpatient and inpatient diagnoses and, in the case of diabetes mellitus, also the prescription of oral and parenteral antidiabetic agents.[28] For detecting myopathy, we used the broader list of conditions previously used for the identification of statin-associated myopathy in German claims data.[29]

All outcomes were recorded at 3 months after discharge from index stay until the first event or end of study time. Follow-up times were censored after 5 years to compute robust 5-year event probabilities.

Statistical Analysis

We summarized baseline characteristics of the patients with means and SDs for normally distributed variables, medians and interquartile ranges for non-normally distributed variables, or percentages and standardized differences for discrete variables. Cochrane Armitage trend test was used to test the change in the proportion of statin therapy over the calendar year. To balance study groups, nearest neighbor propensity score matching was applied using the following variables: discharge year; age; sex; van Walraven score: category 0 (–19 to –1 points), category 1 (0 points), category 2 (1–9 points), and category 3 (10 points and more); congestive heart failure, cardiac arrhythmias; chronic pulmonary disease; renal failure; depression; prior stroke or transient ischemic attack; smoking; obesity; prior myocardial infarction; dyslipidemia; coronary artery disease; diabetes mellitus (complicated and uncomplicated); cancer; hypertension; prior outpatient

diagnosis of PAOD; number of different prescriptions; number of previous inpatient admissions; number of prior PAOD outpatient visits; invasive procedures (peripheral vascular intervention, peripheral vascular intervention, or open-surgical revascularization); and hospital length of stay. The linear van Walraven sum score and most of the comorbidities are based on the list of Elixhauser categories, also used in various other claims data analyses.[30] We evaluated the validity of these comorbidities over time thoroughly in an earlier study.[25]

Incident diabetes mellitus was assessed in a reduced cohort additionally excluding patients with any inpatient or outpatient diagnosis of diabetes mellitus or prescription for antidiabetic agents during the 3 years before the index stay. Since this exclusion affected the balance of the study groups, we performed a second propensity score matching for this cohort (without diabetes mellitus as a matching variable).

Outcomes were estimated using Kaplan-Meier curves (with log-rank test) and Cox proportional hazards models. Using hazard ratios (HRs), we computed the 5-year probability of each outcome with 95% CIs for each study group.

For sensitivity analyses, we estimated Cox proportional hazards models in the unmatched data using the matching variables as covariates. We estimated models adjusting for co-medication during the 3 months after discharge (angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors [ATC code C09A-D], calcium channel blockers [ATC code C08], β-blockers [ATC code C07], and oral anticoagulation [ATC code B01AA, B01AE, or B01AF]), and models stratified by sex, models stratified by age [age <75 years and ≥75 years], models stratified by calendar time (2008–2012 and 2013–2018), and models stratified by statin intensity (low-to-moderate and high).

The data processing was performed with software SAS version 9.04 (SAS Institute Inc) and R software version 3.3.3 (package survival and MatchIt,[31] The R Foundation for Statistical Computing). We reported results using the Reporting of Studies Conducted Using Observational Routinely Collected Health Data statement, the Strengthening the Reporting of Observational Studies in Epidemiology statement,[32] and following international recommendations on medical device evaluation studies.[33]

RESULTS

Unmatched Study Sample

A total of 22 208 symptomatic patients with PAOD (22.2% with CLTI, 50.3% women; Table S2) were hospitalized during the study period from January 1, 2008, to December 31, 2018, undergoing invasive revascularization (Figure 1 and Table 1). The average age was 71.1±11.6 years (median follow-up, 1277 days; interquartile range, 616–1827). In our study sample, the annual proportion of new users after discharge increased between 2008 and 2018 from 17% to 34% in patients with CLTI (P<0.001) and from 22% to 43% in patients with IC (P<0.001) (Figure S1).

In the CLTI group, when compared with nonusers, new users were younger (71.6 versus 76.1 years), less often women (51.0% versus 55.9%), and more often smokers (18.9% versus 12.4%) (Table 1). Moreover, new users experienced fewer comorbidities, with a van Walraven score of >9 points in 29.5% versus 43.0% when compared with nonusers. Dyslipidemia was diagnosed more often in new users than in nonusers (40.5% versus 14.4%). New users were treated less frequently and less intensely before index admission with respect to the number of different prescriptions, prior PAOD outpatient diagnosis, previous inpatient admissions, and prior PAOD outpatient visits.

In the IC group, when compared with nonusers, new users were younger (66.4 versus 69.0 years) and more often smokers (25.0% versus 21.1%), but there were no sizable differences with respect to sex. New users experienced fewer comorbidities, with a van Walraven score of >9 points in 10.7% versus 17.6% when compared with nonusers. Dyslipidemia was diagnosed in 45.4% of the new users and 14.8% of the nonusers. New users were treated less frequently and less intensely before index admission with respect to the number of different prescriptions, prior PAOD outpatient diagnosis, previous inpatient admissions, and prior PAOD outpatient visits.

The proportion of patients undergoing open surgical revascularization (bypass, endarterectomy) when compared with endovascular revascularization was less prevalent in new users than in nonusers for IC (20.7% versus 27.2%).

Matched Study Sample

Using the propensity score, we matched 10 922 patients with PAOD: 4 224 (38.7%) patients with CLTI and 6 698 patients with IC (Figure 1 and Table S3). Demographics and comorbidities of the matched study sample are presented in Table 2. In total, 89.2% new users could be matched to nonusers and no clinically relevant standardized differences among the study groups remained after matching.

Prescription Prevalence for Statins and Antithrombotic Agents

Among 18 095 patients with CLTI and 30 424 patients with IC, 43.4% in the CLTI group and 54% in the IC group received both antithrombotics and statins after

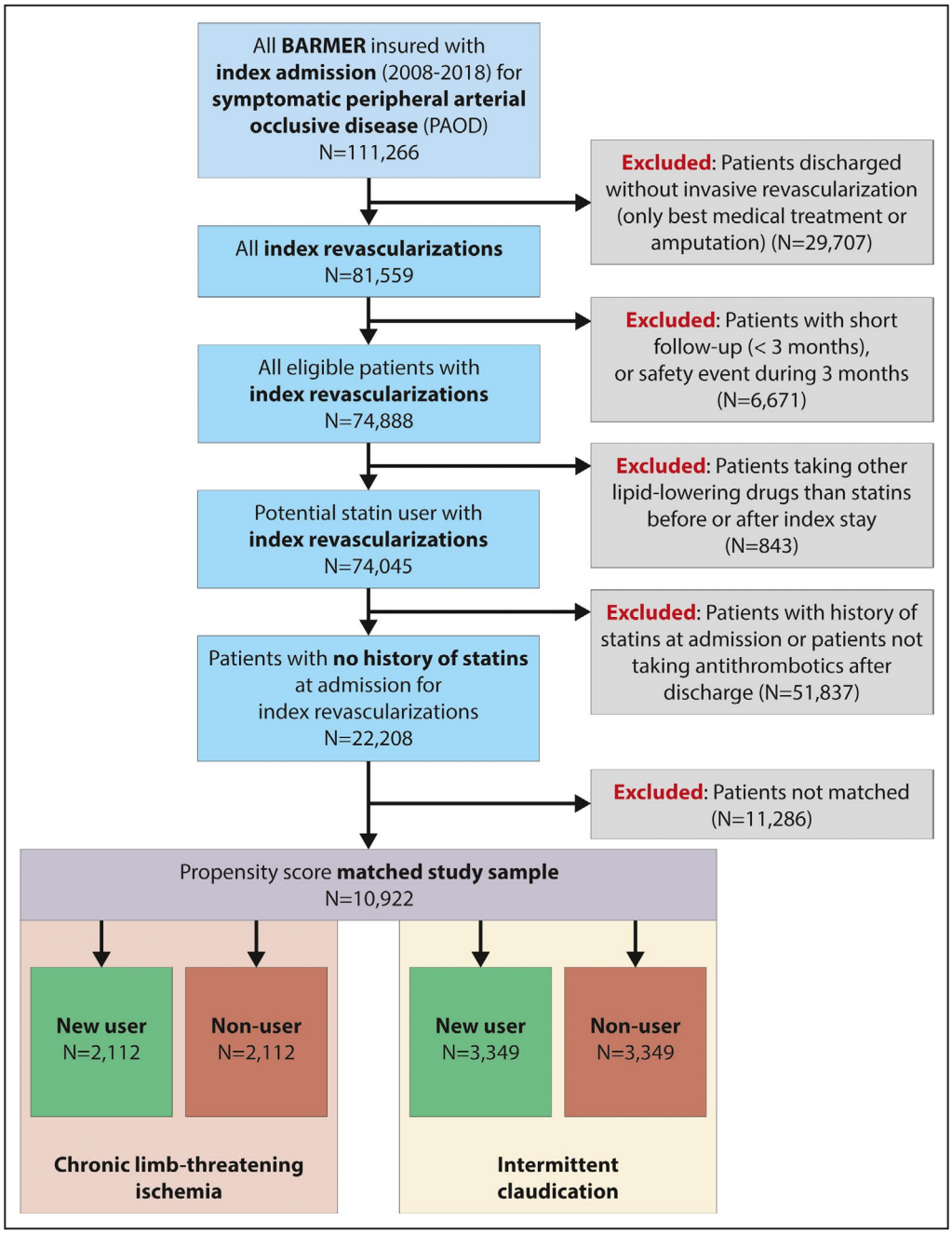


Figure 1. Study flow chart.

index stay, which was 36.4% in CLTI and 39% in IC before admission (Figure 2). Neither receiving statins before or after index stay (nonusers, red flows in Figure 2) was the case in 37.3% (18.5% with and 20.8% without antithrombotics before) of patients with CLTI and 28% (9.9% with and 18.1% without antithrombotics before) in patients with IC. Initiating statin therapy after index stay (new users, green flows in Figure 2) was the case in 13.1% (4.1% with and 9% without antithrombotics before) of patients with CLTI and 13.9% (3.4% with and 10.5% without antithrombotics before) of patients with IC.

Independent Predictors of Receiving Statins in the Matched Study Sample

The most important predictors of initiating statin therapy in the CLTI group were dyslipidemia (odds ratio [OR], 4.50; 95% CI, 4.01–5.06), discharge year (OR, 1.10; 95% CI, 1.08–1.12), age (OR, 0.89; 95% CI, 0.87–0.92), number of different prescriptions (OR, 0.86; 95% CI, 0.82–0.89), and prior myocardial infarction (OR, 1.60; 95% CI, 1.22–2.10) (Figure S2). In the IC group, the most important predictors of initiating statin therapy were dyslipidemia (OR, 5.19; 95% CI, 4.73–5.68), discharge

Table 1. Baseline Characteristics of the Unmatched Study Cohort (N=22 208)

Variable	New Users, CLTI n=2367	Nonusers, CLTI n=7096	Standardized Differences*	New Users, IC n=4227	Nonusers, IC n=8518	Standardized Differences*
Age, mean (SD), y	71.64 (11.73)	76.09 (11.52)	0.382	66.44 (10.27)	69.00 (10.70)	0.245
Women, n (%)	1208 (51.0)	3969 (55.9)	0.098	1981 (46.9)	4008 (47.1)	0.004
Van Walraven score >9, n (%)	698 (29.5)	3052 (43.0)	0.284	454 (10.7)	1503 (17.6)	0.199
Congestive heart failure, n (%)	445 (18.8)	1970 (27.8)	0.213	275 (6.5)	841 (9.9)	0.123
Cardiac arrhythmias, n (%)	519 (21.9)	2414 (34.0)	0.272	373 (8.8)	1288 (15.1)	0.195
Chronic pulmonary disease, n (%)	302 (12.8)	1130 (15.9)	0.09	481 (11.4)	1154 (13.5)	0.066
Renal failure, n (%)	593 (25.1)	2336 (32.9)	0.174	511 (12.1)	1235 (14.5)	0.071
Depression, n (%)	176 (7.4)	591 (8.3)	0.033	196 (4.6)	449 (5.3)	0.029
Prior stroke or TIA, n (%)	99 (4.2)	420 (5.9)	0.079	72 (1.7)	205 (2.4)	0.05
Smoking, n (%)	448 (18.9)	882 (12.4)	0.179	1057 (25.0)	1794 (21.1)	0.094
Obesity, n (%)	206 (8.7)	674 (9.5)	0.028	304 (7.2)	712 (8.4)	0.044
Prior myocardial infarction, n (%)	127 (5.4)	293 (4.1)	0.058	101 (2.4)	196 (2.3)	0.006
Dyslipidemia, n (%)	959 (40.5)	1023 (14.4)	0.611	1919 (45.4)	1261 (14.8)	0.707
Coronary artery disease, n (%)	437 (18.5)	1439 (20.3)	0.046	434 (10.3)	1132 (13.3)	0.094
Diabetes mellitus, any, n (%)	821 (34.7)	2658 (37.5)	0.058	692 (16.4)	1787 (21.0)	0.118
Cancer, any, n (%)	120 (5.1)	464 (6.5)	0.063	166 (3.9)	514 (6.0)	0.097
Hypertension, n (%)	1717 (72.5)	5413 (76.3)	0.086	2771 (65.6)	5820 (68.3)	0.059
Prior outpatient diagnosis PAOD, n (%)	651 (27.5)	2288 (32.2)	0.104	1049 (24.8)	2816 (33.1)	0.183
No. of different prescriptions, median (IQR)	11.00 (5.00–17.00)	14.00 (9.00–21.00)	0.396	8.00 (5.00–13.00)	10.00 (6.00–16.00)	0.304
No. of previous inpatient admissions, total (including index), median (IQR)	2.00 (1.00–3.00)	2.00 (1.00–4.00)	0.237	1.00 (1.00–2.00)	2.00 (1.00–3.00)	0.207
No. of prior PAOD outpatient visits, median (IQR)	1.00 (0.00–3.00)	1.00 (0.00–5.00)	0.145	1.00 (0.00–2.00)	1.00 (0.00–4.00)	0.213
Invasive procedure: OSR, n (%)	914 (38.6)	2714 (38.2)	0.008	876 (20.7)	2317 (27.2)	0.152
Hospital length of stay, days, median (IQR)	12.00 (7.00–21.00)	12.00 (7.00–22.00)	0.009	4.00 (3.00–8.00)	4.00 (3.00–9.00)	0.082

CLTI indicates chronic limb-threatening ischemia; IC, intermittent claudication; IQR, interquartile range; OSR, open surgical revascularization; PAOD, peripheral arterial occlusive disease; and TIA, transient ischemic attack.

*Values >0.1 were deemed to indicate meaningful differences.

year (OR, 1.10; 95% CI, 1.08–1.11), age (OR, 0.92; 95% CI, 0.90–0.94), number of different prescriptions (OR, 0.88; 95% CI, 0.85–0.91), and open surgical repair at index stay (OR, 0.68; 95% CI, 0.61–0.77) (Figure S3).

Long-Term Effectiveness Outcomes in the Matched Study Sample

Compared with nonusers, both in the CLTI and the IC groups, new users had a significant lower probability for all-cause mortality (for CLTI: HR, 0.75 [95% CI, 0.68–0.84]; for IC: HR, 0.80 [95% CI, 0.70–0.92]) (Table 3). Further, statin initiation was associated with a lower risk of major amputation (HR, 0.73; 95% CI, 0.58–0.93) in CLTI and a lower risk for cardiovascular events (HR, 0.80; 95% CI, 0.70–0.92) in IC. In absolute terms, statin initiation was associated with 8.8% lower probability of dying in the CLTI group (37.3% versus 46.1%) and 3.4% lower probability of dying in the IC group (15.5% versus 18.9%). The survival benefit of new users compared with nonusers increased over time in CLTI and was stable in IC (Figure 3). The probability for major amputation was 2.9% lower in the CLTI group (8.4% versus 11.3%) and for cardiovascular events was 3.3% lower in the IC group (15.2% versus 18.5%). The amputation benefit in CLTI increased over time (Figure S4), while the benefit in respect to cardiovascular events in IC was stable (Figure 3).

Long-Term Safety Outcomes in the Reduced Matched Study Sample

We did not detect significant differences in the probability for incident diabetes mellitus (in the reduced sample) or myopathy between the study groups (Table 3 and Figure S4).

Sensitivity Analyses

The results for effectiveness outcomes and safety outcomes were largely similar when fitting the Cox models directly to the unmatched data (Figure S5).

Table 2. Baseline Characteristics of the Matched Study Cohort (N=10 922)

Variable	New Users, CLTI n=2112	Nonusers, CLTI n=2112	Standardized Differences*	New Users, IC n=3349	Nonusers, IC n=3349	Standardized Differences*
Age, mean (SD), y	72.52 (11.64)	72.67 (12.05)	0.012	67.10 (10.31)	67.34 (10.47)	0.023
Women, n (%)	1100 (52.1)	1106 (52.4)	0.006	1564 (46.7)	1589 (47.4)	0.015
Van Walraven score >9, n (%)	673 (31.9)	723 (34.2)	0.05	411 (12.3)	438 (13.1)	0.024
Congestive heart failure, n (%)	422 (20.0)	444 (21.0)	0.026	251 (7.5)	263 (7.9)	0.013
Cardiac arrhythmias, n (%)	494 (23.4)	555 (26.3)	0.067	334 (10.0)	369 (11.0)	0.034
Chronic pulmonary disease, n (%)	279 (13.2)	280 (13.3)	0.001	403 (12.0)	405 (12.1)	0.002
Renal failure, n (%)	562 (26.6)	602 (28.5)	0.042	417 (12.5)	428 (12.8)	0.01
Depression, n (%)	161 (7.6)	170 (8.0)	0.016	161 (4.8)	157 (4.7)	0.006
Prior stroke or TIA, n (%)	96 (4.5)	111 (5.3)	0.033	62 (1.9)	69 (2.1)	0.015
Smoking, n (%)	362 (17.1)	354 (16.8)	0.01	794 (23.7)	804 (24.0)	0.007
Obesity, n (%)	192 (9.1)	189 (8.9)	0.005	249 (7.4)	263 (7.9)	0.016
Prior myocardial infarction, n (%)	111 (5.3)	116 (5.5)	0.01	76 (2.3)	79 (2.4)	0.006
Dyslipidemia, n (%)	705 (33.4)	714 (33.8)	0.009	1041 (31.1)	1046 (31.2)	0.003
Coronary artery disease, n (%)	387 (18.3)	425 (20.1)	0.046	369 (11.0)	393 (11.7)	0.023
Diabetes mellitus, any, n (%)	741 (35.1)	771 (36.5)	0.03	591 (17.6)	586 (17.5)	0.004
Cancer, any, n (%)	114 (5.4)	120 (5.7)	0.012	138 (4.1)	149 (4.4)	0.016
Hypertension, n (%)	1539 (72.9)	1567 (74.2)	0.03	2182 (65.2)	2227 (66.5)	0.028
Prior outpatient diagnosis PAOD, n (%)	604 (28.6)	626 (29.6)	0.023	900 (26.9)	976 (29.1)	0.051
No. of different prescriptions, median (IQR)	11.00 (6.00–18.00)	12.00 (7.00–18.00)	0.043	9.00 (5.00–14.00)	9.00 (5.00–14.00)	0.038
No. of previous inpatient admissions, total (including index), median (IQR)	2.00 (1.00–3.00)	2.00 (1.00–3.00)	0.033	1.00 (1.00–2.00)	1.00 (1.00–2.00)	0.027
No. of prior PAOD outpatient visits, median (IQR)	1.00 (0.00–3.00)	1.00 (0.00–4.00)	0.022	1.00 (0.00–3.00)	1.00 (0.00–3.00)	0.054
Invasive procedure: OSR, n (%)	816 (38.6)	779 (36.9)	0.036	747 (22.3)	783 (23.4)	0.026
Hospital length of stay, days, median (IQR)	12.00 (7.00–22.00)	12.00 (7.00–22.00)	0.008	4.00 (3.00–8.00)	4.00 (3.00–8.00)	0.007

CLTI indicates chronic limb-threatening ischemia; IC, intermittent claudication; IQR, interquartile range; OSR, open surgical revascularization; PAOD, peripheral arterial occlusive disease; and TIA, transient ischemic attack.

*Values >0.1 were deemed to indicate meaningful differences.

Without adjustment for confounding, statin users had even more favorable effectiveness outcomes, but safety outcomes were hardly affected. The effect of statins was robust to the inclusion of other important medication groups, ie, angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors, calcium channel blockers, β-blockers, or oral anticoagulation (Figure S6). The effect of statins did not significantly differ between men and women, except for amputation in patients with CLTI (HR in women: 0.54 [95% CI, 0.29–0.76]; HR in men: 1.10 [95% CI, 0.85–1.42]) (Figure S7). Stratifying the analysis by age revealed that older patients (≥75 years) benefit most from initiating statins for survival and diabetes mellitus in patients with IC (Figure S8). Further, there were no sizeable differences when stratifying by discharge years (Figure S9). The same was true for statin intensity (patients taking high-intensity statins: n=415, 6.2%), where the CIs for low-to-moderate intensity and high-intensity statins overlapped for all outcomes (Figure S10). We found a significant association between high-intensity statin use and myopathy in patients with IC. No differences were detected when stratifying by procedure type at index stay (Figure S11).

DISCUSSION

This is the first real-world study assessing the effectiveness and safety of initiating statin therapy in symptomatic patients with PAOD after revascularization in a large nationwide cohort. Compared with nonusers, new users of statin therapy had a considerably lower relative and absolute probability of all-cause mortality in both CLTI and IC, major amputation in CLTI, and cardiovascular events in IC. At the same time, the

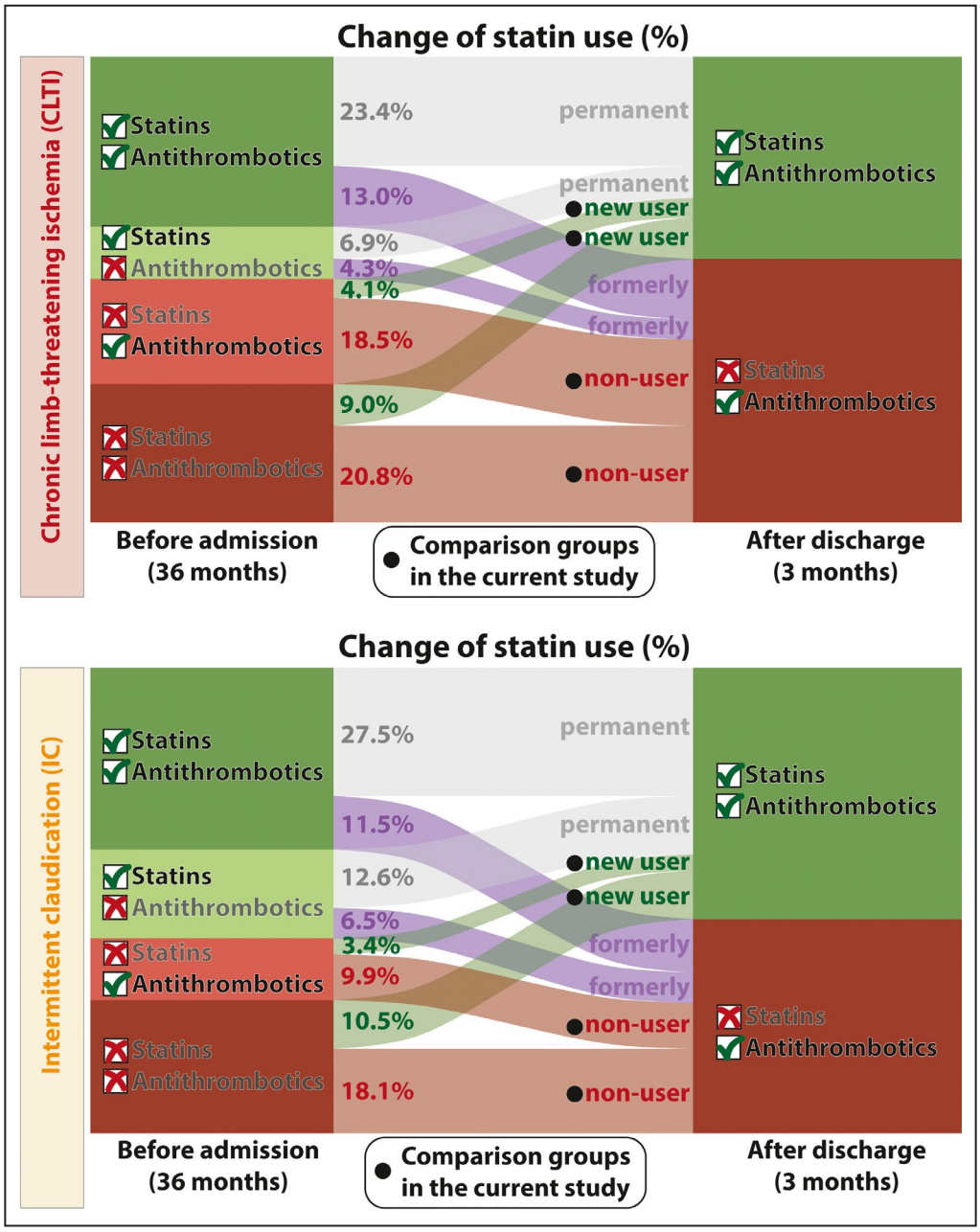


Figure 2. Alluvial diagram illustrating the proportion of new users and nonusers (n=9 463 patients with chronic limb-threatening ischemia [CLTI] and n=12 745 patients with intermittent claudication [IC]) among all statin users meeting the inclusion criteria of the study also showing formerly and permanent use (n=18 095 patients with CLTI and n=30 424 patients with IC).
Shown is the frequency of statin therapy and prescription of antithrombotics during the 3 years before and 3 months after index revascularization for symptomatic peripheral arterial occlusive disease.

incidence of diabetes mellitus and myopathy was not associated with new statin prescription. As same as that documented in primary prevention,[34] we found no evidence for the assumption that new patient groups benefit less from statins, emphasizing the importance of quality improvement and awareness campaigns to further promote their prescription.

Valid guidelines call for more evidence on the comparative effectiveness of pharmacological therapy along the full spectrum of clinical reality.[35] Yet, existing real-world evidence stems from smaller randomized controlled trials with short follow-up or observational studies based on smaller registries, single centers, geographic regions, or predominantly male patients. The particular merit of routinely collected data from health insurance claims is the large sample size, long follow-up, and high variety and completeness of information available to adjust for confounding allowing

Table 3. Probability of Experiencing the Outcomes of Interest Within 5 Years After Index Revascularization in New Users Versus Nonusers of Statin Therapy

Strata	Outcomes of Interest	Probability for New Users (95% CI)	Probability for Nonusers (95% CI)	HR (95% CI)	No.	Events
CLTI	All-cause mortality	37.3 (34.8–39.7)	46.1 (43.5–48.6)	0.75 (0.68–0.84)	4224	1315
CLTI	Major amputation	8.4 (6.9–9.9)	11.3 (9.5–13.1)	0.73 (0.58–0.93)	4224	278
CLTI	Myocardial infarction/stroke/TIA	23.3 (21.0–25.6)	25.7 (23.2–28.1)	0.89 (0.77–1.04)	4224	658
CLTI	Diabetes mellitus	20.3 (17.1–23.3)	20.8 (17.5–23.9)	0.97 (0.77–1.23)	2232	284
CLTI	Myopathy	4.6 (3.4–5.8)	4.0 (2.9–5.2)	1.15 (0.79–1.67)	4224	109
IC	All-cause mortality	15.5 (14.0–17.0)	18.9 (17.3–20.5)	0.80 (0.70–0.92)	6698	805
IC	Major amputation	1.5 (1.0–2.0)	1.6 (1.1–2.1)	0.93 (0.58–1.49)	6698	70
IC	Myocardial infarction/stroke/TIA	15.2 (13.7–16.6)	18.5 (16.9–20.1)	0.80 (0.70–0.92)	6698	788
IC	Diabetes mellitus	15.0 (13.2–16.7)	15.2 (13.3–16.9)	0.99 (0.83–1.18)	4678	490
IC	Myopathy	6.5 (5.5–7.5)	5.4 (4.5–6.4)	1.21 (0.96–1.52)	6698	287

CLTI indicates chronic limb-threatening ischemia; HR, hazard ratio; IC, intermittent claudication; and TIA, transient ischemic attack. All estimates are based on Cox proportional hazards models using the matched data.

study of the full heterogeneity of patients in daily care. Especially, rare and potentially late outcomes, such as major amputations and the incidence of myopathy and diabetes mellitus, could be analyzed with sufficient statistical power.[36,37] We included these safety outcomes, while prior studies focused mostly on effectiveness. Yet, our study present the central findings both for absolute and relative risk differentials. Furthermore, we used both inpatient and outpatient data, and, for the detection of incident diabetes mellitus, corresponding prescriptions. The long lookback and follow-up periods made it possible to minimize the risk of not detecting a large portion of adverse reactions.

Among patients not on statin therapy before index stay, the proportion of statin therapy after index stay doubled during the study period. Yet, still less than half of the patients received statins in 2018, with particularly low rates among patients with CLTI. These interesting and striking results are in line with a previous study concerning sex disparities in optimal pharmacological treatment of symptomatic patients with PAOD in Germany, where only 55% of the patients received a lipid-lowering drug. Notably, there was also preliminary evidence that patient characteristics (eg, age, sex, and comorbidities) were more influential than healthcare variables such as the type of revascularization procedure.[38] Because of the nonrandomized observational study design, all results should be considered as merely hypothesis generating. Hence, it appears challenging to explain the low utilization of statins before as well as after revascularization. Unwarranted variation in best medical treatment can be attributable to a lack of high-level evidence or insufficient application of existing evidence. In terms of statins, similar to antithrombotics, there is good evidence available from many international guidelines.[2,6,7] The relationship between patients, inpatient physicians, and general practitioners is likely affected by a multifactorial system of influencing factors. It seems reasonable to address this healthcare issue with awareness campaigns and actions to improve both prescription prevalence and patient compliance.

Our results confirm findings from a large Swedish cohort study reporting higher statin utilization in patients with IC than in patients with CLTI.[39] Stavroulakis et al[40] presumed that the insufficient use in patients with CLTI might be caused by the paucity of evidence on the benefits of statins with regard to limb outcomes. At the same time, the evidence is accumulating that the walking distance in patients with IC could be positively influenced.[41]

Internationally, large variations in statin utilization rates have been documented, pointing at the role of national healthcare systems (prescription patterns and regulations). For example, only 21% of patients with CLTI in Japan with below-the-knee lesions received statins,[42] while 83% received statins in the US Veterans Affairs Health System.[18] Prescription rates probably differ between reimbursement systems. In Germany, during the study period, medications were solely prescribed within the outpatient sector while hospital physicians communicate their recommendations in the medical report at discharge. Despite continuous efforts in raising awareness for this issue,[17] missed opportunities caused by low undertreatment of patients with PAOD remain.[11]

Recently, Arya et al[18] reported a reduction in all-cause mortality and amputation-free survival of ≈20% for low-to-moderate statins compared with antiplatelets only, which is in line with our findings. Interestingly, our sensitivity analyses suggest that in patients with CLTI, women seem to benefit to a larger extent from

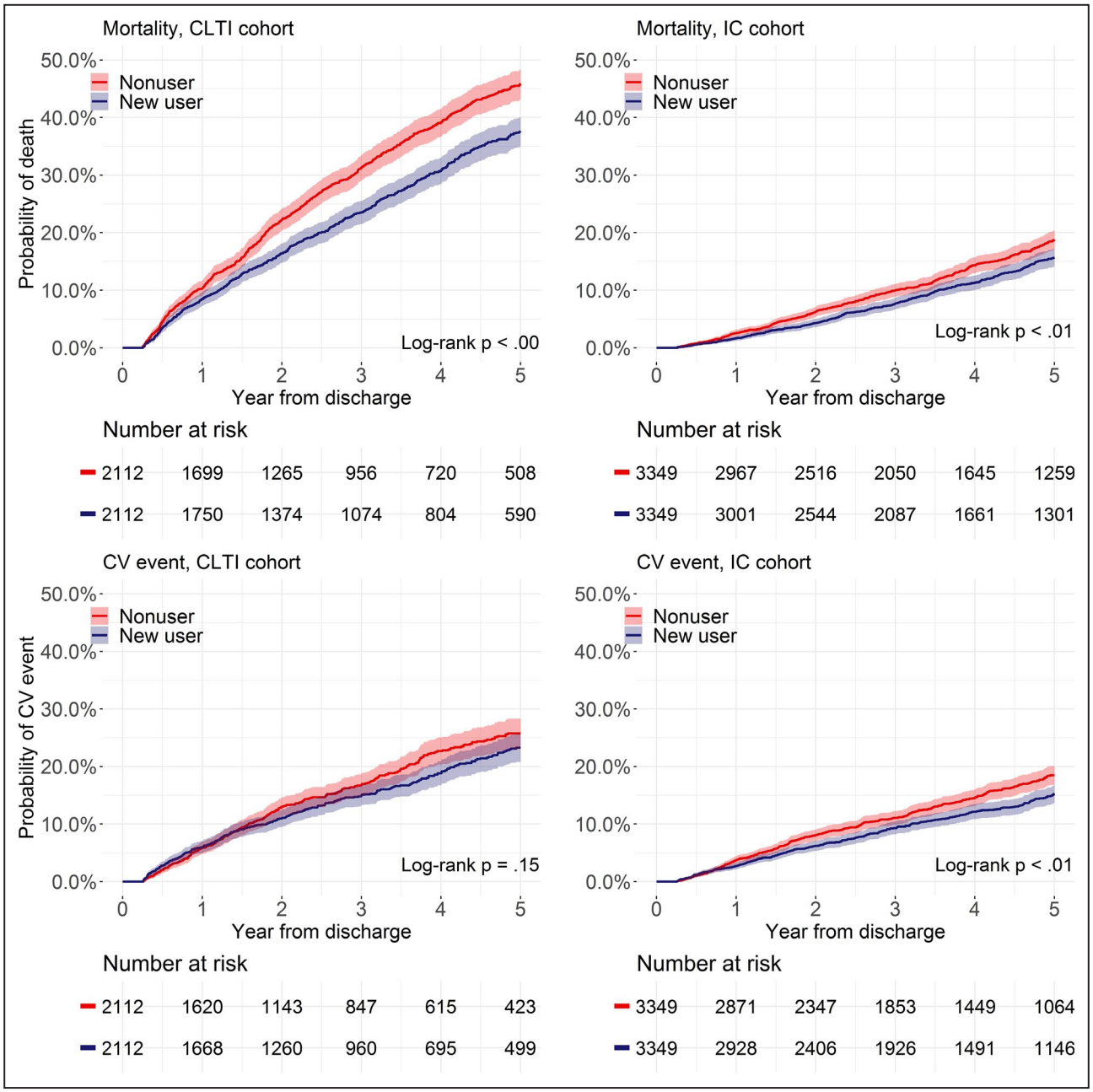


Figure 3. Kaplan-Meier curve of 5-year all-cause mortality (upper panel) and 5-year probability for cardiovascular event (myocardial infarction, stroke, or transient ischemic attack; lower panel) in propensity score–matched cohorts including 95% Wald CI and log-rank test (*P* value).
CLTI indicates chronic limb-threatening ischemia; and IC, intermittent claudication.

statin initiation when compared with men concerning amputation risk. Women were diagnosed more often with asymptomatic or even atypical disease symptoms without appropriate and timely treatment.[43] Thus, they might be more dependent on adequate secondary prevention for preventing severe limb outcomes when compared with their male counterparts.

Statins significantly reduced the risk for major cardiovascular events in most prior studies ranging from reductions in event rates between 10% and 62% (Table S4). Confirming prior reports, our results for the subgroup of patients with IC are situated in the lower end of this range, while the effects were nonsignificant in patients with CLTI. Reports from Swedish patients with PAOD who underwent revascularization also documented more pronounced effects in the IC group than in the CLTI group.[39]

Although many potential adverse reactions have been presumed in the literature, we focused on the established safety outcomes of incident myopathy

and diabetes mellitus.[37] Our study results are in line with prior evidence on the safety of statin therapy in patients with PAOD.[19] Collins et al[37] estimated a minor incident diabetes mellitus risk of ≈1% for a more general population. Moreover, recent guidelines state that the frequency of statin-induced diabetes mellitus strongly depends on the study sample.[44] For example, we even documented a tendency for lowered diabetes mellitus risk for statin initiation among patients with IC aged ≥75 years. This seems to contradict prior evidence, and future studies may focus on the role of age as a modifier in the relationship between diabetes mellitus and statins. Also based on German claims data, Ihle et al[29] reported ≈2% of statin-induced myopathy while Collins et al[37] presumed 0.05%. In our study, the increase in risk ranged in between these estimates with 1.1% in patients with IC and 0.6% in patients with CLTI, and both values being nonsignificant in the final analysis. Interestingly, we detected a significant association between statins and myopathy only for high-intensity statin users in patients with IC in our sensitivity analysis (HR, 2.00; 95% CI, 1.17–3.41). This might be a plausible finding and proof of a dose relationship, as statin toxicity indeed increases with statin dose.[45]

Study Limitations

This is a retrospective propensity score–matched health insurance claims data analysis, so there is no possibility to randomize patients and observe them prospectively. Consequently, the results of this study should be viewed as hypothesis generating and not hypothesis testing. Our propensity score analysis can prevent bias but not fully exclude all sources of bias and residual confounding, eg, that caused by confounding by indication, as compared with randomization. The study groups differed with respect to some of the measured covariates, so that differences in unobserved characteristics that likely confounded our results cannot be ruled out. Yet, as is the case for randomized controlled trials, the quality of observational studies is crucial for assessing the validity of their outcomes. This study applied a rigorous study design with fixed lookback and follow-up, approved methods, transparent reporting of intermediate steps, and extensive sensitivity analyses. We believe that the risk for distortion caused by residual confounding is low in our study since results are broadly in line with findings from randomized controlled trials and prior observational studies (Table S4). Our sample covered only patients insured at one of many different health insurance funds in Germany. Although slightly different from the population composition in Germany,[46] our population-based sample is comparable to current European populations. We, therefore, believe that our results exhibit a larger degree of external validity than veteran data, more narrowly defined subgroups in trials or data from small regional registries or single-center studies. We were not able to address all contraindications, statin intolerance, or other adverse reactions. However, the prevalence of intolerance is unlikely to be larger than a few percent, as previous studies in patients with PAOD have demonstrated. It is therefore unlikely a potential explanation for the low utilization of statin therapy.[5]

The inexistent association of statin use and diabetes mellitus or myopathy risk in our study sample might be caused by insufficiently differentiating by statin type. Since statins differ, inter alia, in derivation and metabolism, varying strengths and limitations of each drug are possible in heterogeneous study populations.[47] To ensure that every patient receives the safest and most effective statin, further investigations stratified by the drug, regarding risk factors in distinct patient groups, are necessary to increase adherence and avert discontinuation.

CONCLUSIONS

We documented increased long-term survival and freedom from amputation and cardiovascular events for initiating statin therapy after revascularization. At the same time, safety concerns about the onset of diabetes mellitus and myopathy could not be confirmed. Our findings indicate that new users of statin therapy benefit as much as common users, emphasizing the importance of quality improvement and awareness campaigns to improve prescription rates.

ARTICLE INFORMATION

Received August 11, 2020; accepted October 12, 2020.

Affiliations

From the Department of Vascular Medicine, Research Group GermanVasc, University Medical Center Hamburg-Eppendorf, Hamburg, Germany (F.P., J.K., T.K., E.S.D., C.-A.B.); and BARMER, Wuppertal, Germany (U.M.).

Acknowledgments

The authors are grateful for the kind support and submission of data from BARMER. Open access funding enabled and organized by Projekt DEAL.

Author contributions: Frederik Peters: conceptualization, methodology, validation, formal analysis, investigation, data curation, writing – original draft, writing – review and editing, visualization. Jenny Kuchenbecker: methodology, validation, formal analysis, data curation, writing – review and editing. Thea Kreutzburg: methodology, validation, formal analysis, data curation, writing – review and editing. Ursula Marschall: writing – review and editing, resources, data curation, validation. Sebastian Debus: writing – review and editing. Christian-Alexander Behrendt: conceptualization, methodology, validation, investigation, writing – original draft, writing – review and editing, visualization, supervision, project administration, funding acquisition.

Sources of Funding

The presented analyses were part of the IDOMENEO project (Funded by the German Joint Federal Committee; grant number 01VSF16008). The GermanVasc research group is additionally supported by the German

Stifterverband and the Corona Foundation (grant number S199/10061/2015), by the German Joint Federal Committee (RABATT study; grant number 01VSF18035), and receives research funds from Bayer Vital GmbH, B. Braun Melsungen AG, and the Foundation of the University Heart and Vascular Center Hamburg. The funders had no influence on the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the article; and decision to submit the article for publication.

Disclosures

None.

Supplementary Material

Tables S1–S4
Figures S1–S11
References 48-71

REFERENCES

1. Yusuf S. Two decades of progress in preventing vascular disease. *Lancet*. 2002;360:2–3.
2. Aboyans V, Ricco JB, Bartelink ME, Bjorck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, et al. 2017 ESC guidelines on the diagnosis and treatment of peripheral arterial diseases, in collaboration with the european society for vascular surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteriesendorsed by: The european stroke organization (ESO)the task force for the diagnosis and treatment of peripheral arterial diseases of the european society of cardiology (ESC) and of the european society for vascular surgery (ESVS). *Eur Heart J*. 2018;39:763–816.
3. Naylor AR, Ricco JB, de Borst GJ, Debus S, de Haro J, Halliday A, Hamilton G, Kakisis J, Kakkos S, Lepidi S, et al. Editor's choice - management of atherosclerotic carotid and vertebral artery disease: 2017 clinical practice guidelines of the european society for vascular surgery (ESVS). *Eur J Vasc Endovasc Surg*. 2018;55:3–81.
4. Morley RL, Sharma A, Horsch AD, Hinchliffe RJ. Peripheral artery disease. *BMJ*. 2018;360:j5842.
5. De Martino RR, Eldrup-Jorgensen J, Nolan BW, Stone DH, Adams J, Bertges DJ, Cronenwett JL, Goodney PP. Vascular Study Group of New England. Perioperative management with antiplatelet and statin medication is associated with reduced mortality following vascular surgery. *J Vasc Surg*. 2014;59:1615–1621, 1621 e1611.
6. Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, Mills JL, Ricco JB, Suresh KR, Murad MH, et al. Global vascular guidelines on the management of chronic limb-threatening ischemia. *Eur J Vasc Endovasc Surg*. 2019;58:S1–S109 e133.
7. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, Fleisher LA, Fowkes FG, Hamburg NM, Kinlay S, et al. 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral artery disease: A report of the american college of cardiology/american heart association task force on clinical practice guidelines. *Circulation*. 2017;135:e726–e779.
8. Criqui MH, Aboyans V. Epidemiology of peripheral artery disease. *Circ Res*. 2015;116:1509–1526.
9. Mustapha JA, Katzen BT, Neville RF, Lookstein RA, Zeller T, Miller LE, Jaff MR. Determinants of long-term outcomes and costs in the management of critical limb ischemia: a population-based cohort study. *J Am Heart Assoc*. 2018;7:e009724. DOI: 10.1161/JAHA.118.009724.
10. Norgren L, Patel MR, Hiatt WR, Wojdyla DM, Fowkes FGR, Baumgartner I, Mahaffey KW, Berger JS, Jones WS, Katona BG, et al. Outcomes of patients with critical limb ischaemia in the euclid trial. *Eur J Vasc Endovasc Surg*. 2018;55:109–117.
11. Subherwal S, Patel MR, Kober L, Peterson ED, Jones WS, Gislason GH, Berger J, Torp-Pedersen C, Fosbol EL. Missed opportunities: Despite improvement in use of cardioprotective medications among patients with lower-extremity peripheral artery disease, underuse remains. *Circulation*. 2012;126:1345–1354.
12. Hirsch AT, Murphy TP, Lovell MB, Twillman G, Treat-Jacobson D, Harwood EM, Mohler ER 3rd, Creager MA, Hobson RW 2nd, Robertson RM, et al. Gaps in public knowledge of peripheral arterial disease: The first national pad public awareness survey. *Circulation*. 2007;116:2086–2094.
13. McDermott MM, Mehta S, Ahn H, Greenland P. Atherosclerotic risk factors are less intensively treated in patients with peripheral arterial disease than in patients with coronary artery disease. *J Gen Intern Med*. 1997;12:209–215.
14. Byrne P, Cullinan J, Smith SM. Statins for primary prevention of cardiovascular disease. *BMJ*. 2019;367:l5674.
15. Krumholz HM. Statins evidence: When answers also raise questions. *BMJ*. 2016;354:i4963.
16. Ahmadizar F, Ochoa-Rosales C, Glisic M, Franco OH, Muka T, Stricker BH. Associations of statin use with glycaemic traits and incident type 2 diabetes. *Br J Clin Pharmacol*. 2019;85:993–1002.
17. Aday AW, Everett BM. Statins in peripheral artery disease: What are we waiting for? *Circulation*. 2018;137:1447–1449.
18. Arya S, Khakharia A, Binney ZO, DeMartino RR, Brewster LP, Goodney PP, Wilson PWF. Association of statin dose with amputation and survival in patients with peripheral artery disease. *Circulation*. 2018;137:1435–1446.
19. Ramos R, Comas-Cufi M, Marti-Lluch R, Ballo E, Ponjoan A, Alves-Cabratosa L, Blanch J, Marrugat J, Elosua R, Grau M, et al. Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: Retrospective cohort study. *BMJ*. 2018;362:k3359.
20. Foley TR, Singh GD, Kokkinidis DG, Choy HK, Pham T, Amsterdam EA, Rutledge JC, Waldo SW, Armstrong EJ, Laird JR. High-intensity statin therapy is associated with improved survival in patients with peripheral artery disease. *J Am Heart Assoc*. 2017;6:e005699. DOI: 10.1161/JAHA.117.005699.
21. Reynolds K, Mues KE, Harrison TN, Qian L, Chen S, Hsu JY, Philip KJ, Monda KL, Reading SR, Brar SS. Trends in statin utilization among adults with severe peripheral artery disease including critical limb ischemia in an integrated healthcare delivery system. *Vasc Med*. 2019:1358863X19871100.
22. Anderson GF, Chalkidou K. Spending on medical care: More is better? *JAMA*. 2008;299:2444–2445.
23. Peters F, Kreutzburg T, Kuchenbecker J, Debus ES, Marschall U, L'Hoest H, Behrendt CA. A retrospective cohort study on the provision and outcomes of pharmacological therapy after revascularization for peripheral arterial occlusive disease: A study protocol. *BMJ Surg Interv Health Technologies*. 2020;e000020.
24. Malyar N, Furstenberg T, Wellmann J, Meyborg M, Luders F, Gebauer K, Bunzemeier H, Roeder N, Reinecke H. Recent trends in morbidity and in-hospital outcomes of in-patients with peripheral arterial disease: A nationwide population-based analysis. *Eur Heart J*. 2013;34:2706–2714.
25. Kreutzburg T, Peters F, Riess HC, Hischke S, Marschall U, Kriston L, L'Hoest H, Sedrakyan A, Debus ES, Behrendt CA. Editor's choice—comorbidity patterns among patients with peripheral arterial occlusive disease in Germany: a trend analysis of health insurance claims data. *Eur J Vasc Endovasc Surg*. 2020;59:59–66.
26. Czwikla J, Jobski K, Schink T. The impact of the lookback period and definition of confirmatory events on the identification of incident cancer cases in administrative data. *BMC Med Res Methodol*. 2017;17:122.
27. Ohlmeier C, Langner I, Hillebrand K, Schmedt N, Mikolajczyk R, Riedel O, Garbe E. Mortality in the German Pharmacoepidemiological Research Database (GEPARD) compared to national data in Germany: Results from a validation study. *BMC Public Health*. 2015;15:570.
28. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: Population based study. *BMJ*. 2013;346:f2610.
29. Ihle P, Dippel FW, Schubert I. Statin-associated myopathy. Assessment of frequency based on data of all statutory health insurance funds in Germany. *Pharmacol Res Perspect*. 2018;6:e00404.
30. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ. A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. *Med Care*. 2009;47:626–633.
31. Ho DE, Imai K, King G, Stuart E. Matching as nonparametric preprocessing for reducing model dependence in parametric causal inference. *Political Analysis*. 2007;15:199–236.
32. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, Initiative S. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *J Clin Epidemiol*. 2008;61:344–349.

33. Sedrakyan A, Marinac-Dabic D, Normand SL, Mushlin A, Gross T. A framework for evidence evaluation and methodological issues in implantable device studies. *Med Care*. 2010;48:S121–128.
34. Ramos R, Garcia-Gil M, Comas-Cufi M, Quesada M, Marrugat J, Elosua R, Sala J, Grau M, Marti R, Ponjoan A, et al. Statins for prevention of cardiovascular events in a low-risk population with low ankle brachial index. *J Am Coll Cardiol*. 2016;67:630–640.
35. Lawrence PF, Gloviczki P. Global vascular guidelines for patients with critical limb-threatening ischemia. *J Vasc Surg*. 2019;69:1653–1654.
36. Behrendt CA, Peters F, Mani K. The swinging pendulum of evidence—is there a reality behind results from randomized trials and real-world data? Lessons learned from the paclitaxel debate. *Eur J Vasc Endovasc Surg*. 2020;59:510–511.
37. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, Blumenthal R, Danesh J, Smith GD, DeMets D. Interpretation of the evidence for the efficacy and safety of statin therapy. *Lancet*. 2016;388:2532–2561.
38. Peters F, Kreutzburg T, Riess H, Heidemann F, Marschall U, L'Hoest H, Debus E, Sedrakyan A, Behrendt CA. Editor´s Choice—Optimal pharmacological treatment of symptomatic peripheral arterial occlusive disease and evidence of female patient disadvantage: An analysis of health insurance claims data. *Eur J Vasc Endovasc Surg*. 2020;60:421–429.
39. Sigvant B, Kragsterman B, Falkenberg M, Hasvold P, Johansson S, Thuresson M, Nordanstig J. Contemporary cardiovascular risk and secondary preventive drug treatment patterns in peripheral artery disease patients undergoing revascularization. *J Vasc Surg*. 2016;64:e1003.
40. Stavroulakis K, Borowski M, Torsello G, Bisdas T. Association between statin therapy and amputation-free survival in patients with critical limb ischemia in the CRITISCH registry. *J Vasc Surg*. 2017;66:1534–1542.
41. Harris SK, Roos MG, Landry GJ. Statin use in patients with peripheral arterial disease. *J Vasc Surg*. 2016;64:1881–1888.
42. Tomoi Y, Soga Y, Iida O, Hirano K, Suzuki K, Kawasaki D, Yamauchi Y, Miyashita Y, Tazaki J, Nobuyoshi M. Efficacy of statin treatment after endovascular therapy for isolated below-the-knee disease in patients with critical limb ischemia. *Cardiovasc Interv Ther*. 2013;28:374–382.
43. Vavra AK, Kibbe MR. Women and peripheral arterial disease. *Womens Health*. 2009;5:669–683.
44. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2019;73:e285–e350.
45. Tomaszewski M, Stepien KM, Tomaszewska J, Czuczwar SJ. Statin-induced myopathies. *Pharmacol Rep*. 2011;63:859–866.
46. Hoffmann F, Icks A. Structural differences between health insurance funds and their impact on health services research: results from the Bertelsmann Health-Care Monitor. *Gesundheitswesen*. 2012;74:291–297.
47. Sirtori CR. The pharmacology of statins. *Pharmacol Res*. 2014;88:3–11.
48. Kokkinidis DG, Arfaras-Melainis A, Giannopoulos S, Katsaros I, Jawaid O, Jonnalagadda AK, Parikh SA, Secemsky EA, Giri J, Kumbhani DJ, et al. Statin therapy for reduction of cardiovascular and limb-related events in critical limb ischemia: a systematic review and meta-analysis. *Vasc Med*. 2020:1358863X19894055.
49. Armitage JBC, Barnes E, Betteridge DJ, Blackwell L, Blazing M, Bowman L, Braunwald E, Byington R, Cannon C, Clearfield M. Efficacy and safety of statin therapy in older people: a meta-analysis of individual participant data from 28 randomised controlled trials. *Lancet*. 2019;393:407–415.
50. Parmar GM, Novak Z, Spangler E, Patterson M, Passman MA, Beck AW, Pearce BJ. Statin use improves limb salvage after intervention for peripheral arterial disease. *J Vasc Surg*. 2019;70:539–546.
51. Hsu CY, Chen YT, Su YW, Chang CC, Huang PH, Lin SJ. Statin therapy reduces future risk of lower-limb amputation in patients with diabetes and peripheral artery disease. *J Clin Endocrinol Metab*. 2017;102:2373–2381.
52. Matsubara Y, Matsumoto T, Inoue K, Matsuda D, Yoshiga R, Yoshiya K, Furuyama T, Maehara Y. Sarcopenia is a risk factor for cardiovascular events experienced by patients with critical limb ischemia. *J Vasc Surg*. 2017;65:1390–1397.
53. Rodriguez F, Maron DJ, Knowles JW, Virani SS, Lin S, Heidenreich PA. Association between intensity of statin therapy and mortality in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol*. 2017;2:47–54.
54. Proietti M, Raparelli V, Laroche C, Dan GA, Janion M, Popescu R, Sinagra G, Vijgen J, Boriani G, Maggioni AP, et al. Adverse outcomes in patients with atrial fibrillation and peripheral arterial disease: a report from the EUROObservational research programme pilot survey on atrial fibrillation. *Europace*. 2017;19:1439–1448.
55. Suckow BD, Kraiss LW, Schanzer A, Stone DH, Kalish J, DeMartino RR, Cronenwett JL, Goodney PP. Statin therapy after infrainguinal bypass surgery for critical limb ischemia is associated with improved 5-year survival. *J Vasc Surg*. 2015;61:126–133.
56. Antoniou GA, Fisher RK, Georgiadis GS, Antoniou SA, Torella F. Statin therapy in lower limb peripheral arterial disease: systematic review and meta-analysis. *Vascul Pharmacol*. 2014;63:79–87.
57. De Martino RR, Eldrup-Jorgensen J, Nolan BW, Stone DH, Adams J, Bertges DJ, Cronenwett JL, Goodney PP. Perioperative management with antiplatelet and statin medication is associated with reduced mortality following vascular surgery. *J Vasc Surg*. 2014;59:1615–1621, 1621.e1.
58. Dosluoglu HH, Davari-Farid S, Pourafkari L, Harris LM, Nader ND. Statin use is associated with improved overall survival without affecting patency and limb salvage rates following open or endovascular revascularization. *Vasc Med*. 2014;19:86–93.
59. Faglia E, Clerici G, Scatena A, Caminiti M, Curci V, Morabito A, Prisco V, Greco R, Edmonds M. Effectiveness of combined therapy with angiotensin-converting enzyme inhibitors and statins in reducing mortality in diabetic patients with critical limb ischemia: an observational study. *Diabetes Res Clin Pract*. 2014;103:292–297.
60. Kumbhani DJ, Steg PG, Cannon CP, Eagle KA, Smith SC Jr, Goto S, Ohman EM, Elbez Y, Sritara P, Baumgartner I, et al. Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: Insights from the reach registry. *Eur Heart J*. 2014;35:2864–2872.
61. Westin GG, Armstrong EJ, Bang H, Yeo KK, Anderson D, Dawson DL, Pevec WC, Amsterdam EA, Laird JR. Association between statin medications and mortality, major adverse cardiovascular event, and amputation-free survival in patients with critical limb ischemia. *J Am Coll Cardiol*. 2014;63:682–690.
62. Sohn MW, Meadows JL, Oh EH, Budiman-Mak E, Lee TA, Stone NJ, Pearce WB. Statin use and lower extremity amputation risk in nonelderly diabetic patients. *J Vasc Surg*. 2013;58(1578–1585):e1571.
63. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, Ward K, Ebrahim S. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2013:CD004816.
64. Aiello FA, Khan AA, Meltzer AJ, Gallagher KA, McKinsey JF, Schneider DB. Statin therapy is associated with superior clinical outcomes after endovascular treatment of critical limb ischemia. *J Vasc Surg*. 2012;55:371–379; discussion 380.
65. Dosluoglu HH, Lall P, Harris LM, Dryjski ML. Long-term limb salvage and survival after endovascular and open revascularization for critical limb ischemia after adoption of endovascular-first approach by vascular surgeons. *J Vasc Surg*. 2012;56:361–371.
66. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the jupiter trial. *Lancet*. 2012;380:565–571.
67. Mills EJ, O'Regan C, Eyawo O, Wu P, Mills F, Berwanger O, Briel M. Intensive statin therapy compared with moderate dosing for prevention of cardiovascular events: a meta-analysis of >40 000 patients. *Eur Heart J*. 2011;32:1409–1415.
68. Dosluoglu HH, Lall P, Nader ND, Harris LM, Dryjski ML. Insulin use is associated with poor limb salvage and survival in diabetic patients with chronic limb ischemia. *J Vasc Surg*. 2010;51:1178–1189; discussion 1188–1179.
69. Schanzer A, Hevelone N, Owens CD, Beckman JA, Belkin M, Conte MS. Statins are independently associated with reduced mortality in patients undergoing infrainguinal bypass graft surgery for critical limb ischemia. *J Vasc Surg*. 2008;47:774–781.
70. Aung PP, Maxwell HG, Jepson RG, Price JF, Leng GC. Lipid-lowering for peripheral arterial disease of the lower limb. *Cochrane Database Syst Rev*. 2007:CD000123.
71. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet*. 2002;360:7–22.

Supplementary Material

Long-term efficacy and safety of initiating statin therapy after index revascularization in patients with peripheral arterial occlusive disease

Frederik Peters[1] MSc PhD, f.peters@uke.de, ORCID 0000-0001-5832-8410;

Jenny Kuchenbecker[1] MSc, j.kuchenbecker@uke.de,

Thea Kreutzburg[1] MSc, t.kreutzburg@uke.de, ORCID 0000-0001-7476-778X;

Ursula Marschall[2] MD, ursula.marschall@barmer.de,

Christian-Alexander Behrendt[1] MD, behrendt@hamburg.de, ORCID 0000-0003-0406-3319

[1] Department of Vascular Medicine, Research Group GermanVasc, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

[2] BARMER, Wuppertal, Germany

†Correspondence to:

Dr Christian-Alexander Behrendt, Department of Vascular Medicine, Research Group GermanVasc, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

E-mail: ch.behrendt@uke.de

Twitter: @VASCevidence

Telephone: +49-40-7410-18087

Telefax: +49-40-7410-54840

Supplementary figures: 11
Supplementary tables: 4

Supplemental Material

Table S1: International classification of diseases (ICD) 10th revision, operational and procedure coding (OPS), and anatomical-therapeutical-chemical (ATC) classification used for this study. TIA: Transient ischemic attack

Variable	ICD code (or OPS or ATC if indicated)
Symptomatic peripheral arterial occlusive disease	**<2015**: I70.21 Pelvic-leg arteries with exercise induced pain, walking distance < 200m, **Fontaine stage II** I70.22 Pelvic-leg arteries with rest pain, **Fontaine stage III** I70.23-24 Pelvic-leg arteries with ulcerations and/or gangrene, **Fontaine stage IV** **≥ 2015**: I70.21-22 Pelvic-leg arteries with exercise induced pain, **Fontaine stage II** I70.23 Pelvic-leg arteries with rest pain, **Fontaine stage III** I70.24-25 Pelvic-leg arteries with ulcerations and/or gangrene, **Fontaine stage IV** **Others**: E10.50-51 Type 1 diabetes mellitus with peripheral vascular complications E10.7 Type 1 diabetes mellitus with diabetic foot syndrome E11.50-51 Type 2 diabetes mellitus with peripheral vascular complications E11.7 Type 2 diabetes mellitus with diabetic foot syndrome I73.0 Other peripheral vascular diseases, Raynaud syndrome I73.1 Other peripheral vascular diseases, Thrombangiitis obliterans I73.8 Other peripheral vascular diseases I73.9 Other peripheral vascular diseases I74.0 Arterial embolism and thrombosis, aorta abdominalis I74.1 Arterial embolism and thrombosis, aorta I74.2 Arterial embolism and thrombosis, upper extremities I74.3 Arterial embolism and thrombosis, lower extremities I74.4 Arterial embolism and thrombosis, arteries of the extremities I74.5 Arterial embolism and thrombosis, aorta iliacal I74.8 Arterial embolism and thrombosis, other arteries I74.9 Arterial embolism and thrombosis, other arteries L03.01-2, L03.11 Cellulitis of finger and toe including acute lymphangitis L98.4 Chronic ulcer of skin, not elsewhere classified R02 Gangrene, not elsewhere classified
Medications	
Lipid lowering drugs	ATC C10
Statins	C10AA, C10BA, C10BX
Antithrombotics	B01
Antidiabetics	A10
Angiotensin II receptor blockers or angiotensin-converting-enzyme inhibitors	C09A-D
Calcium channel blockers	C08
Beta-blockers	C07
Oral anticoagulation	B01AA, B01AE, B01AF
Covariates	
Stroke or TIA	I61, I63, I64, G45
Dyslipidemia	E78
Coronary artery disease	I20-25
Smoking	F17
Myocardial infarction	I20.0, I21-I24
Cancer	Metastatic cancer: C77–C80 and solid tumor without metastasis: C00–C26, C30–C34, C37–C41, C43, C45–C58, C60–C76, C97
Polypharmacy	Number of different prescriptions during year prior to index admission
Procedure	Amputation, peripheral vascular intervention, open surgical revascularization
Amputation	OPS 5-864 Major amputation, above the ankle 5-865 Minor amputation, below the ankle
Peripheral vascular intervention	8-836, 8-840, 8-841, 8-842, 8-843, 8-844, 8-845, 8-846, 8-847, 8-848, 8-849, 8-83c, 8-84a
Open surgical revascularization	5-380, 5-381, 5-382, 5-383, 5-384, 5-38a.4, 5-38a.c, 5-38c, 5-38d, 5-38e, 5-38f, 5-393, 5-394, 5-395, 5-396, 5-98a
Outcomes	
Major amputation	OPS 5-864
Cardiovascular event	I20.0, I21-I24 Myocardial infarction, I61, I63, I64, G45 stroke/TIA
Incident diabetes	E10, E11, E12, E13, E14 or ATC A10
Incident myopathy	G72.0, G72.8, G72.9, M60.8, M60.9, M79.1

Table S2: Baseline characteristics of the unmatched study cohort excluding patients with prior diagnosis of diabetes and myopathy (N=13,561). (SD: Standard deviation; IQR: Interquartile range; PAOD: Peripheral arterial occlusive disease; TIA: Transient ischemic attack; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; OSR: Open surgical revascularization; Std. Diffs: Standardized differences (values above 0.1 deemed to indicate meaningful differences)

Variable	New user, CLTI N=1293	Nonuser, CLTI N=3645	Std. Diffs.	New user, IC N=3031	Nonuser, IC N=5592	Std. Diffs.
Age, years, mean (SD)	71.15 (12.23)	75.59 (12.19)	0.364	65.82 (10.32)	68.23 (10.91)	0.227
Female sex, n (%)	703 (54.4)	2208 (60.6)	0.126	1457 (48.1)	2788 (49.9)	0.036
Van Walraven Score >9, n (%)	328 (25.4)	1427 (39.1)	0.298	276 (9.1)	859 (15.4)	0.192
Congestive heart failure, n (%)	191 (14.8)	840 (23.0)	0.212	157 (5.2)	454 (8.1)	0.118
Cardiac arrhythmias, n (%)	247 (19.1)	1099 (30.2)	0.259	226 (7.5)	746 (13.3)	0.194
Chronic pulmonary disease, n (%)	167 (12.9)	635 (17.4)	0.126	341 (11.3)	769 (13.8)	0.076
Renal failure, n (%)	256 (19.8)	967 (26.5)	0.16	289 (9.5)	653 (11.7)	0.07
Depression, n (%)	96 (7.4)	283 (7.8)	0.013	139 (4.6)	293 (5.2)	0.03
Prior stroke or TIA, n (%)	46 (3.6)	194 (5.3)	0.086	47 (1.6)	117 (2.1)	0.041
Smoking, n (%)	301 (23.3)	576 (15.8)	0.189	817 (27.0)	1287 (23.0)	0.091
Obesity, n (%)	53 (4.1)	218 (6.0)	0.086	163 (5.4)	327 (5.8)	0.02
Prior myocardial infarction, n (%)	59 (4.6)	113 (3.1)	0.076	63 (2.1)	117 (2.1)	0.001
Dyslipidemia, n (%)	517 (40.0)	462 (12.7)	0.652	1343 (44.3)	760 (13.6)	0.72
Coronary artery disease, n (%)	191 (14.8)	611 (16.8)	0.055	255 (8.4)	640 (11.4)	0.102
Diabetes, any, n (%)	27 (2.1)	100 (2.7)	0.043	30 (1.0)	60 (1.1)	0.008
Cancer, any, n (%)	65 (5.0)	245 (6.7)	0.072	120 (4.0)	328 (5.9)	0.088
Hypertension, n (%)	879 (68.0)	2614 (71.7)	0.081	1878 (62.0)	3585 (64.1)	0.045
Prior outpatient diagnosis PAOD, n (%)	261 (20.2)	907 (24.9)	0.113	624 (20.6)	1663 (29.7)	0.212
No of different prescriptions, median (IQR)	9.00 (5.00, 15.00)	12.00 (7.00, 19.00)	0.386	7.00 (4.00, 12.00)	9.00 (5.00, 15.00)	0.275
No of previous inpatient admissions, total (incl. index), median (IQR)	1.00 (1.00, 3.00)	2.00 (1.00, 4.00)	0.25	1.00 (1.00, 2.00)	1.00 (1.00, 3.00)	0.216
No of prior PAOD outpatient visits, median (IQR)	0.00 (0.00, 2.00)	1.00 (0.00, 2.00)	0.129	1.00 (0.00, 2.00)	1.00 (0.00, 3.00)	0.237
Invasive procedure: OSR, n (%)	558 (43.2)	1579 (43.3)	0.003	628 (20.7)	1579 (28.2)	0.176
Hospital length of stay, days, median (IQR)	11.00 (6.00, 19.00)	12.00 (7.00, 20.00)	0.056	4.00 (3.00, 7.00)	4.00 (3.00, 8.00)	0.08

Table S3: Baseline characteristics of the matched study cohort excluding patients with prior diagnosis of diabetes or myopathy (N=6910). (SD: Standard deviation; IQR: Interquartile range; PAOD: Peripheral arterial occlusive disease; TIA: Transient ischemic attack; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; OSR: Open surgical revascularization; Std. Diffs: Standardized differences (values above 0.1 deemed to indicate meaningful differences)

Variable	New user, CLTI N=1116	Nonuser, CLTI N=1116	Std. Diffs.	New user, IC N=2339	Nonuser, IC N=2339	Std. Diffs.
Age, years, mean (SD)	71.97 (12.24)	72.12 (12.65)	0.012	66.33 (10.38)	66.88 (10.72)	0.052
Female sex, n (%)	616 (55.2)	621 (55.6)	0.009	1120 (47.9)	1157 (49.5)	0.032
Discharge year, mean (SD)	303 (27.2)	312 (28.0)	0.018	246 (10.5)	279 (11.9)	0.045
Van Walraven Score >9, n (%)	174 (15.6)	167 (15.0)	0.017	139 (5.9)	154 (6.6)	0.026
Congestive heart failure, n (%)	230 (20.6)	241 (21.6)	0.024	205 (8.8)	213 (9.1)	0.012
Cardiac arrhythmias, n (%)	154 (13.8)	170 (15.2)	0.041	279 (11.9)	286 (12.2)	0.009
Chronic pulmonary disease, n (%)	233 (20.9)	226 (20.3)	0.016	231 (9.9)	266 (11.4)	0.049
Renal failure, n (%)	87 (7.8)	81 (7.3)	0.02	110 (4.7)	139 (5.9)	0.055
Depression, n (%)	44 (3.9)	51 (4.6)	0.031	40 (1.7)	39 (1.7)	0.003
Prior stroke or TIA, n (%)	238 (21.3)	236 (21.1)	0.004	613 (26.2)	617 (26.4)	0.004
Smoking, n (%)	50 (4.5)	66 (5.9)	0.065	129 (5.5)	134 (5.7)	0.009
Obesity, n (%)	43 (3.9)	52 (4.7)	0.04	48 (2.1)	48 (2.1)	<0.001
Prior myocardial infarction, n (%)	341 (30.6)	344 (30.8)	0.006	651 (27.8)	656 (28.0)	0.005
Dyslipidemia, n (%)	160 (14.3)	176 (15.8)	0.04	217 (9.3)	222 (9.5)	0.007
Coronary artery disease, n (%)	24 (2.2)	29 (2.6)	0.029	26 (1.1)	17 (0.7)	0.04
Diabetes, any, n (%)	59 (5.3)	68 (6.1)	0.035	98 (4.2)	106 (4.5)	0.017
Cancer, any, n (%)	753 (67.5)	766 (68.6)	0.025	1440 (61.6)	1488 (63.6)	0.042
Hypertension, n (%)	235 (21.1)	230 (20.6)	0.011	531 (22.7)	539 (23.0)	0.008
Prior outpatient diagnosis PAOD, n (%)	10.00 (5.00, 16.00)	10.00 (5.00, 16.00)	0.059	8.00 (4.00, 12.00)	8.00 (5.00, 13.00)	0.051
No of different prescriptions, median (IQR)	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	0.014	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	0.045
No of previous inpatient admissions, total (incl. Index), median (IQR)	0.00 (0.00, 2.00)	0.00 (0.00, 2.00)	0.009	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	0.014
No of prior PAOD outpatient visits, median (IQR)	485 (43.5)	477 (42.7)	0.014	525 (22.4)	561 (24.0)	0.036
Invasive procedure: OSR, n (%)	11.00 (6.00, 19.00)	11.00 (6.00, 19.00)	0.018	4.00 (3.00, 8.00)	4.00 (3.00, 8.00)	0.017
Hospital length of stay, days, median (IQR)	1164.00 (582.50, 1827.00)	1034.50 (486.25, 1827.00)	0.12	1418.00 (741.50, 1827.00)	1393.00 (726.50, 1827.00)	0.015

Table S4: Main studies (References main text: 18-21, 34, 39, 40, 42) on effectiveness and safety of statins in patients. PAOD: Peripheral arterial occlusive disease; IC: Intermittent claudication; CLTI: Critical limb threatening ischemia; AFS: Amputation-free survival; HR: Hazard ratio; OR: Odds ratio; RR: Risk ratio; IRR: Incidence Rate ratio; RCT: Randomized controlled trial; obs: Observational study; meta: Meta-analysis; HI: High-intensity; DM: Diabetes mellitus; N/A: Not applicable; n.s.: Not significant

Author	Year	Type	Country	N	Exposure	Age, mean years	Female	Patients with PAOD	IC	CLTI	Follow-up, years	Prevalence statins	HR, Survival	HR, Major vascular event	HR, AFS	HR, Myopathy	HR, Diabetes
Kokkinidis	2020	meta	INTL	26,985	statins	68.5-77	0%-54.8%	yes	0%	100%	-	50%	0.62	0.50	n.s.	-	-
Armitage	2019	meta	UK	186,854	statins	63.0	28%	unknown	-	-	median 4.9	N/A	0.88 (IRR)	0.79 (IRR)	-	-	-
Parmar	2019	obs	US	488	statins	-	44%	yes	20%	67%	-	41%	-	-	0.30	-	-
Reynolds	2019	obs	US	11,059	statins	68.6	40%	yes	69%	31%	median 4.2	60%	0.80 IC/0.81 CLTI	-	-	-	-
Arya	2018	obs	US	155,647	statins	67.0	2%	yes	-	-	median 5.9	72%	0.83	-	0.81	-	-
Ramos	2018	obs	ES	46,864	statins	77.0	63%	unknown	-	-	median 5.6	16%	n.s./0.84 (DM)	-	-	n.s./n.s.	n.s./n.s.
Foley	2017	obs	US	909	HI statin	68.0	40%	yes	46%	54%	median 1.4	83%	0.53	0.58	n.s.	-	-
Hsu	2017	obs	TW	69,332	statins	63.0	51%	yes	-	-	mean 5.7	16%	0.72	-	0.75	-	-
Matsubara	2017	obs	JP	114	statins	72.1	31%	yes	0%	100%	-	23%	-	0.38	-	-	-
Rodriguez	2017	obs	US	509,766	HI statin	68.5	2%	yes	-	-	mean 1.3	82%	0.91	-	-	-	-
Stavroulakis	2017	obs	DE	1,200	statins	74.5	34%	yes	0%	100%	-	57%	0.40	0.41	n.s.	-	-
Proietti	2016	obs	INTL	328	statins	72.9	34%	yes	-	-	max 1	39%	0.64	-	-	-	-
Ramos	2016	obs	ES	5,480	statins	67.0	44%	yes	0%	0%	median 3.6	28%	0.81	0.80	-	n.s.	n.s.
Sigvant	2016	obs	SE	18,742	statins	74.3	49%	yes	37%	63%	-	60%	-	0.7 IC /0.76 CLTI	-	-	-
Suckow	2015	obs	US	2,067	statins	67.0	29%	yes	33%	67%	complete 1	74%	0.70	-	-	-	-
Antoniou	2014	meta	INTL	19,368	statins	-	-	yes	-	-	-	52%	0.60	n.s.	-	-	-
De Martino	2014	obs	US	14,489	statins	70.0	34%	yes	-	-	-	78%	0.70 (OR)	-	-	-	-
Dosluoglu	2014	obs	US	717	statins	68	0%	yes	34%	66%	mean 4.2	55%	0.74	-	-	-	-
Faglia	2014	obs	IT	553	statins	71.7	30%	yes	0%	100%	mean 2.2	45%	n.s.	-	-	-	-
Kumbhani	2014	obs	INTL	5,861	statins	69.0	27%	yes	43%	57%	complete 4	62%	n.s.	0.85	0.57	-	-
Westin	2014	obs	US	380	statins	68.5	44%	yes	0%	100%	median 1.1	65%	0.49	0.53	0.59	-	-
Sohn	2013	obs	US	83,953	statins	52.0	-	yes	-	-	mean 4.9	-	-	-	0.57	-	-
Taylor	2013	meta	INTL	48,060	statins	-	-	unknown	-	-	-	N/A	0.86	0.75	-	n.s.	n.s.
Tomoi	2013	obs	JP	812	statins	71.6	31%	yes	0%	100%	mean 1.6	21%	n.s.	-	n.s.	-	-
Aiello	2012	obs	US	646	statins	77.0	48%	yes	0%	100%	mean 0.8	49%	0.49 (OR)	-	-	-	-
Dosluoglu	2012	obs	US	433	statins	71.1	0%	yes	0%	100%	mean 2.3	27%	0.60	-	0.70	-	-
Ridker	2012	RCT	US	17,603	rosuvastatin	66.0	37%	unknown	-	-	median 2	N/A	n.s.	0.67	-	-	n.s.
Mills	2011	meta	INTL	41,778	HI statin	55.5	24%	unknown	-	-	mean 2.5	N/A	n.s.	0.90	-	2.86 (RR)	-
Dosluoglu	2010	obs	US	746	statins	69.3	1%	yes	27%	73%	mean 2.2	58%	1.40 (nonuse)	-	-	-	-
Schanzer	2008	obs	INTL	1,404	statins	68.5	39%	yes	0%	100%	max 1	45%	0.67	-	-	-	-
Aung	2007	meta	INTL	10,049	lipid lowering	-	-	yes	-	-	-	N/A	n.s.	n.s.	-	-	-
Collins	2002	RCT	INTL	20,536	simvastatin	-	25%	unknown	-	-	mean 5	N/A	0.87 (IRR)	0.76 (IRR)	-	-	-
our study	**2020**	**obs**	**DE**	**22,208**	**statins**	**71.1**	**50%**	**yes**	**0.57**	**0.43**	**median 3.5**	**50%**	**0.75 IC /0.80 CLTI**	**0.80 IC /n.s. CLTI**	**n.s. IC /0.73 CLTI**	**n.s.**	**n.s.**

Figure S1: Time trend in the proportion of unmatched patients initiating statin therapy after index stay (N=22,208) among all statin-naïve patients and Cochrane-Armitage trend test (p-value). CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; PAOD: Peripheral arterial occlusive disease.

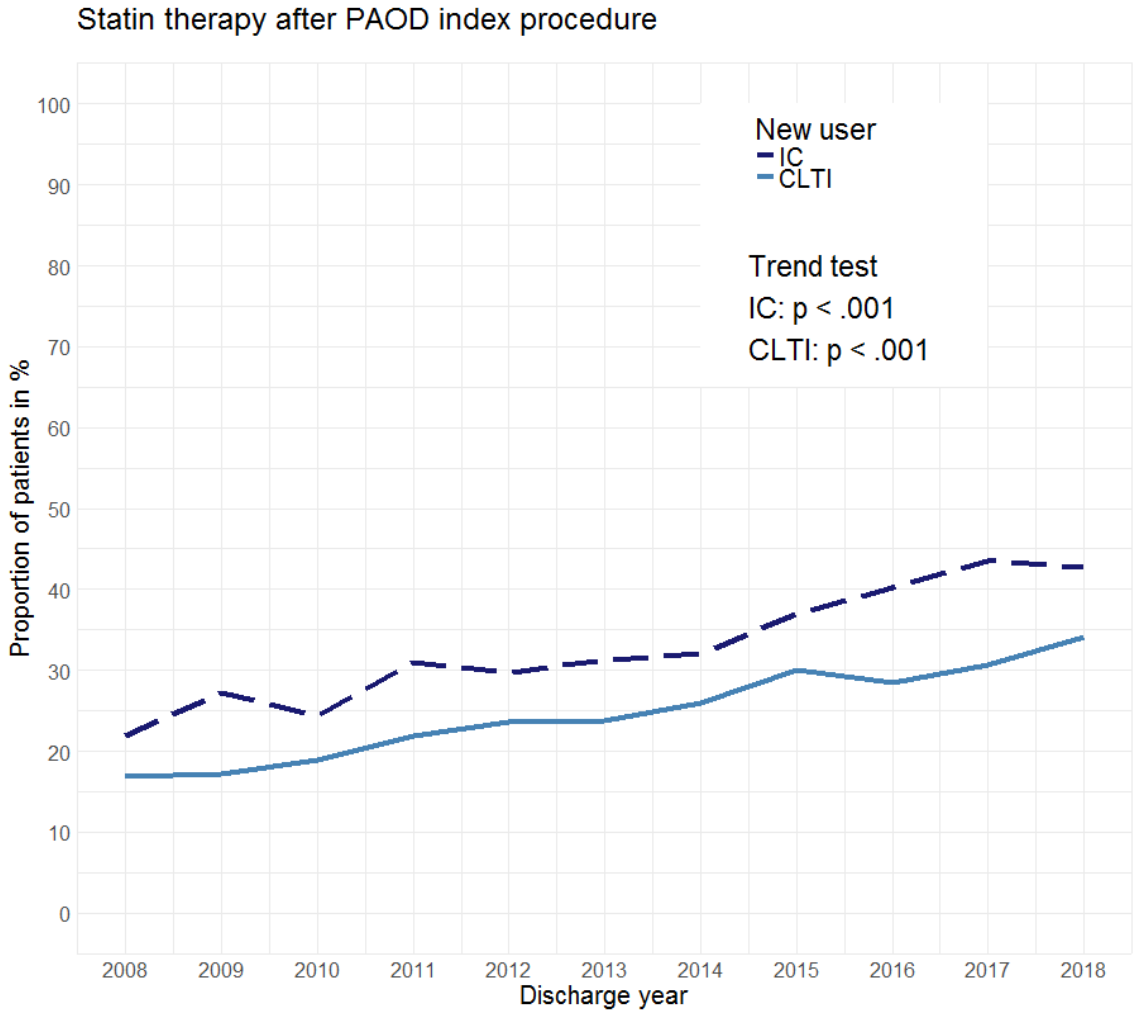
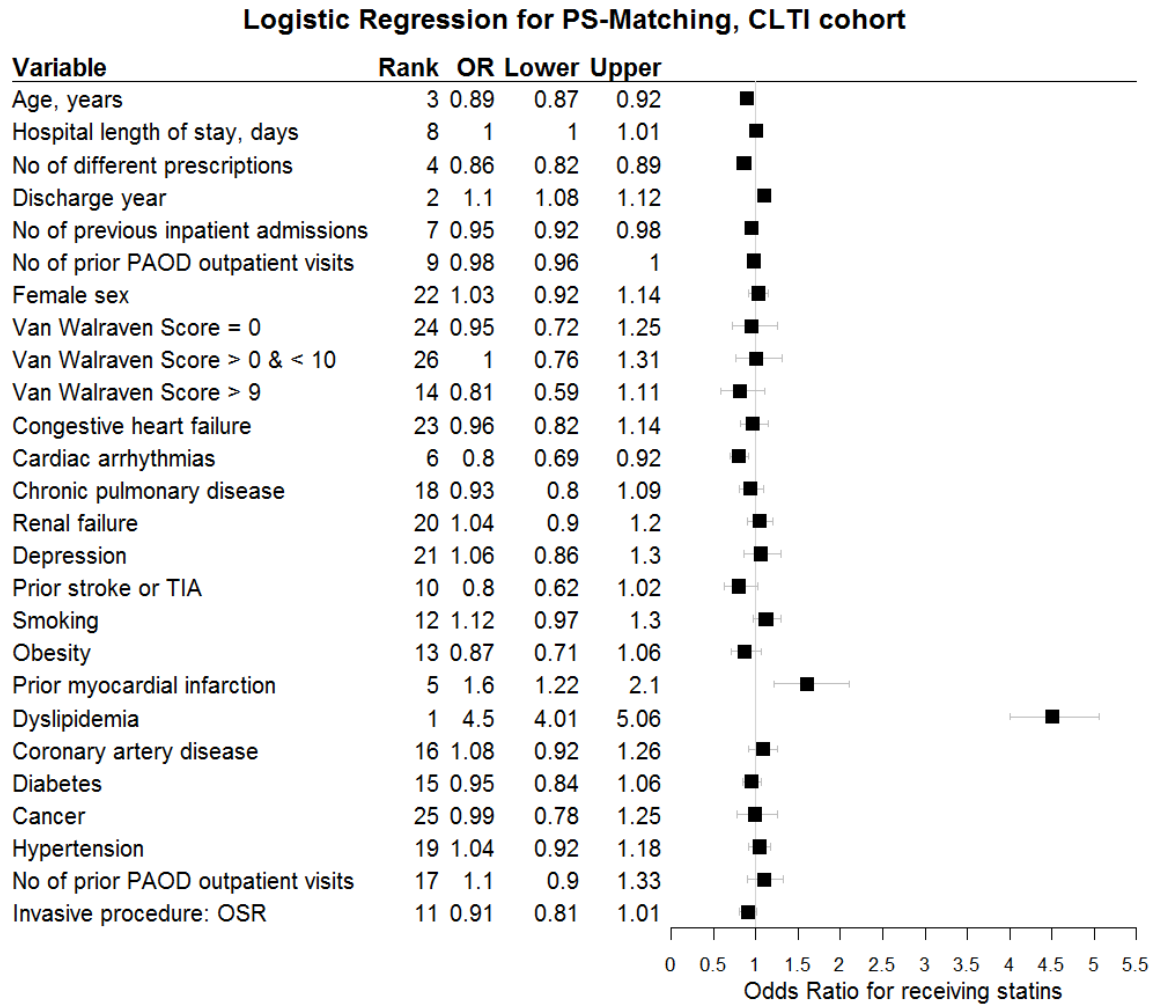
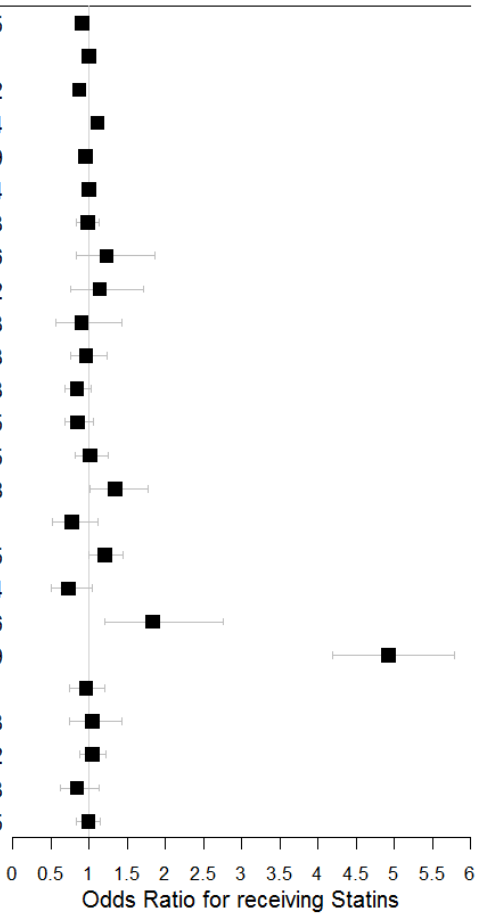


Figure S2: Odds ratios of the probability to be a new user vs. nonuser after index discharge used in the propensity score matched patients with CLTI (N=4,224); full matching (upper panel) and restricted diabetes matching (lower panel); CLTI: Chronic limb-threatening ischemia; OR: Odds Ratio; PS: Propensity Score; Rank based on variable importance according to recursive partitioning; PAOD: Peripheral arterial occlusive disease; OSR: Open surgical revascularization; TIA: Transient ischemic attack.



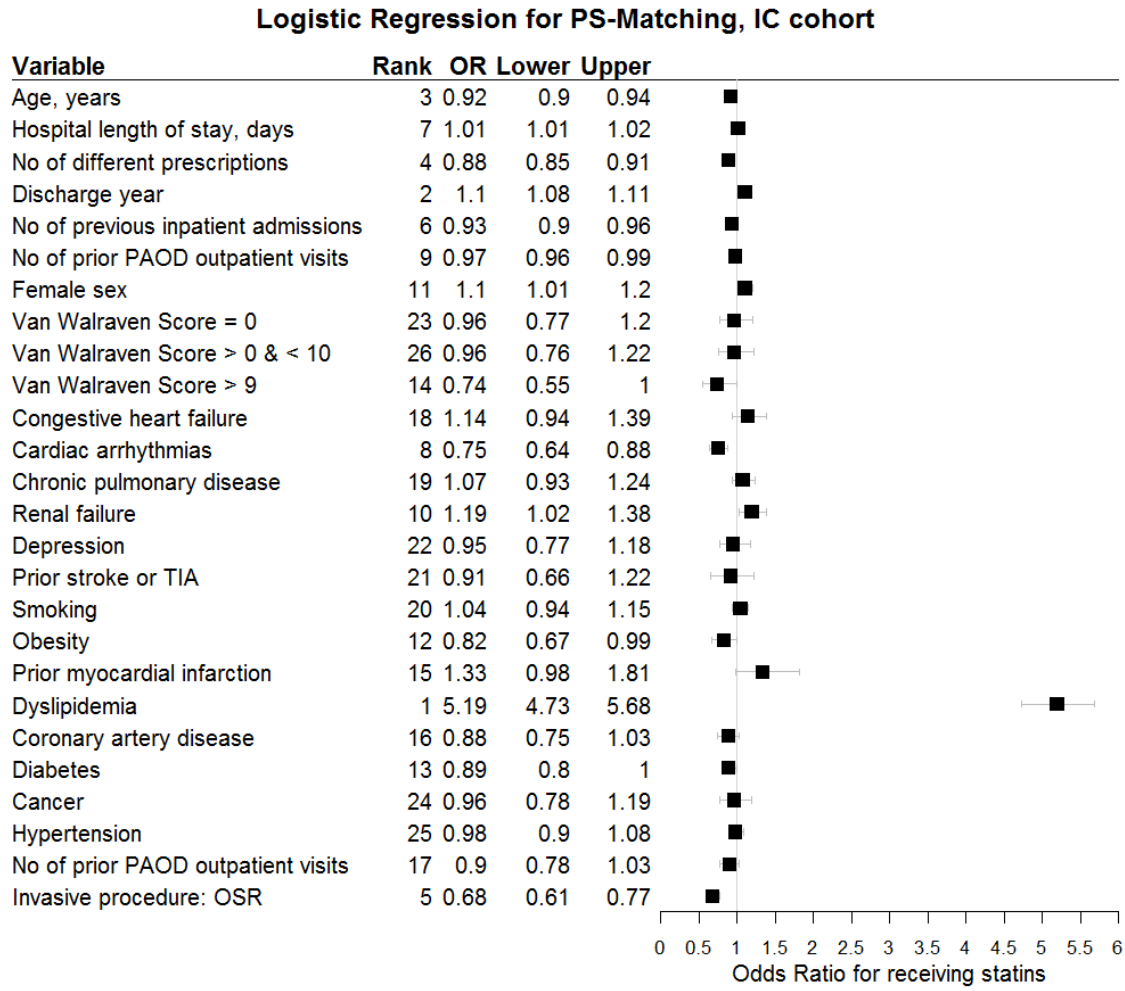
Logistic Regression for PS-Matching, CLTI cohort, Diabetes matching

Variable	Rank	OR	Lower	Upper
Age, years	3	0.91	0.88	0.95
Hospital length of stay, days	15	1	1	1.01
No of different prescriptions	4	0.87	0.82	0.92
Discharge year	2	1.11	1.08	1.14
No of previous inpatient admissions	6	0.95	0.91	0.99
No of prior PAOD outpatient visits	24	1	0.97	1.04
Female sex	20	0.98	0.84	1.13
Van Walraven Score = 0	14	1.23	0.83	1.86
Van Walraven Score > 0 & < 10	16	1.14	0.76	1.72
Van Walraven Score > 9	17	0.9	0.57	1.43
Congestive heart failure	21	0.96	0.76	1.23
Cardiac arrhythmias	10	0.84	0.68	1.03
Chronic pulmonary disease	11	0.85	0.68	1.05
Renal failure	25	1.01	0.82	1.25
Depression	7	1.34	1.01	1.78
Prior stroke or TIA	12	0.77	0.52	1.11
Smoking	8	1.21	1	1.45
Obesity	9	0.73	0.5	1.04
Prior myocardial infarction	5	1.83	1.2	2.76
Dyslipidemia	1	4.92	4.19	5.79
Coronary artery disease	19	0.96	0.75	1.21
Cancer	22	1.04	0.75	1.43
Hypertension	18	1.04	0.88	1.22
No of prior PAOD outpatient visits	13	0.84	0.62	1.13
Invasive procedure: OSR	23	0.99	0.84	1.15



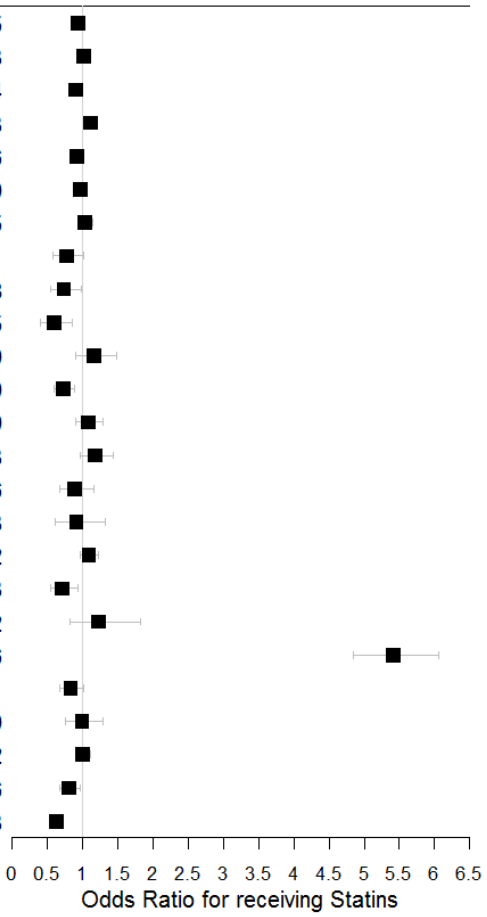
71

Figure S3: Odds ratios of the probability to be a new user vs. nonuser after index discharge used in the propensity score matched patients IC (N=6698); full matching (upper panel) and restricted diabetes matching (lower panel); IC: Intermittent claudication; OR: Odds Ratio; PS: Propensity Score; Rank based on variable importance according to recursive partitioning; PAOD: Peripheral arterial occlusive disease; OSR: Open surgical revascularization; TIA: Transient ischemic attack.



Logistic Regression for PS-Matching, IC cohort, Diabetes matching

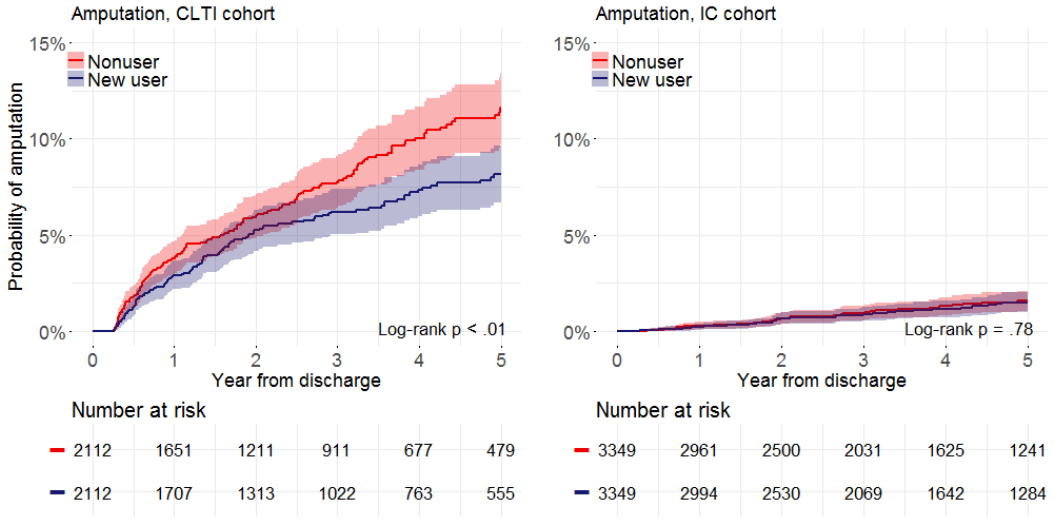
Variable	Rank	OR	Lower	Upper
Age, years	4	0.93	0.9	0.95
Hospital length of stay, days	7	1.02	1.01	1.03
No of different prescriptions	5	0.9	0.86	0.94
Discharge year	2	1.11	1.09	1.13
No of previous inpatient admissions	6	0.92	0.88	0.96
No of prior PAOD outpatient visits	9	0.97	0.95	0.99
Female sex	22	1.03	0.93	1.15
Van Walraven Score = 0	14	0.77	0.58	1.01
Van Walraven Score > 0 & < 10	13	0.73	0.55	0.98
Van Walraven Score > 9	10	0.59	0.4	0.85
Congestive heart failure	18	1.16	0.9	1.49
Cardiac arrhythmias	8	0.72	0.59	0.89
Chronic pulmonary disease	20	1.08	0.91	1.29
Renal failure	16	1.18	0.97	1.43
Depression	21	0.89	0.68	1.16
Prior stroke or TIA	23	0.91	0.61	1.33
Smoking	17	1.09	0.97	1.22
Obesity	12	0.71	0.54	0.93
Prior myocardial infarction	19	1.23	0.82	1.82
Dyslipidemia	1	5.41	4.84	6.06
Coronary artery disease	15	0.83	0.68	1.01
Cancer	24	0.99	0.76	1.29
Hypertension	25	1	0.9	1.12
No of prior PAOD outpatient visits	11	0.81	0.68	0.96
Invasive procedure: OSR	3	0.63	0.55	0.73



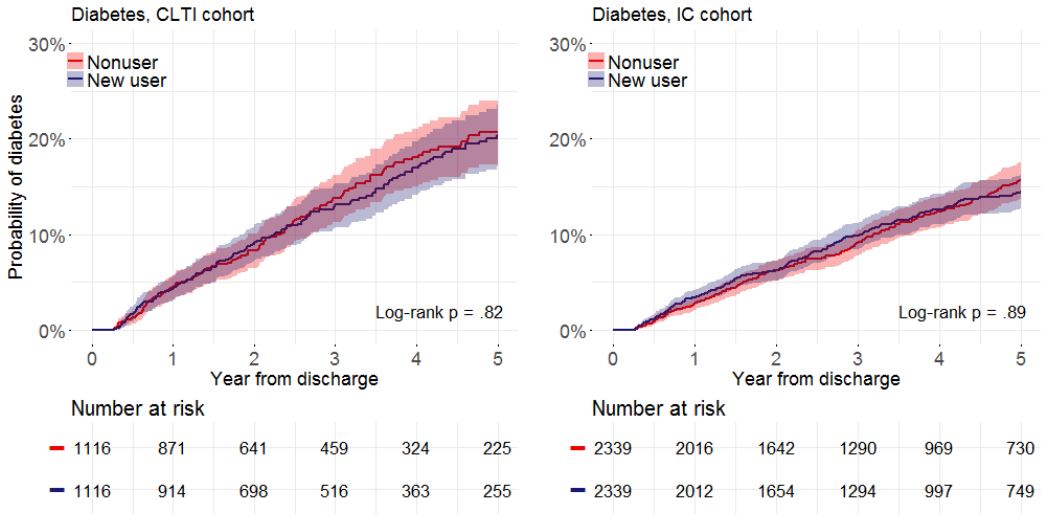
80

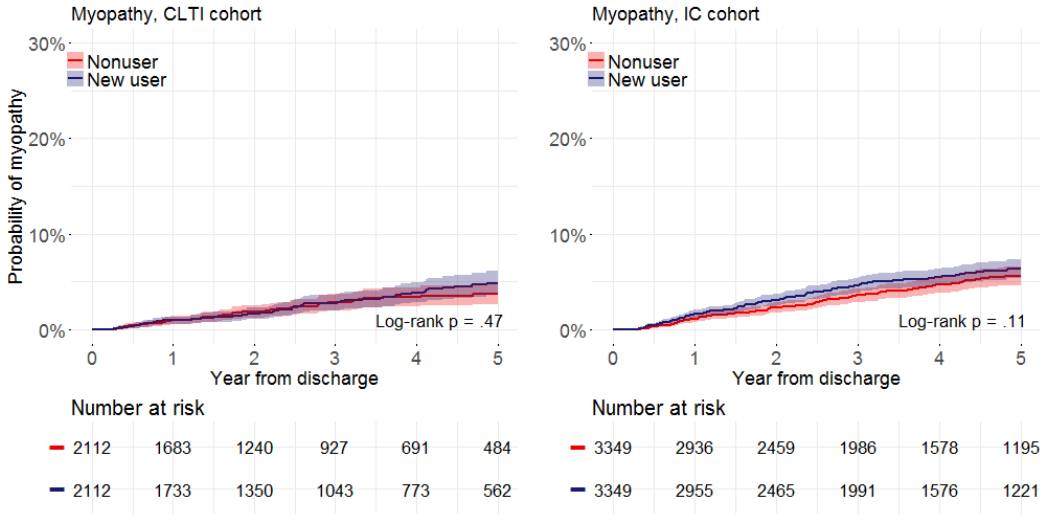
81

Figure S4: Kaplan Maier curve of 5-year probability of major amputation (upper panel), incident diabetes (center panel), and incident myopathy (lower panel) in propensity score (PS) matched cohorts including 95% Wald confidence interval and log rank test (p-value). CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication



86





87

Figure S5: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; effect of statins only (empty model) vs. full adjustment (full model); HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular

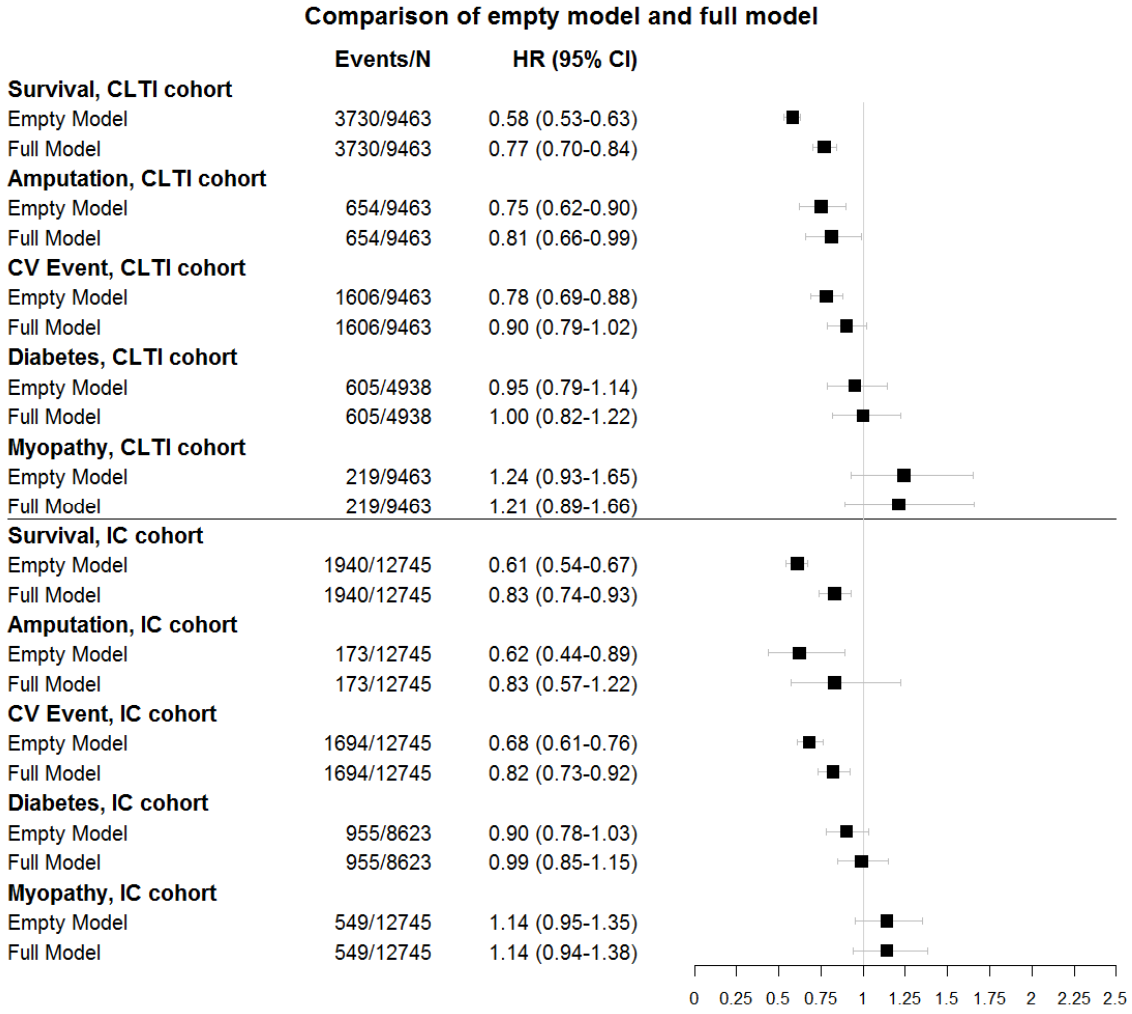


Figure S6: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; full adjustment (full model) vs. additionally adjusting for comedications; HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular

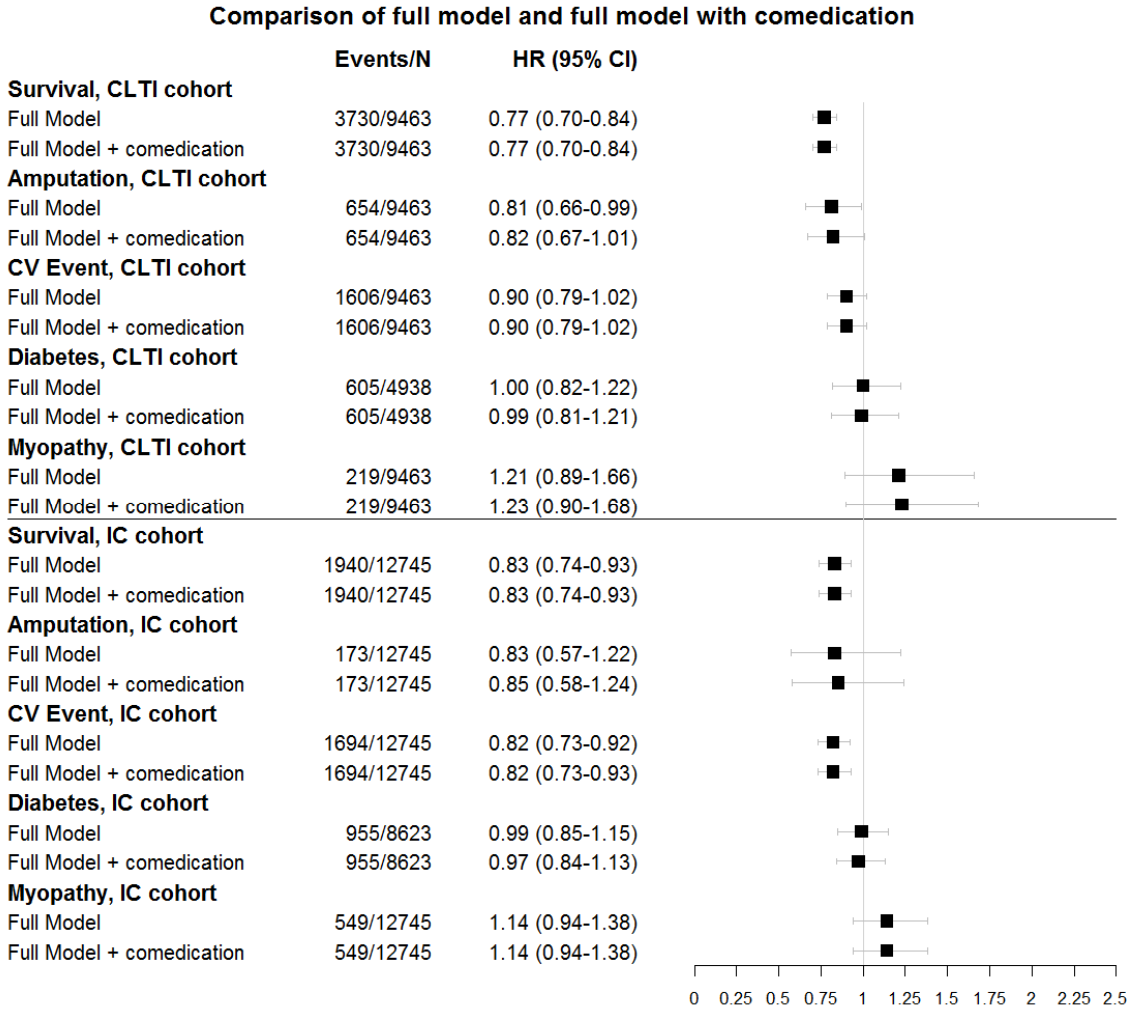


Figure S7: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; females vs. males; HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular

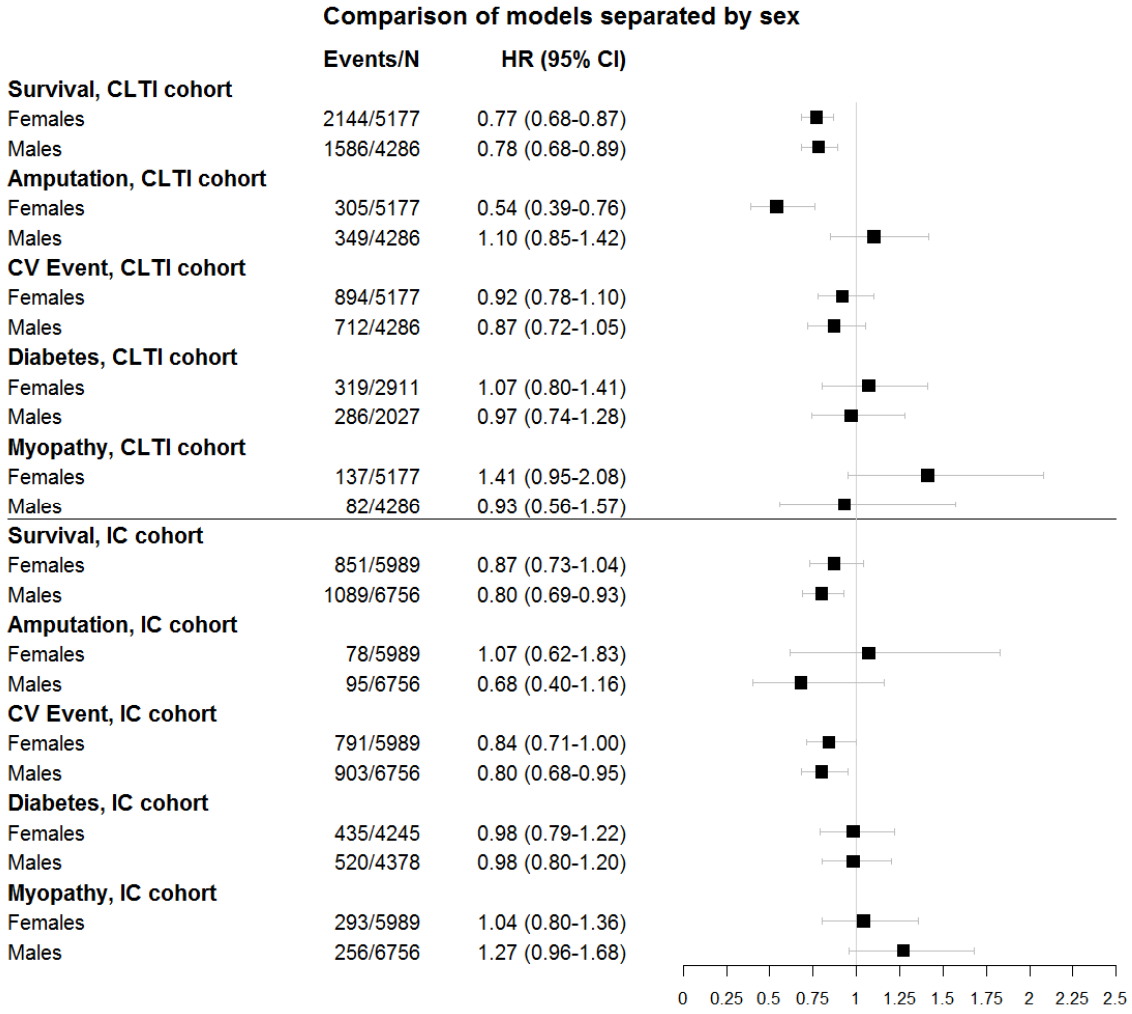


Figure S8: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; younger patients (ages 74 and below) vs. older patients (ages 75 and above); HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular

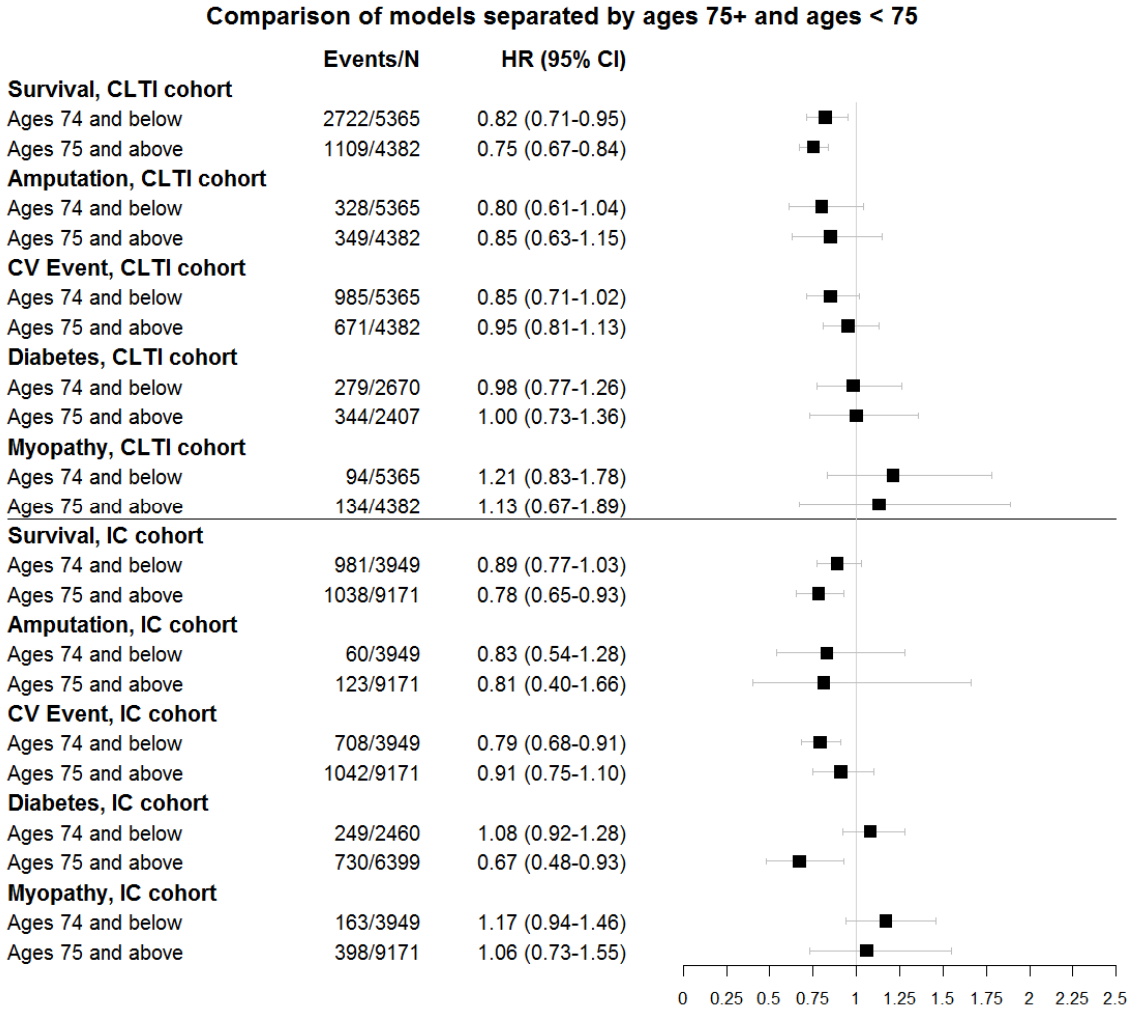


Figure S9: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; Discharge year 2009-2012 vs. 2013-2018; HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular

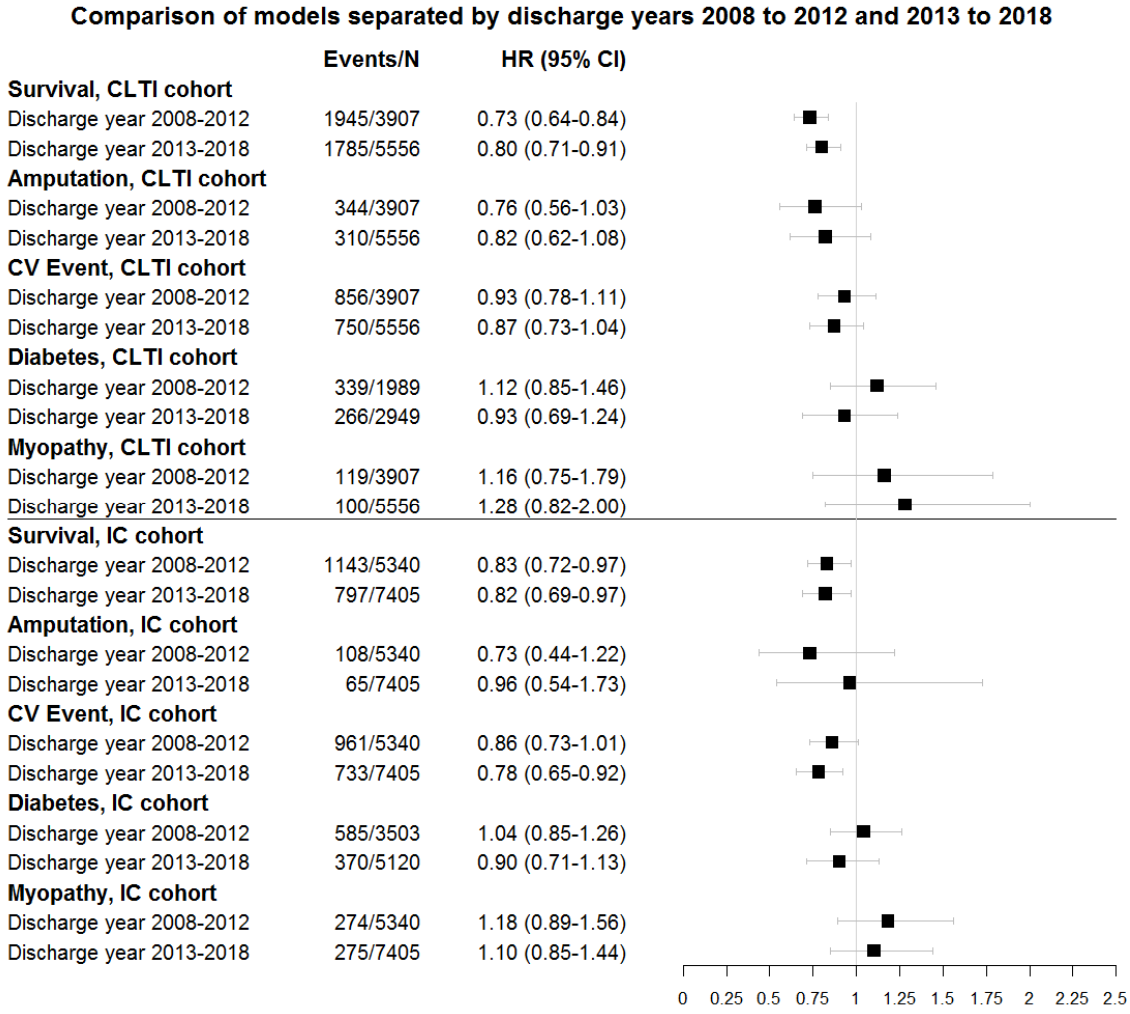
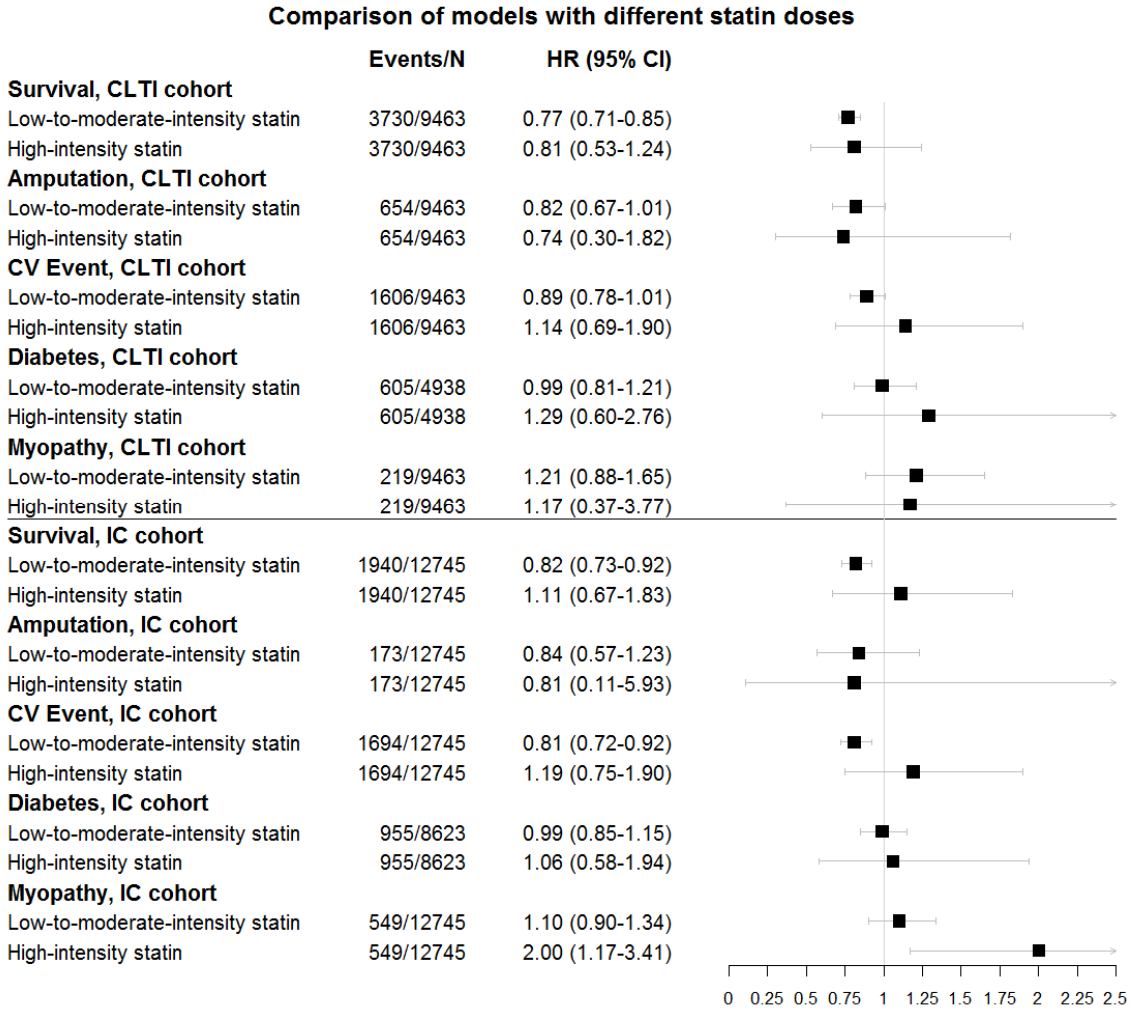


Figure S10: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; Low-to-moderate statin intensity vs. high intensity; HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular



Note: Statin intensity was extracted from linking the pharmaceutical registration number (PZN) of each prescription with public databases on dose and agent; Following to 2013 AHA/ACC lipid guidelines, we grouped atorvastatin 40-80 mg and rosuvastatin 20-40 mg as high intensity treatment (N=415, 6.2%) and all other prescriptions as moderate and low intensity treatment (N=6179, 93.8%).

Figure S11: Sensitivity analysis: Cox proportional hazard results using the unmatched data set (N=22,208) for long-term effectiveness and safety outcomes; Peripheral vascular intervention (PVI) vs. open surgical repair (OSR) at index revascularization; HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular