ORIGINAL RESEARCH

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

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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. 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. 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. Yet, this subgroup exhibits particularly low utilization rates of statins as compared with patients with coronary artery disease or a history of stroke.
The underutilization of statin therapy has been predominantly ascribed to the lack of awareness about risks and therapy options among providers and patients and concerns about adverse reactions such as myopathy and onset of diabetes mellitus. 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 and offer additional benefits at high-intensity doses. 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. 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.

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).

**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. A regular random sample validation of internal and external validity was done to ensure reproducibility and generalizability to the national population.
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 claudica-
tion (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 diagno-
sis 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 emb-
bolism 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 (de-
noted 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 set26 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 se-
lection bias caused by prevalent users.5

The following patients were excluded: patients
aged <40 years, patients with prior major amputa-
tion or recorded myopathy (outpatient or inpatient),
patients discharged without revascularization (ampu-
tation 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 pre-
scription. 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 informa-
tion about the death of the insured person is complete
and validated.27

Secondary outcomes were incident major ampu-
tation and cardiovascular events (myocardial infarction,
stroke, or transient ischemic attack), obtained from pri-
mary and secondary inpatient diagnoses.

Safety outcomes were incident diabetes mellitus
and incident myopathy. Specifically, incidence was de-
finned 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 measur-
ing incident outcomes, we evaluated both outpatient
and inpatient diagnoses and, in the case of diabetes
mellitus, also the prescription of oral and parenteral an-
ti diabetic 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 dis-
charge 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 pa-
tients 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, near-
est neighbor propensity score matching was ap-
plied 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 pulmo-
nary disease; renal failure; depression; prior stroke
or transient ischemic attack; smoking; obesity; prior
myocardial infarction; dyslipidemia; coronary artery
disease; diabetes mellitus (complicated and un-
complicated); cancer; hypertension; prior outpatient

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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 C07], 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
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...
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 significantly 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).
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 anti-coagulation (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

**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)             | 628 (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.
incidence of diabetes mellitus and myopathy was not associated with new statin prescription. As same as that documented in primary prevention, 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. 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

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.
A 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 non-randomized 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

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.
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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. 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.

Although many potential adverse reactions have been presumed in the literature, we focused on the established safety outcomes of incident myopathy.
and diabetes mellitus. Our study results are in line with prior evidence on the safety of statin therapy in patients with PAOD. \cite{19} Collins et al\cite{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.\cite{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\cite{29} reported ≈2% of statin-induced myopathy while Collins et al\cite{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.\cite{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,\cite{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.\cite{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.\cite{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**

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Supplementary Material

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

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Supplementary figures: 11
Supplementary tables: 4
## 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: |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I70.21 Pelvic-leg arteries with exercise induced pain, walking distance < 200m, **Fontaine stage II** |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I70.22 Pelvic-leg arteries with rest pain, **Fontaine stage III** |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I70.23-24 Pelvic-leg arteries with ulcerations and/or gangrene, **Fontaine stage IV** |
| ≥ 2015: |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I70.21-22 Pelvic-leg arteries with exercise induced pain, **Fontaine stage II** |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I70.23 Pelvic-leg arteries with rest pain, **Fontaine stage III** |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I70.24-25 Pelvic-leg arteries with ulcerations and/or gangrene, **Fontaine stage IV** |
| Others: |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;E10.50-51 Type 1 diabetes mellitus with peripheral vascular complications |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;E10.7 Type 1 diabetes mellitus with diabetic foot syndrome |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;E11.50-51 Type 2 diabetes mellitus with peripheral vascular complications |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;E11.7 Type 2 diabetes mellitus with diabetic foot syndrome |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I73.0 Other peripheral vascular diseases, Raynaud syndrome |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I73.1 Other peripheral vascular diseases, Thrombangiitis obliterans |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I73.8 Other peripheral vascular diseases |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I73.9 Other peripheral vascular diseases |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I74.0 Arterial embolism and thrombosis, aorta abdominalis |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I74.1 Arterial embolism and thrombosis, aorta |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I74.2 Arterial embolism and thrombosis, upper extremities |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I74.3 Arterial embolism and thrombosis, lower extremities |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I74.4 Arterial embolism and thrombosis, arteries of the extremities |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I74.5 Arterial embolism and thrombosis, aorta iliacal |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;I74.8 Arterial embolism and thrombosis, other arteries |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;L03.01-2, L03.11 Cellulitis of finger and toe including acute lymphangitis |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;L98.4 Chronic ulcer of skin, not elsewhere classified |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;R02 Gangrene, not elsewhere classified |
| Medications | |
| Lipid lowering drugs | ATC C10 |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;Statins | C10AA, C10BA, C10BX |
| Antithrombotics | B01 |
| Antidiabetics | A10 |
| Angiotensin II receptor blockers or angiotensin-converting-enzyme inhibitors | C09A-D |
| Calcium channel blockers | C08 |
| Betablockers | 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 |
| &nbsp;&nbsp;&nbsp;&nbsp;&nbsp;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, G72.9, 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       | 28 (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 (63.8)         | 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     | Follow-up, years | Prevalence statins | HR, Survival | HR, Major vascular event | HR, AFS | HR, Myopathy | HR, Diabetes |
|-----------------|------|------|---------|-------|----------|----------------|--------|-------------------|--------|----------------|-------------------|-------------|--------------------------|---------|-------------|-------------|
| Kokkinidis      | 2020 | meta | INTL    | 25,965| statins  | 68.5-77% 0%-54.8% | yes | 0% | 100% | 50% | 0.62 | 0.50 | n.a. | - | - | - |
| 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   | - | 44% | yes | 20% | 67% | 41% | - | - | - | - | - | - |
| Reynolds        | 2019 | Obs  | US      | 11,059| statins  | 66.8 | 40% | yes | 69% | 31% | median 4.2 | 60% | 0.80 (IC0.81 CLTI) | - | - | - | - |
| Arya            | 2018 | Obs  | US      | 155,647| statins  | 67.0 | 2% | yes | - | median 5.9 | 72% | 0.83 | - | - | - | - |
| Ramos           | 2018 | Obs  | ES      | 46,864| statins  | 77.0 | 63% | unknown | - | median 5.6 | 16% | n.s./0.84 (DM) | - | - | n.a/n.s. | n.s/n.s. |
| Foley           | 2017 | Obs  | US      | 909   | Hi statin | 68.0 | - | 46% | 54% | median 1.4 | 83% | 0.53 | 0.58 | n.a. | - | - |
| Hau             | 2017 | Obs  | TW      | 69,332| statins  | 63.0 | 51% | yes | - | mean 5.7 | 16% | 0.72 | - | 0.75 | - | - |
| Matsubara       | 2017 | Obs  | JP      | 114   | - | 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.a. | - | - |
| Pietroli        | 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 | 26% | 0.81 | 0.80 | n.s. | n.s. | - |
| Szigován        | 2017 | Obs  | SE      | 18,742| statins  | 74.3 | 49% | yes | 37% | 63% | - | 0.7 IC0.76 CLTI | - | - | - | - |
| Suckow          | 2015 | Obs  | US      | 2,067 | statins  | 67.0 | 29% | yes | 33% | 67% | complete 1 | 74% | 0.70 | - | - | - | - |
| Antonioudi      | 2014 | meta | INTL    | 19,368| statins  | - | - | yes | - | - | - | 0.60 | n.a. | - | - | - | - |
| De Martino      | 2014 | Obs  | US      | 14,400| statins  | 70.0 | 34% | yes | - | - | - | 0.70 (OR) | n.a. | - | - | - |
| 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% | 22% | 45% | n.a. | - | - | - |
| Kumbhani        | 2014 | Obs  | INTL    | 5,800 | statins  | 69.0 | 27% | yes | 43% | 57% | complete 4 | 62% | n.a. | 0.85 | 0.57 | - | - |
| Westin          | 2014 | Obs  | US      | 380   | statins  | 68.6 | 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| - | unknown | unknown | N/A | 0.86 | 0.75 | - | - | - | - | - | - |
| Tomoi           | 2013 | Obs  | JP      | 812   | statins  | 71.6 | 31% | yes | 0% | 100% | mean 1.6 | 21% | n.a. | - | - | - | - |
| Aletto          | 2012 | Obs  | US      | 646   | statins  | 77.0 | 48% | yes | 0% | 100% | mean 0.8 | 49% | 0.49 | (OR) | - | - | - |
| Dosluoglu       | 2012 | Obs  | US      | 433   | statins  | 71.0 | 0% | yes | - | 100% | 23% | 0.60 | - | 0.70 | - | - |
| Rödler          | 2012 | RCT  | US      | 17,504| rosuvastatin | 66.0 | 37% | yes | - | median 2 | N/A | n.a. | 0.67 | - | - | - |
| Mills           | 2011 | meta | INTL    | 41,778| Hi statin | 55.5 | 24% | unknown | - | mean 2.5 | N/A | 0.90 | - | 2.86 (RR) | - | - |
| Dosluoglu       | 2010 | Obs  | US      | 746   | statins  | 69.8 | 1% | yes | 27% | 73% | mean 2.2 | 56% | 1.40 (nonuse) | - | - | - | - |
| Schanzer        | 2008 | Obs  | INTL    | 1,404 | statins  | 68.5 | 39% | yes | - | 100% | max 1 | 45% | n.a. | - | - | - | - |
| Aung            | 2007 | meta | INTL    | 10,049| lipid lowering | - | - | yes | - | - | - | N/A | n.a. | - | - | - | - |
| Collins         | 2002 | RCT  | INTL    | 20,536| simvastatin | 71.1 | 56% | yes | - | 0.57 | 0.43 | median 3.5 | 56% | 0.75 IC 0.80 CLTI | 0.80 IC 0.73 CLTI | n.a. | n.a. | - |

our study 2020 | obs | DE | 22,208 | statins  | 71.1 | 56% | yes | - | 0.57 | 0.43 | median 3.5 | 56% | 0.75 IC 0.80 CLTI | 0.80 IC 0.73 CLTI | n.a. | n.a. | - |
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   | 1.01  |       |   |
| 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  | 1.66  |   |
| 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  |   |

**Odds Ratio for receiving Statins**
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.

| Variable                                      | Rank | OR Lower | OR Upper |
|-----------------------------------------------|------|----------|----------|
| Age, years                                    | 3    | 0.92     | 0.94     |
| Hospital length of stay, days                 | 7    | 1.01     | 1.02     |
| No of different prescriptions                 | 4    | 0.88     | 0.91     |
| Discharge year                                | 2    | 1.1      | 1.11     |
| No of previous inpatient admissions           | 6    | 0.93     | 0.96     |
| No of prior PAOD outpatient visits            | 9    | 0.97     | 0.99     |
| Female sex                                    | 11   | 1.1      | 1.2      |
| Van Walraven Score = 0                        | 23   | 0.96     | 1.2      |
| Van Walraven Score > 0 & < 10                 | 26   | 0.96     | 1.22     |
| Van Walraven Score > 9                        | 14   | 0.74     | 1        |
| Congestive heart failure                      | 18   | 1.14     | 1.39     |
| Cardiac arrhythmias                           | 8    | 0.75     | 0.88     |
| Chronic pulmonary disease                     | 19   | 1.07     | 1.24     |
| Renal failure                                 | 10   | 1.19     | 1.38     |
| Depression                                    | 22   | 0.95     | 1.1     |
| Prior stroke or TIA                           | 21   | 0.91     | 1.22     |
| Smoking                                       | 20   | 1.04     | 1.15     |
| Obesity                                       | 12   | 0.82     | 0.99     |
| Prior myocardial infarction                   | 15   | 1.33     | 1.81     |
| Dyslipidemia                                  | 1    | 5.19     | 47.3     |
| Coronary artery disease                       | 16   | 0.88     | 1.03     |
| Diabetes                                      | 13   | 0.89     | 1.1     |
| Cancer                                        | 24   | 0.96     | 1.19     |
| Hypertension                                  | 25   | 0.98     | 1.08     |
| No of prior PAOD outpatient visits            | 17   | 0.9      | 1.03     |
| Invasive procedure: OSR                       | 5    | 0.68     | 0.77     |
### Logistic Regression for PS-Matching, IC cohort, Diabetes matching

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

Odds Ratio for receiving Statins
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.
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

| Survival, CLTI cohort | Events/N   | HR (95% CI) |
|-----------------------|------------|-------------|
| Empty Model           | 3730/9463  | 0.58 (0.53-0.63) |
| Full Model            | 3730/9463  | 0.77 (0.70-0.84) |
| Amputation, CLTI cohort | Events/N   | HR (95% CI) |
| Empty Model           | 654/9463   | 0.75 (0.62-0.90) |
| Full Model            | 654/9463   | 0.81 (0.66-0.99) |
| CV Event, CLTI cohort | Events/N   | HR (95% CI) |
| Empty Model           | 1606/9463  | 0.78 (0.69-0.88) |
| Full Model            | 1606/9463  | 0.90 (0.79-1.02) |
| Diabetes, CLTI cohort | Events/N   | HR (95% CI) |
| Empty Model           | 605/4938   | 0.95 (0.79-1.14) |
| Full Model            | 605/4938   | 1.00 (0.82-1.22) |
| Myopathy, CLTI cohort | Events/N   | HR (95% CI) |
| Empty Model           | 219/9463   | 1.24 (0.93-1.65) |
| Full Model            | 219/9463   | 1.21 (0.89-1.66) |
| Survival, IC cohort   | Events/N   | HR (95% CI) |
| Empty Model           | 1940/12745 | 0.61 (0.54-0.67) |
| Full Model            | 1940/12745 | 0.83 (0.74-0.93) |
| Amputation, IC cohort | Events/N   | HR (95% CI) |
| Empty Model           | 173/12745  | 0.62 (0.44-0.89) |
| Full Model            | 173/12745  | 0.83 (0.67-1.22) |
| CV Event, IC cohort   | Events/N   | HR (95% CI) |
| Empty Model           | 1694/12745 | 0.68 (0.61-0.76) |
| Full Model            | 1694/12745 | 0.82 (0.73-0.92) |
| Diabetes, IC cohort   | Events/N   | HR (95% CI) |
| Empty Model           | 955/8623   | 0.90 (0.78-1.03) |
| Full Model            | 955/8623   | 0.99 (0.85-1.15) |
| Myopathy, IC cohort   | Events/N   | HR (95% CI) |
| Empty Model           | 549/12745  | 1.14 (0.95-1.35) |
| Full Model            | 549/12745  | 1.14 (0.94-1.38) |
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 comediations; HR: Hazard ratio; CI: Confidence interval; CLTI: Chronic limb-threatening ischemia; IC: Intermittent claudication; CV Cardiovascular

| Comparison of full model and full model with comedication | Events/N | HR (95% CI) |
|----------------------------------------------------------|----------|-------------|
| Survival, CLTI cohort                                    |          |             |
| Full Model                                               | 3730/9463| 0.77 (0.70-0.84) |
| Full Model + comedication                                | 3730/9463| 0.77 (0.70-0.84) |
| Amputation, CLTI cohort                                  |          |             |
| Full Model                                               | 654/9463 | 0.81 (0.66-0.99) |
| Full Model + comedication                                | 654/9463 | 0.82 (0.67-1.01) |
| CV Event, CLTI cohort                                    |          |             |
| Full Model                                               | 1606/9463| 0.90 (0.79-1.02) |
| Full Model + comedication                                | 1606/9463| 0.90 (0.79-1.02) |
| Diabetes, CLTI cohort                                    |          |             |
| Full Model                                               | 605/4938 | 1.00 (0.82-1.22) |
| Full Model + comedication                                | 605/4938 | 0.99 (0.81-1.21) |
| Myopathy, CLTI cohort                                    |          |             |
| Full Model                                               | 219/9463 | 1.21 (0.89-1.66) |
| Full Model + comedication                                | 219/9463 | 1.23 (0.90-1.66) |
| Survival, IC cohort                                      |          |             |
| Full Model                                               | 1940/12745| 0.83 (0.74-0.93) |
| Full Model + comedication                                | 1940/12745| 0.83 (0.74-0.93) |
| Amputation, IC cohort                                    |          |             |
| Full Model                                               | 173/12745| 0.83 (0.57-1.22) |
| Full Model + comedication                                | 173/12745| 0.85 (0.58-1.24) |
| CV Event, IC cohort                                      |          |             |
| Full Model                                               | 1694/12745| 0.82 (0.73-0.92) |
| Full Model + comedication                                | 1694/12745| 0.82 (0.73-0.93) |
| Diabetes, IC cohort                                      |          |             |
| Full Model                                               | 955/8623 | 0.99 (0.85-1.15) |
| Full Model + comedication                                | 955/8623 | 0.97 (0.84-1.13) |
| Myopathy, IC cohort                                      |          |             |
| Full Model                                               | 549/12745| 1.14 (0.94-1.38) |
| Full Model + comedication                                | 549/12745| 1.14 (0.94-1.38) |
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

| Comparison of models separated by sex | Events/N | HR (95% CI) |
|--------------------------------------|----------|-------------|
| **Survival, CLTI cohort**            |          |             |
| Females                              | 2144/5177| 0.77 (0.68-0.87) |
| Males                                | 1586/4286| 0.78 (0.68-0.89) |
| **Amputation, CLTI cohort**          |          |             |
| Females                              | 305/5177 | 0.54 (0.39-0.76) |
| Males                                | 349/4286 | 1.10 (0.85-1.42) |
| **CV Event, CLTI cohort**            |          |             |
| Females                              | 894/5177 | 0.92 (0.78-1.10) |
| Males                                | 712/4286 | 0.87 (0.72-1.10) |
| **Diabetes, CLTI cohort**            |          |             |
| Females                              | 319/2911 | 1.07 (0.80-1.41) |
| Males                                | 288/2027 | 0.97 (0.74-1.28) |
| **Myopathy, CLTI cohort**            |          |             |
| Females                              | 137/5177 | 1.41 (0.95-2.08) |
| Males                                | 82/4286  | 0.93 (0.56-1.57) |

| **Survival, IC cohort**              |          |             |
| Females                              | 851/5989 | 0.87 (0.73-1.04) |
| Males                                | 1089/6756| 0.80 (0.69-0.93) |
| **Amputation, IC cohort**            |          |             |
| Females                              | 78/5989  | 1.07 (0.62-1.83) |
| Males                                | 95/6756  | 0.68 (0.40-1.16) |
| **CV Event, IC cohort**              |          |             |
| Females                              | 791/5989 | 0.84 (0.71-1.00) |
| Males                                | 903/6756 | 0.80 (0.68-0.95) |
| **Diabetes, IC cohort**              |          |             |
| Females                              | 435/4245 | 0.98 (0.79-1.22) |
| Males                                | 520/4375 | 0.98 (0.80-1.20) |
| **Myopathy, IC cohort**              |          |             |
| Females                              | 293/5989 | 1.04 (0.80-1.36) |
| Males                                | 256/6756 | 1.27 (0.96-1.68) |
**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

### Comparison of models separated by ages 75+ and ages < 75

| Model                        | Events/N          | HR (95% CI)          |
|------------------------------|-------------------|----------------------|
| **Survival, CLTI cohort**    |                   |                      |
| Ages 74 and below            | 2722/5365         | 0.82 (0.71-0.95)     |
| Ages 75 and above            | 1108/4382         | 0.75 (0.67-0.84)     |
| **Amputation, CLTI cohort**  |                   |                      |
| Ages 74 and below            | 328/5365          | 0.80 (0.61-1.04)     |
| Ages 75 and above            | 349/4382          | 0.85 (0.63-1.15)     |
| **CV Event, CLTI cohort**    |                   |                      |
| Ages 74 and below            | 985/5365          | 0.85 (0.71-1.02)     |
| Ages 75 and above            | 671/4382          | 0.95 (0.81-1.13)     |
| **Diabetes, CLTI cohort**    |                   |                      |
| Ages 74 and below            | 279/2670          | 0.98 (0.77-1.26)     |
| Ages 75 and above            | 344/2407          | 1.00 (0.73-1.36)     |
| **Myopathy, CLTI cohort**    |                   |                      |
| Ages 74 and below            | 94/5365           | 1.21 (0.83-1.78)     |
| Ages 75 and above            | 134/4382          | 1.13 (0.67-1.89)     |
| **Survival, IC cohort**      |                   |                      |
| Ages 74 and below            | 981/3949          | 0.89 (0.77-1.03)     |
| Ages 75 and above            | 1038/9171         | 0.78 (0.65-0.93)     |
| **Amputation, IC cohort**    |                   |                      |
| Ages 74 and below            | 60/3949           | 0.83 (0.54-1.28)     |
| Ages 75 and above            | 123/9171          | 0.81 (0.40-1.66)     |
| **CV Event, IC cohort**      |                   |                      |
| Ages 74 and below            | 708/3949          | 0.79 (0.68-0.91)     |
| Ages 75 and above            | 1042/9171         | 0.91 (0.75-1.10)     |
| **Diabetes, IC cohort**      |                   |                      |
| Ages 74 and below            | 249/2460          | 1.08 (0.92-1.28)     |
| Ages 75 and above            | 730/6399          | 0.87 (0.48-0.93)     |
| **Myopathy, IC cohort**      |                   |                      |
| Ages 74 and below            | 163/3949          | 1.17 (0.94-1.46)     |
| Ages 75 and above            | 398/9171          | 1.06 (0.73-1.55)     |
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

Comparison of models separated by discharge years 2008 to 2012 and 2013 to 2018

| Model                      | Events/N         | HR (95% CI)   |
|----------------------------|------------------|---------------|
| **Survival, CLTI cohort**  |                  |               |
| Discharge year 2008-2012   | 1945/3907        | 0.73 (0.64-0.84) |
| Discharge year 2013-2018   | 1785/5556        | 0.80 (0.71-0.91) |
| **Amputation, CLTI cohort**|                  |               |
| Discharge year 2008-2012   | 344/3907         | 0.76 (0.56-1.03) |
| Discharge year 2013-2018   | 310/5556         | 0.82 (0.62-1.08) |
| **CV Event, CLTI cohort**  |                  |               |
| Discharge year 2008-2012   | 858/3907         | 0.93 (0.78-1.11) |
| Discharge year 2013-2018   | 750/5556         | 0.87 (0.73-1.04) |
| **Diabetes, CLTI cohort**  |                  |               |
| Discharge year 2008-2012   | 339/1989         | 1.12 (0.85-1.46) |
| Discharge year 2013-2018   | 268/2949         | 0.93 (0.69-1.24) |
| **Myopathy, CLTI cohort**  |                  |               |
| Discharge year 2008-2012   | 119/3907         | 1.16 (0.75-1.79) |
| Discharge year 2013-2018   | 100/5556         | 1.28 (0.82-2.00) |

**Survival, IC cohort**

| Events/N | HR (95% CI)   |
|-----------|---------------|
| 1143/5340 | 0.83 (0.72-0.97) |
| 797/7405  | 0.82 (0.69-0.97) |

**Amputation, IC cohort**

| Events/N | HR (95% CI)   |
|-----------|---------------|
| 108/5340  | 0.73 (0.44-1.22) |
| 65/7405   | 0.96 (0.54-1.73) |

**CV Event, IC cohort**

| Events/N | HR (95% CI)   |
|-----------|---------------|
| 961/5340  | 0.86 (0.73-1.01) |
| 733/7405  | 0.78 (0.65-0.92) |

**Diabetes, IC cohort**

| Events/N | HR (95% CI)   |
|-----------|---------------|
| 585/3503  | 1.04 (0.85-1.26) |
| 370/5120  | 0.90 (0.71-1.13) |

**Myopathy, IC cohort**

| Events/N | HR (95% CI)   |
|-----------|---------------|
| 274/5340  | 1.18 (0.89-1.56) |
| 275/7405  | 1.10 (0.85-1.44) |
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

| Survival, CLTI cohort | Events/N | HR (95% CI) |
|-----------------------|----------|-------------|
| Low-to-moderate-intensity statin | 3730/9463 | 0.77 (0.71-0.85) |
| High-intensity statin | 3730/9463 | 0.81 (0.53-1.24) |
| Amputation, CLTI cohort | | |
| Low-to-moderate-intensity statin | 654/9463 | 0.82 (0.67-1.01) |
| High-intensity statin | 654/9463 | 0.74 (0.30-1.82) |
| CV Event, CLTI cohort | | |
| Low-to-moderate-intensity statin | 1606/9463 | 0.89 (0.78-1.01) |
| High-intensity statin | 1606/9463 | 1.14 (0.69-1.90) |
| Diabetes, CLTI cohort | | |
| Low-to-moderate-intensity statin | 605/4938 | 0.99 (0.81-1.21) |
| High-intensity statin | 605/4938 | 1.29 (0.60-2.76) |
| Myopathy, CLTI cohort | | |
| Low-to-moderate-intensity statin | 219/9463 | 1.21 (0.88-1.65) |
| High-intensity statin | 219/9463 | 1.17 (0.37-3.77) |
| Survival, IC cohort | | |
| Low-to-moderate-intensity statin | 1940/1274 | 0.82 (0.73-0.92) |
| High-intensity statin | 1940/1274 | 1.11 (0.67-1.83) |
| Amputation, IC cohort | | |
| Low-to-moderate-intensity statin | 173/1274 | 0.84 (0.57-1.23) |
| High-intensity statin | 173/1274 | 0.81 (0.11-5.93) |
| CV Event, IC cohort | | |
| Low-to-moderate-intensity statin | 1694/1274 | 0.81 (0.72-0.92) |
| High-intensity statin | 1694/1274 | 1.19 (0.75-1.90) |
| Diabetes, IC cohort | | |
| Low-to-moderate-intensity statin | 955/8623 | 0.99 (0.85-1.15) |
| High-intensity statin | 955/8623 | 1.06 (0.58-1.94) |
| Myopathy, IC cohort | | |
| Low-to-moderate-intensity statin | 549/1274 | 1.10 (0.90-1.34) |
| High-intensity statin | 549/1274 | 2.00 (1.17-3.41) |

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

| Procedure                        | Events/N  | HR (95% CI)     |
|----------------------------------|-----------|-----------------|
| **Survival, CLTI cohort**        |           |                 |
| PVI                              | 2300/5835 | 0.75 (0.67-0.84)|
| OSR                              | 1430/3628 | 0.80 (0.69-0.92)|
| **Amputation, CLTI cohort**      |           |                 |
| PVI                              | 323/5835  | 0.76 (0.56-1.03)|
| OSR                              | 331/3628  | 0.86 (0.65-1.13)|
| **CVD, CLTI cohort**             |           |                 |
| PVI                              | 1011/5835 | 0.89 (0.76-1.04)|
| OSR                              | 595/3628  | 0.91 (0.74-1.12)|
| **Diabetes, CLTI cohort**        |           |                 |
| PVI                              | 325/2801  | 0.91 (0.70-1.20)|
| OSR                              | 280/2137  | 1.16 (0.87-1.55)|
| **Myopathy, CLTI cohort**        |           |                 |
| PVI                              | 132/5835  | 1.38 (0.93-2.03)|
| OSR                              | 87/3628   | 0.97 (0.57-1.65)|
| **Survival, IC cohort**          |           |                 |
| PVI                              | 1325/9552 | 0.80 (0.70-0.91)|
| OSR                              | 615/3193  | 0.87 (0.70-1.08)|
| **Amputation, IC cohort**        |           |                 |
| PVI                              | 81/9552   | 1.03 (0.62-1.73)|
| OSR                              | 92/3193   | 0.71 (0.40-1.24)|
| **CVD, IC cohort**               |           |                 |
| PVI                              | 1233/9552 | 0.78 (0.68-0.89)|
| OSR                              | 461/3193  | 0.90 (0.72-1.14)|
| **Diabetes, IC cohort**          |           |                 |
| PVI                              | 696/6416  | 1.04 (0.88-1.23)|
| OSR                              | 259/2207  | 0.83 (0.61-1.13)|
| **Myopathy, IC cohort**          |           |                 |
| PVI                              | 423/9552  | 1.12 (0.90-1.39)|
| OSR                              | 128/3193  | 1.18 (0.77-1.78)|