Statins and Major Adverse Limb Events in Patients with Peripheral Artery Disease: A Systematic Review and Meta-Analysis

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Abstract

Background Statins are guidelines recommended in patients with peripheral artery disease (PAD) for the prevention of cardiovascular (CV) events. Comprehensive meta-data on the impact of statins on major adverse limb events (MALE) in PAD patients are lacking. We examined the association of statin use with MALE in patients with PAD.

Methods We performed a systematic review (registered at PROSPERO: number CRD42019137111) and metanalysis of studies retrieved from PubMed (via MEDLINE) and Cochrane (CENTRAL) databases addressing the impact of statin on MALE including amputation and graft occlusion/revascularization. Secondary endpoints were all-cause death, composite CV endpoints, CV death, and stroke.

Results We included 51 studies with 138,060 PAD patients, of whom 48,459 (35.1%) were treated with statins. The analysis included 2 randomized controlled trials, 20 prospective, and 29 retrospective studies. Overall, 11,396 MALE events, 21,624 deaths, 4,852 composite CV endpoints, 4,609 CV deaths, and 860 strokes were used for the analysis. Statins reduced MALE incidence by 30% (pooled hazard ratio [HR]: 0.702; 95% confidence interval [CI]: 0.605–0.815) and amputations by 35% (HR: 0.654; 95% CI: 0.522–0.819), all-cause mortality by 39% (pooled HR: 0.608, 95% CI: 0.543–0.680), CV death by 41% (HR: 0.594; 95% CI: 0.455–0.777), composite CV endpoints by 34% (pooled HR: 0.662; 95% CI: 0.591–0.741) and ischemic stroke by 28% (pooled HR: 0.718; 95% CI: 0.620–0.831).

Conclusion Statins reduce the incidence of MALE, all-cause, and CV mortality in patients with PAD. In PAD, a high proportion of MALE events and deaths could be prevented by implementing a statin prescription in this patient population.

Keywords
- statin
- peripheral artery disease
- major adverse limb event
- stroke
- amputation
- cardiovascular death
- all-cause death

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Introduction

Peripheral artery disease (PAD) is a vascular disease of atherosclerosis origin affecting a large population of >200 million individuals worldwide.[1,2] These data likely underestimate the true PAD prevalence as in many cases patients with PAD are asymptomatic and may be discovered only by measuring the ankle–brachial index (ABI), which is recommended as diagnostic tool for the screening of PAD.[3] Furthermore, as PAD prevalence increases by age, the burden of PAD is likely to increase in the next future in parallel with aging population.[4]

PAD is usually associated with classic risk factors of atherosclerosis such as hypertension, diabetes, dyslipidemia, and smoking habit, which account for an enhanced risk of cardiovascular (CV) disease such as myocardial infarction (MI), stroke, and CV death.[5] Furthermore, PAD patients experience progression of atherosclerotic PAD, which may result in recurrent surgical intervention and/or limb amputation. Based on this, PAD therapy is aimed at preventing CV complications and includes antiplatelet drugs such as aspirin and clopidogrel.[6] Statins are also used because of the well-known cardioprotective effects[7] and a recent analysis including >190,000 PAD patients showed that statins were administered in approximately 80% of PAD patients.[8] However, in broad populations of symptomatic PAD included in clinical trials, the statin use at baseline is lower at 73%.[9] The clinical efficacy of statins has been investigated by Ramos et al in a matched-case control study showing that PAD patients on treatment with statins were less likely to die or experience major CV events compared with controls during a follow-up of approximately 4 years.[10] Such beneficial effect was essentially related to the reduction of coronary heart disease while no effect on stroke was found. The cardioprotective effects of statins in PAD was partly corroborated by a meta-analysis that included 19,368 PAD patients, which showed a reduction of total mortality and stroke while MI and CV death were unaffected[11]; no data regarding progression of PAD including major adverse limb events (MALE) were reported.

Recent guidelines on PAD treatment by the American Heart Association and European Society of Cardiology (Class I Level A) suggest the use of statins to prevent CV diseases.[3,12]

However, it remains to be elucidated if statins affect MALE including peripheral revascularization or limb amputation.

To further explore the impact of statins on PAD outcomes, we performed a systematic review and meta-analysis that included >138,000 PAD patients treated or not with statins, in whom the efficacy of statins on MALE and mortality was investigated.

Methods

Eligibility Criteria and Research Strategy

We performed a systematic review of the literature searching MEDLINE via PubMed and Cochrane (CENTRAL) database using a combination of the following keywords "statin," "PAD," "limb," "ischemia," "MI," "stroke," and "mortality." The research strategy was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with no time restrictions until March 8, 2019 (►**Supplementary Fig. S1** [available in the online version]). The systematic review was registered at PROSPERO (https://www.crd.york.ac.uk/PROSPERO) with registration number CRD42019137111.

We included only journal articles in English language with full text available. We included observational (both prospective $n = 20$ and retrospective $n = 29$) cohort studies, and two randomized controlled trials (RCT). We excluded cross-sectional and case–control studies, case reports, editorials/comments, letters, review and metanalysis, and experimental studies.

Study Selection and Quality Assessment

Two physicians (F.D.S. and D.M.) independently screened the titles and abstracts of manuscripts identified through the database searches to identify studies potentially eligible for further assessment. A third physician (D.P.) reviewed eligible studies for appropriateness and completeness. The study selection was performed in multiple phases. In the first phase, potentially relevant studies were obtained by combined searches of electronic databases using the selected above-mentioned keywords. Then, studies not in English language, not involving humans, or not addressing study question were excluded. In the second phase, studies were reviewed and selected according to the inclusion and exclusion criteria. The quality of observational studies was assessed by the Newcastle–Ottawa scale.[13] Studies with a score ≥7 were considered of good quality. Quality assessment of each study is reported in ►**Supplementary Table S1** [available in the online version]).

Endpoints: the type of endpoint reported in each study is given in ►**Supplementary Table S2** [available in the online version]). Definitions used for MALE, composite CV endpoints are reported in ►**Supplementary Tables S3** and **S4** [available in the online version]). In particular, MALE had multiple definitions including amputation ($n = 12$), loss of patency or graft occlusion/restenosis ($n = 12$), or a composite of amputation and repeat revascularization ($n = 8$) (►**Supplementary Table S3** [available in the online version]).

Composite CV endpoints (►**Supplementary Table S4** [available in the online version]) included all-cause or CV death (with myocardial infarction and stroke) in 13 studies, while 4 studies reported only nonfatal events such as myocardial infarction/coronary revascularization and stroke/transient ischemic attack.

Statistical Analysis

Meta-analyses for each endpoint separately were performed based on both linear fixed and random effects, using the logarithm of hazard ratios (HRs) as outcome. Inverse variance weights were used in all cases. I^2 statistics were used to assess the heterogeneity across the studies. When I^2 was above a prespecified cutoff of 25% for the fixed-effects model, a random-effects model was finally used. Additionally, meta-regression analysis was performed for age, sex, diabetes, previous MI, and duration of treatment. Results of meta-regression were

also summarized by means of bubble plots, with bubbles proportional to the inverse variance of each study and trends estimated through nonparametric local polynomial regression. When a study did not report the HR for statin use or its associated 95% confidence interval (CI), these were approximated using the available data (essentially using the cumulative incidence stratified by treatment group[14] for further details).

Publication bias was assessed by means of funnel plots. Funnel plot asymmetry was then formally assessed by means of rank correlation tests. A further sensitivity analysis was performed by removing one study at a time and replicating the meta-analysis. A forest plot was finally used to visually assess that removal of one single study in no case lead to a leave-one-out pooled HR outside the 95% CI obtained with the entire data.

Ethical Review

Given the study type (review article), an ethical approval was not required.

Results

Study Characteristics and Results of Individual Studies

PRISMA flow diagram showing study search strategy is reported in ►**Supplementary Fig. S1** [available in the online version]). After screening, 72 potentially eligible studies were identified and considered for detailed analysis (►**Supplementary Fig. S1** [available in the online version]); 51 studies were included in the metanalysis: 20 prospective, 2 randomized clinical trials, and 29 retrospective studies (►**Table 1**).

►**Table 1** shows the clinical setting/definition of PAD for each study. A total of 138,060 patients with PAD were included (►**Table 1**), of whom 48,459 (35.1%) were on treatment with statins and 88,337 were not (in two studies it was not possible to calculate the number of patients in each group).

Major Adverse Limb Events

Overall, 32 studies reported data on MALE including 116,733 patients, 37,790 treated, and 77,883 not treated with statins. ►**Supplementary Table S3** (available in the online version)

Table 1 Study design and clinical setting/definition of peripheral artery disease

Number of studies	Study (year)	Study design	Number of patients	Patients on statins	Patients not on statins	Clinical setting/definition of PAD
1	Aronow et al (2002)[27]	P	660	318	342	Symptomatic PAD or history of surgery
2	Mohler III et al (2003)[28]	RCT	354	240	114	Stable intermittent claudication, ABI $\leq$0.9
3	Abbruzzese et al (2004)[29]	R	172	88	84	Patients undergoing infrainguinal arterial surgery
4	Schillinger et al (2004)[30]	P	515	269	246	Angiographically proven PAD
5	HPSCG et al (2007)[31]	RCT	6,748	3,384	3,364	Intermittent claudication or previous peripheral arterial revascularization procedure, amputation, or aneurysm repair
6	Kumbhani et al (2014)[32]	R	5,861	3,643	2,218	Symptomatic PAD
7	Westin et al (2014)[33]	P	380	246	134	Critical limb ischemia
8	Dosluoglu et al (2014)[34]	R	717	397	320	Intermittent claudication and CLI undergoing revascularization
9	Ward et al (2005)[35]	R	446	72	374	Patients undergoing Infrainguinal bypass surgery for atherosclerotic PAD
10	De Liefde et al (2008)[36]	P	2,109	668	1,441	Intermittent claudication, pain in the legs or ulcerations, and single-stage treadmill-walking test
11	Jones et al (2015)[37]	P	908	676	242	Patients undergoing lower extremity revascularization procedures
12	Vrsalović et al (2015)[38]	P	319	194	125	PAD: clinical examination, ankle brachial index measurement, duplex sonography and/or computed tomography or magnetic resonance, angiography, and confirmed with peripheral angiography
13	Lee et al (2016)[39]	R	342	287	55	Symptomatic PAD undergoing endovascular treatment
14	Matsubara et al (2017)[40]	R	114	26	88	Patients with CLI or undergoing revascularization
15	Siracuse et al (2017)[41]	P	1,014	794	220	Patients undergoing percutaneous vascular intervention
16	Kumakura et al (2019)[42]	P	932	467	465	Symptomatic PAD or femoropopliteal artery stenosis $\geq$70% on angiography or ultrasound
17	Khan et al (2018)[43]	R	1,204	718	486	Patients undergoing endovascular and open revascularization for chronic limb ischemia
18	Feringa et al (2007)[44]	P	1,374	481	893	PAD (ABI $<$ 0.9)
19	Feringa et al (2007)[45]	P	425	158	267	Diabetic patients with PAD (ABI $<$ 0.9)

Table 1 (*Continued*)

Number of studies	Study (year)	Study design	Number of patients	Patients on statins	Patients not on statins	Clinical setting/definition of PAD
20	Vidula et al (2010)[46]	P	579	242	337	PAD (ABI < 0.9)
21	Tomoi et al (2013)[47]	R	812	169	643	CLI undergoing endovascular therapy
22	Hsu et al (2017)[48]	R	64,902	11,409	52,493	PAD (International Classification of Diseases definition)
23	Pasqualini et al (2007)[49]	P	357	62	295	Lower extremity arterial disease
24	Suckow et al (2015)[50]	P	2,067	1,537	530	CLI or symptomatic PAD undergoing infrainguinal bypass surgery
25	Tern et al (2018)[51]	R	678	447	231	Ultrasonography diagnosis of PAD
26	O'Donnell et al (2017)[52]	R	931	717	214	Patients undergoing revascularization (endovascular or surgical) for CLI
27	Iida (2015)[53]	P	314	81	233	CLI undergoing endovascular treatment
28	Isma et al (2008)[54]	P	259	59	200	Critical limb ischemia
29	Schanzer et al (2008)[55]	P	1,404	636	768	CLI undergoing lower extremity bypass graft
30	Aiello et al (2012)[56]	R	646	319	327	Critical limb ischemia
31	Faglia et al (2014)[57]	P	553	250	303	Diabetic patients with CLI
32	Parmar et al (2019)[58]	R	488	199	289	PAD with surgical or endovascular interventions
33	Henke et al (2004)[59]	P	293	164	129	Patients undergoing infrainguinal bypass surgery
34	Carter et al (2007)[60]	R	197	120	77	Patients undergoing lower limb arterial bypass surgery for occlusive disease
35	Stavroulakis et al (2017)[61]	P	816	445	371	Critical limb ischemia
36	Thatipelli et al (2007)[62]	R	395	119	276	PAD (ABI < 0.9)
37	Van Gestel et al (2008)[63]	R	3,371	810	2,561	Patients undergoing elective vascular surgery for PAD
38	Randon et al (2010)[64]	R	92	31	61	Patients with CLI undergoing infrapopliteal arterial reconstruction
39	Scali et al (2011)[65]	R	116	55	61	Patients undergoing crural bypass graft for CLI
40	Iida et al (2012)[66]	R	60			Patient undergoing angioplasty for infrapopliteal lesion
41	Siracuse et al (2012)[67]	R	218	142	76	Patients undergoing intervention for superficial femoral artery occlusion
42	Baril et al (2013)[68]	R	5,706	3,847	1,859	Patients undergoing infrainguinal lower extremity bypass
43	Saqib et al (2013)[69]	R	210	113	97	CLI undergoing endovascular treatment
44	Vogel et al (2013)[70]	R	22,954	1,1619	11,335	Symptomatic PAD
45	Todoran et al (2012)[71]	P	136	121	15	Patients undergoing angioplasty or stenting of superficial femoral artery for claudicatio intermittens or CLI
46	Siracuse et al (2014)[72]	R	221	106	115	Patients undergoing endovascular interventions for below-knee popliteal artery lesions
47	Spiliopoulos et al (2015)[73]	R	214			Diabetic patients treated with infrapopliteal drug eluting stent
48	Kim et al (2016)[74]	R	135	91	44	Patients with previous endovascular treatment
49	Klingelhoefer et al (2016)[75]	R	244	120	124	Symptomatic PAD with previous prosthetic above knee femoropopliteal bypass
50	Maehaffey et al (2017)[76]	R	3,848	1,172	2,676	CLI undergoing revascularization
51	De Grijs et al (2018)[77]	R	250	131	119	Patients undergoing stenting of the superficial femoral or popliteal artery

Abbreviations: ABI, ankle–brachial index; CLI critical limb ischemia; P, prospective; PAD, peripheral artery disease; R, retrospective; RCT, randomized clinical trial.

reports the definition of MALE used in each study. The total number of MALE events was 11,396 (►**Table 2**). The pooled HR for statin treatment in preventing MALE was 0.702 (95% CI: 0.605–0.815; ►**Fig. 1**, **Panel A**).

When we performed a subanalysis on studies including only limb amputation as the endpoint ($n = 12$), we found that statins reduced amputation rate by 35% (pooled HR: 0.654; 95% CI: 0.522–0.819; ►**Fig. 1**, **Panel B**). The effect of statins on the

Table 2 Number of events according to each endpoint in patients treated or not with statins

	Number of studies	Total number of patients	Total number of events	Incidence rate (per 100 patient-years)
Major adverse limb events	32	116,733	11,396[a]	2.4
Amputation only	12	99,313	7,257[b]	
Other composite major adverse limb events	20	17,420	4,139[b]	
All-cause mortality	31	99,607	21,624[a]	4.5
Myocardial Infarction[d]	10	17,791	1,341	2.7
Composite cardiovascular endpoints	17	22,795	4,852[c]	6.3
Cardiovascular death	9	75,371	4,609	1.1
Stroke	7	14,386	860	1.4

[a]Data missing in two studies.
[b]Data missing in one study.
[c]Data missing in four studies.
[d]This endpoint was not used for the metanalysis given the high heterogeneity of the definition of the endpoints used in the studies (►**Supplementary Table S6**, available in the online version).

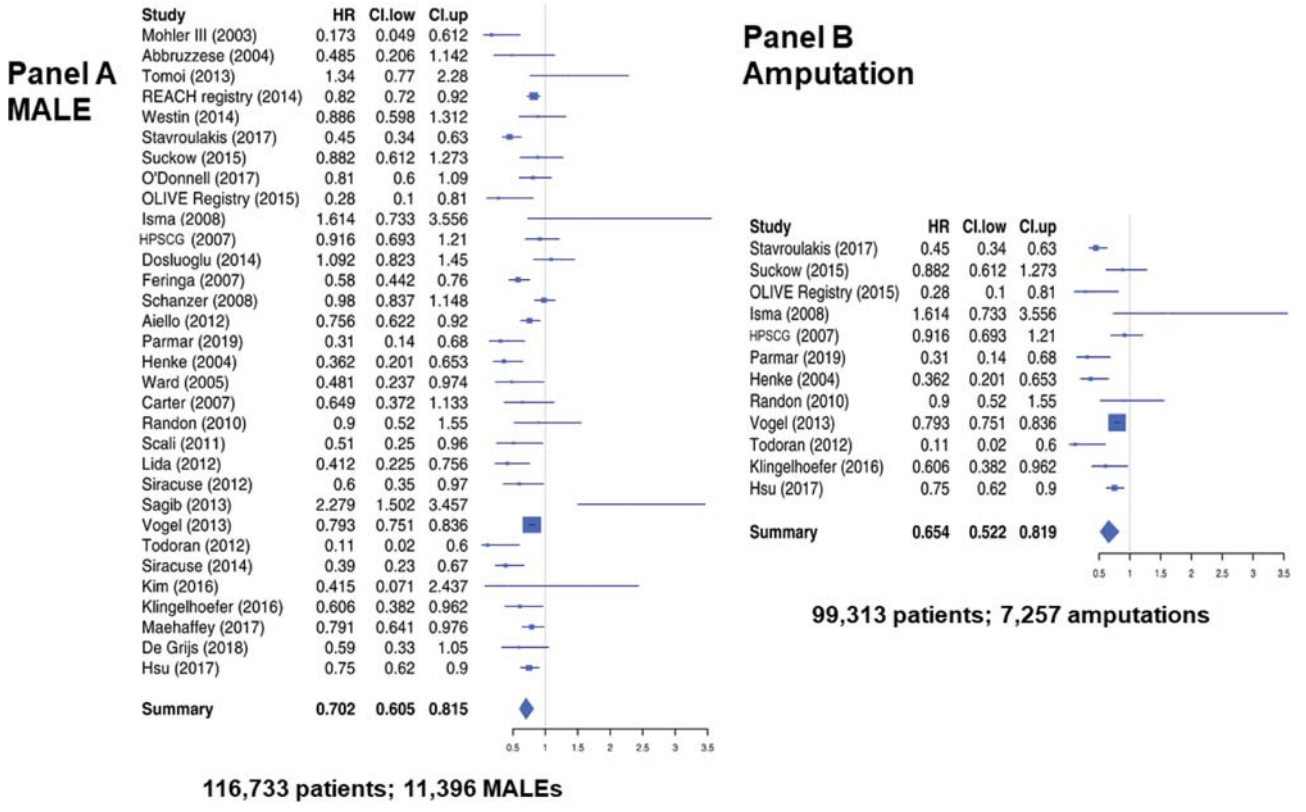

Fig. 1 Forest plot for major adverse limb events (major adverse limb event **A**) and limb amputations (**B**).

rate of MALE was not modified by age, sex, follow-up length, or diabetes (►**Supplementary Fig. S2**, Panels A–D [available in the online version]).

All-Cause Mortality

A total of 31 studies reported data on all-cause mortality according to statin treatment. A total of 99,607 PAD patients were included, with a total 21,624 deaths.

The pooled HR for statin treatment in preventing all-cause mortality was 0.608 (95% CI: 0.543–0.680; ►**Fig. 2**). The effect of statins on the mortality was not modified by age, sex, follow-up length, or diabetes (►**Supplementary Fig. S3**, Panels A–D [available in the online version]).

Composite Cardiovascular Endpoints, Stroke, and Cardiovascular Mortality

A total of 17 studies reported data on composite CV endpoints. Detailed definition of composite endpoint for each study is reported in ►**Supplementary Table S5** (available in the online version). The pooled HR for statin

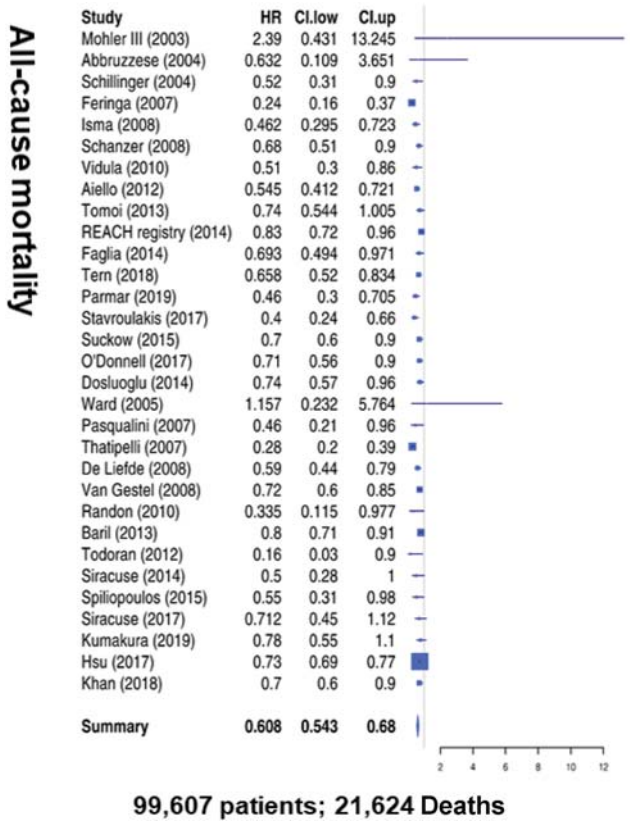

Fig. 2 Forest plot for all-cause mortality.

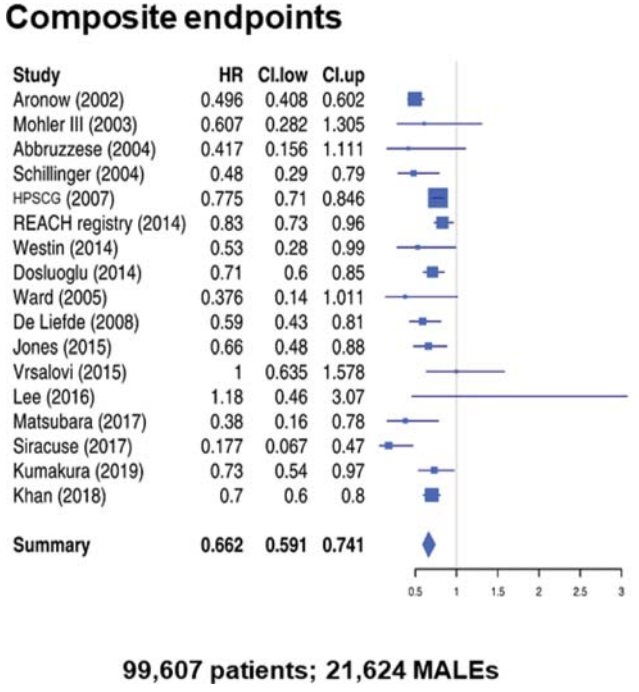

Fig. 3 Forest plot for composite cardiovascular endpoints (►**Supplementary Table S3** for definitions).

treatment in preventing composite CV endpoints was 0.662 (95% CI: 0.591–0.741; ►**Fig. 3**). For studies with a composite CV endpoint, there was a significant effect of sex ($p = 0.02$) and age ($p = 0.01$) while no significant effect of follow-up length and diabetes was found (►**Supplementary Fig. S4**, Panels A–D [available in the online version]).

Nine studies reported data on CV death including 75,371 patients and 4,609 deaths. The pooled HR for statin treatment in preventing CV death was 0.594 (95% CI: 0.455–0.777) (►**Supplementary Fig. S5**, Panel A [available in the online version]).

Seven studies reported data on stroke including 14,386 patients and 860 strokes. The pooled HR for statin treatment in preventing stroke was 0.718 (95% CI: 0.620–0.831; ►**Supplementary Fig. S5**, Panel B [available in the online version]).

The effects of statins on the rate of CV death and stroke were not modified by age, sex, follow-up length, or diabetes (►**Supplementary Table S4** [available in the online version]).

Funnel plots for each outcome are reported in ►**Supplementary Fig. S6**, Panels A–E (available in the online version). Formal tests for publication bias did not show evidence of such. Additional sensitivity analyses were performed by removing one study at a time. These also provided no evidence of sensitivity as in no case removal of a single study lead to qualitatively different results with respect to pooled HR or their significance ►**Supplementary Fig. S7**, Panels A–D (available in the online version).

Results of meta-regression analysis for each endpoint are reported in ►**Supplementary Table S5** (available in the online version).

Regarding MI, 10 studies were found to be eligible from the strategy search. However, given the high heterogeneity of definitions used to diagnose MI, lack of a formal definition and adjudication of MI events in three studies, the quality of studies was too low to perform a reliable analysis on the effect of statins on MI. Definitions used for diagnosis of MI are reported in ►**Supplementary Table S6** (available in the online version).

Discussion

This is the first metanalysis investigating the effect of statin treatment on MALEs in patients with PAD. We found that in PAD patients treated with statins, the incidence of MALE was reduced by 30% as compared with those not treated. In addition, we found a significant reduction of all-cause (39%) and CV mortality (41%), composite CV endpoints (34%), and of ischemic stroke (28%) associated with statins. Conversely, we found no significant association between statin use and MI reduction.

The recent Surveillance of CV Events in Antiplatelet-Treated ArterioSclerosis Obliterans patients in JapaN (SEASON) prospective registry study including 6,565 patients showed an incidence of MALE of 1.75 per 100 patient-years in PAD patients, with history of lower extremity revascularization/amputation, chronic kidney disease, diabetes, and ABI <0.4 or <0.7 being risk factors for MALEs.[15] We found a 30% reduction in MALE in PAD patients treated with statins, which was consistent also when we considered only a major vascular

endpoint, as amputation. This finding is of clinical impact because despite the rate of amputation is decreasing over time, it is still high and associated with a substantial risk of death and reamputation (7.7 and 10.2%, respectively).[16] Thus, after a major amputation, PAD is associated with an approximately 20% of in-hospital[17] and long-term mortality (incidence 3.74 per 100 patient-years).[15]

The 39 and 41% reduction of total and CV mortality related to statin treatment observed in our analysis is higher than that observed in primary and secondary prevention trials with statins, in which total mortality and CV death were reduced roughly by 15 to 31%.[18] Our data are also consistent with a previous meta-analysis showing a reduction of total mortality by approximately 40%[11]; conversely, CV mortality showed a trend to a reduction; however, that did not reach significance. Therefore, our data indicate that the use of statin may provide a substantial benefit by reducing total and CV mortality rate also in the clinical setting of PAD.

Recent data from the EUCLID (Examining Use of Ticagrelor in Peripheral Artery Disease) trial showed that the incidence of stroke in PAD is high, estimated at 0.87 per 100 patient-years, in patients already on treatment with antiplatelets.[19] Our finding that statin treatment is associated with a reduction of 28% of ischemic stroke suggests that statin represent an additional therapy to reduce cerebrovascular events in this setting.

Results from this metanalysis have clinical implications. Patients with PAD should be prescribed on statin treatment not only for the prevention of CV events but also for reducing the incidence of MALE and mortality. We found that only one third of patients with PAD included in the various studies were on treatment with statins. This is of concern as the proportion of patients with PAD treated with statins is highly variable and still low in many cases, ranging from 11 to 79% as reported by a recent meta-analysis.[20] Also, after amputation, $<$50% of patients is treated with statins[21]; this translates in a high proportion of patients who are not optimally managed and are exposed to a residual risk of recurrent MALE and death, which are potentially preventable with statins. These results are even more important considering that one in seven patients with vascular disease has a recurrent CV event or MALE with high health-related costs (i.e., estimated at $21,752 annually for a person aged 65 years).[22] The only recent therapeutic advance for the prevention of MALE in patients with stable PAD has been reported by the COMPASS trial, which tested the efficacy of combining low-dose rivaroxaban (2.5 mg twice day) with aspirin (100 mg/day) compared with aspirin (100 mg/day) alone.[23] Thus, in patients with PAD, defined as intermittent claudication with ABI $<$0.90 or stenosis $\geq$50%, or previous aorta-femoral or lower extremity bypass surgery, percutaneous transluminal angioplasty of iliac or infra-inguinal arteries or limb or foot amputation for arterial vascular disease, the use of rivaroxaban plus aspirin significantly reduced the rate of MACE/MALE compared with aspirin alone (HR: 0.70; 95% CI: 0.55–0.88).[24]

Our analysis has strengths and limitations to be acknowledged. First, the heterogeneity of studies included in the metanalysis is generally high, indicating that further research on more homogeneous subpopulations might be useful. It is possible that the estimated effects might be modulated even though main predictors were recorded and assessed in our study (including history of MI, diabetes, gender, age, etc.). Lack of information on statin types and doses on different endpoints is another limitation of the study; future studies such as a network or individual-patient metanalysis will explore this issue. Finally, we have no data on LDL cholesterol levels, which may potentially affect the efficacy of statin treatment. In this context, a recent publication of the PCSK9 inhibitor drug evolocumab in PAD demonstrated that a further reduction in LDL-cholesterol levels on top of maximal dose statin was associated with significant reductions in MACE and MALE.[25] For MALE, there was a linear relationship between the reduction in LDL-C and reduction in MACE.[25]

An unexplored issue for this analysis is the effect of statins on acute limb ischemia, which occurs in PAD patients with a rate of 1.3%/year.[26] A limitation of the current analysis is that ALI was not included in any definition of MALE.

In conclusion, statins reduce the incidence of MALEs and mortality in patients with PAD. A still high proportion of patients with PAD is not optimally treated with statins.

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Conflict of Interest
None declared.

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