ORIGINAL RESEARCH

High-Intensity Statin Therapy Is Associated With Improved Survival in Patients With Peripheral Artery Disease

T. Raymond Foley, MD; Gagan D. Singh, MD; Damianos G. Kokkinidis, MD; Ho-Hin K. Choy, MD; Thai Pham, MD; Ezra A. Amsterdam, MD; John C. Rutledge, MD; Stephen W. Waldo, MD; Ehrin J. Armstrong, MD; John R. Laird, MD

Background—The relative benefit of higher statin dosing in patients with peripheral artery disease has not been reported previously. We compared the effectiveness of low- or moderate-intensity (LMI) versus high-intensity (HI) statin dose on clinical outcomes in patients with peripheral artery disease.

Methods and Results—We reviewed patients with symptomatic peripheral artery disease who underwent peripheral angiography and/or endovascular intervention from 2006 to 2013 who were not taking other lipid-lowering medications. HI statin use was defined as atorvastatin 40–80 mg or rosuvastatin 20–40 mg. Baseline demographics, procedural data, and outcomes were retrospectively analyzed. Among 909 patients, 629 (69%) were prescribed statins, and 124 (13.6%) were treated with HI statin therapy. Mean low-density lipoprotein level was similar in patients on LMI versus HI (80±30 versus 87±44 mg/dL, *P*=0.14). Demographics including age (68±12 versus 67±10 years, *P*=0.25), smoking history (76% versus 80%, *P*=0.42), diabetes mellitus (54% versus 48%, *P*=0.17), and hypertension (88% versus 89%, *P*=0.78) were similar between groups (LMI versus HI). There was a higher prevalence of coronary artery disease (56% versus 75%, *P*=0.0001) among patients on HI statin (versus LMI). After propensity weighting, HI statin therapy was associated with improved survival (hazard ratio for mortality: 0.52; 95% confidence interval, 0.33–0.81; *P*=0.004) and decreased major adverse cardiovascular events (hazard ratio: 0.58; 95% confidence interval 0.37–0.92, *P*=0.02).

Conclusions—In patients with peripheral artery disease who were referred for peripheral angiography or endovascular intervention, HI statin therapy was associated with improved survival and fewer major adverse cardiovascular events compared with LMI statin therapy. **(*J Am Heart Assoc*. 2017;6:e005699. DOI: 10.1161/JAHA.117.005699.)**

Key Words: amputation • critical limb ischemia • peripheral artery disease • statin • survival

Peripheral artery disease (PAD) affects >200 million people worldwide.[1] Two thirds of patients with PAD have concomitant coronary or cerebrovascular atherosclerotic disease, accounting for a significantly increased risk of heart attack, stroke, and cardiovascular mortality in this population.[2–4]

HMG–coenzyme A reductase inhibitors, commonly referred to as statins, have been associated with reduced peripheral ischemic events and improved all-cause and cardiac-related mortality rates in patients with PAD.[5,6] Among patients with critical limb ischemia (CLI), the most severe manifestation of PAD, statin therapy has also been associated with reduced mortality and improved amputation-free survival.[7–9] Despite compelling evidence and guideline recommendations, patients with PAD are undertreated medically and are significantly less likely than patients with coronary artery disease (CAD) to receive statin therapy.[10,11]

Current American College of Cardiology (ACC) and American Heart Association (AHA) guidelines provide a class 1 recommendation supporting high-intensity statin therapy (eg, rosuvastatin 20–40 mg, atorvastatin 40–80 mg) for all patients aged <75 years with atherosclerotic cardiovascular disease, including PAD.[12] This recommendation includes an ACC/AHA level of evidence A, consistent with data from multiple large-scale studies. Importantly, the evidence cited for this recommendation is derived from trials evaluating a variety of statin intensities for secondary prevention in patients with CAD.[13–15] To date, there is no direct data comparing outcomes in patients with PAD treated with LMI or

From the Section of Cardiology, Denver VA Medical Center and University of Colorado School of Medicine, Aurora, CO (T.R.F., D.G.K., S.W.W., E.J.A.); Section of Cardiology, University of California, Davis, Sacramento, CA (G.D.S., H.-H.K.C., T.P., E.A.A., J.C.R., J.R.L.).

An accompanying Table S1 is available at http://jaha.ahajournals.org/content/6/7/e005699/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Ehrin J. Armstrong MD, VA Denver Medical Center, 1055 Clermont Street, Denver, CO 80220. E-mail: ehrin.armstrong@gmail.com

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Clinical Perspective

What Is New?

- The findings of this study, which is the first to evaluate the clinical impact of statin intensity in patients with PAD, demonstrate that high-intensity (HI) statin therapy is associated with improved survival and fewer major adverse cardiovascular events in this vulnerable patient population compared with low- or moderate-intensity (LMI) statin therapy.

What Are the Clinical Implications?

- This study provides novel evidence in support of current professional society guidelines recommending HI statin therapy for patients with PAD and highlights the importance of improved physician awareness about the benefits of statin therapy in this patient population.

HI statin therapy, and previous research has failed to demonstrate a beneficial effect of HI statin therapy on endothelial function in patients with PAD.[16] We hypothesized that among patients with symptomatic PAD referred for angiography and possible endovascular intervention, HI statin therapy would be associated with improved survival and fewer major adverse cardiovascular events (MACE) compared with LMI statin therapy.

Methods

This retrospective study used data from the PAD–University of California (UC) Davis Registry, which comprises all patients with a clinical diagnosis of PAD who underwent lower extremity angiography or endovascular intervention at the UC Davis Medical Center between 2006 and 2013. All patients in the registry with CLI or claudication who were not taking other lipid-lowering medications were included in the analysis. The study protocol was approved by the institutional review board at the UC Davis Medical Center with a waiver of informed consent.

Demographic, clinical, laboratory, and procedural data were obtained through preprocedure clinical notes, admission history, in-patient documentation, and angiographic review. Comorbidities that may affect physician prescribing of guideline-directed medical therapies—including patient history of myocardial infarction, stroke, and CAD—were also recorded. Medical prescribing patterns were verified by pharmacy prescriptions, both preprocedure and during follow-up. Medication prescription data were obtained from both pharmacy orders and standardized preprocedure evaluation that included current medications. Each patient's utilization of guideline-recommended medical therapy (eg, aspirin, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, statins) within the 3 months before the procedure and at 2 years after the procedure was assessed. All records were reviewed by trained chart abstractors and verified by a board-certified cardiologist.

Claudication was classified as Rutherford category 1–3 disease (mild, moderate, or severe claudication, respectively). CLI was classified as Rutherford category 4–6 disease (ischemic rest pain, minor tissue loss, or major tissue loss, respectively). Patient outcomes were determined by review of postprocedural clinical visits as well as electronic medical record documentation of subsequent hospitalizations and discharge summaries. Mortality was confirmed by chart documentation or the Social Security Death Index. The abstractors for these end points were blinded to other data analysis.

Outcomes

The primary end point was overall survival at 3 years. Secondary end points were MACE, major adverse limb events (MALE), and amputation-free survival (AFS). MACE was defined as fatal or nonfatal myocardial infarction, stroke, or cardiovascular death. MALE was defined as amputation or target lesion revascularization. AFS was defined as freedom from major amputation and all-cause death.

Statistical Analysis

Continuous variables and frequencies are presented as mean±SD, and categorical variables are presented as percentages. Continuous variables were compared using the Wilcoxon rank sum test, and categorical values were compared using χ^2 or Fisher exact tests. Propensity scoring was used to adjust for confounding in HI and LMI statin therapy, defined as the conditional probability of being treated with an HI or LMI statin, given a patient's measured demographic and clinical characteristics. To calculate the propensity score, we developed a logistic model for HI statin treatment using stepwise logistic regression analysis. Baseline covariates in the model included age, sex, race, history of diabetes mellitus, CAD, congestive heart failure, hypertension, stroke, end-stage renal disease, carotid disease, chronic obstructive pulmonary disease, smoking status, and concomitant use of medications including β-blockers, aspirin, and clopidogrel. Diagnostic tests to demonstrate balance of covariates after inverse probability of treatment weighting included calculation of the standardized difference before and after weighting to verify propensity score overlap between groups. Standardized mean difference calculation confirmed covariate balance after propensity weighting (Table S1). We performed a sensitivity analysis by adjusting further after inverse probability of treatment weighting for covariates that had a standardized mean difference >0.1 after

inverse probability of treatment weighting. This sensitivity analysis revealed similar point estimates for primary and secondary end points.[17] To determine the best estimate for the treatment effect of HI and LMI statin use, proportional hazards marginal structural models were developed via weighting using the propensity score. Marginal structural models were developed to adjust for time-dependent confounding of statin prescription. Multiple methodologies were used to validate the propensity model and have been described previously.[8]

A subgroup analysis was also performed to investigate the primary and secondary end points stratified by the clinical manifestations of PAD (eg, claudication versus CLI). All analyses were performed using STATA software (version 13.1). Hazard ratios (HRs) are provided with 95% confidence intervals (CIs). For all tests, a P value <0.05 was considered significant.

Results

Study Population

A total of 909 patients with claudication or CLI were included in the overall cohort, and 629 (69%) of these patients were prescribed a statin medication. Among patients treated with a statin, 124 (19.7%) were prescribed a HI medication and followed for a median of 1.4 years (526 days). Atorvastatin (35%) and simvastatin (36%) were the most commonly prescribed statins, accounting for 71% of the total prescribed statins.

Patients prescribed LMI and HI statins had similar baseline comorbidities (Table 1), with the exception of a significantly higher prevalence of CAD among patients receiving HI statins (77%) compared with those treated with LMI statins (P<0.0001). Patients on HI statins had a higher prevalence of proximal left anterior descending CAD (24% versus 13%, P=0.003), 2-vessel CAD (12% versus 5%, P=0.005), and 3-vessel CAD (27 versus 15%, P=0.002). Consistent with a higher prevalence of clinically recognized CAD, patients prescribed HI statins were significantly more likely to be prescribed aspirin, dual antiplatelet therapy with aspirin and clopidogrel, and β-blockers (Table 1). The overall cohort was characterized by a high prevalence of current or prior tobacco use (76% versus 80% in the LMI and HI statin groups, respectively; P=0.48) and diabetes mellitus (54% versus 48% in the LMI and HI statin groups, respectively; P=0.11).

Baseline lipid profiles did not differ between the LMI and HI statin groups (total cholesterol 145±38 versus 155±54 mg/dL, respectively, P=0.11; low-density lipoprotein [LDL] 80±30 versus 87±44 mg/dL, respectively, P=0.14). The majority of patients prescribed HI statins presented with CLI (60%), whereas the majority of patients prescribed LMI statins presented with claudication (54%).

Table 1. Baseline Patient Characteristics

Variable	LMI Statin (n=505)	HI Statin (n=124)	P Value
Age, y	69±12	67±10	0.16
Male, %	305 (60)	73 (59)	0.75
BMI, kg/m^2	28±6	28±5	0.71
Current/former smoker, %	386 (76)	99 (80)	0.42
Diabetes mellitus, %	275 (54)	59 (48)	0.17
A1c, %	7.6±2.1	7.9±2.2	0.46
CHF, %	121 (24)	32 (26)	0.67
Ejection fraction, %	53±17 (16)	52±17	0.56
CVA/TIA, %	100 (20)	25 (20)	0.78
HTN, %	444 (88)	110 (89)	0.77
ESRD, %	71 (14)	18 (15)	0.89
Creatinine, mg/dL	1.7±1.8	1.6±1.6	0.51
GFR, mL/min	60±30	65±26	0.12
CAD (%)	283 (56)	96 (77)	0.0001
Proximal LAD disease	67 (13)	30 (24)	0.003
Left main disease	12 (2)	6 (5)	0.14
One-vessel disease	30 (6)	9 (7)	0.6
Two-vessel disease	26 (5)	15 (12)	0.005
Three-vessel disease	78 (15)	34 (27)	0.002
Aspirin, %	368 (73)	109 (88)	0.0001
DAPT, %	127 (25)	48 (39)	0.003
ACEI/ARB, %	331 (66)	86 (69)	0.6
β-Blocker, %	294 (58)	87 (70)	0.02
Cholesterol panel			
Total cholesterol, mg/dL	145±38	155±54	0.11
LDL, mg/dL	80±30	87±44	0.14
HDL, mg/dL	40±16	41±17	0.63
Triglycerides, mg/dL	129±66	146±111	0.12
Procedure type			0.23
Diagnostic, %	106 (21)	24 (19)	
Intervention, %	378 (75)	100 (81)	
Presentation			0.008
Claudication	236 (47)	50 (40)	
CLI	269 (54)	74 (60)	

Values are mean±SD or n (%). A1c indicates glycosylated hemoglobin A1c; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CLI, critical limb ischemia; CVA, cerebrovascular accident; DAPT, dual antiplatelet therapy; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HDL, high-density lipoprotein; HI, high intensity; HTN, hypertension; LAD, left anterior descending; LDL, low-density lipoprotein; LMI, low or moderate intensity; TIA, transient ischemic attack.

Baseline ankle brachial indexes, toe brachial indexes, and angiographic vessel runoff did not differ significantly between the 2 groups (Table 2). Baseline ankle brachial index values

Table 2. Additional Patient Characteristics

Variable	LMI Statin (N=505)	HI Statin (N=124)	*P* Value
Vessel runoff			0.49
No or 1-vessel runoff (%)	321 (64)	80 (65)	
Two- or 3-vessel runoff (%)	184 (36)	44 (35)	
ABI	0.55±0.29	0.52±0.30	0.58
TBI	0.23±0.19	0.22±0.20	0.8

Values are n (%). ABI indicates ankle brachial index; HI, high intensity; LMI, low or moderate intensity; TBI, toe brachial index.

were 0.55±0.29 in the LMI group and 0.52±0.30 in the HI group (*P*=0.58), reflecting a population with advanced PAD. Consistent with this, the majority of patients had 1-vessel runoff on angiography.

Outcomes by Intensity of Statin Therapy

The event rates and HRs for the clinical outcomes are summarized in Table 3. In unadjusted analysis, HI statin use was associated with a numerical reduction in overall mortality (HR: 0.68; 95% CI, 0.45–1.02) and a nonsignificant trend toward reduced MACE (HR: 0.83; 95% CI, 0.57–1.20) and improved AFS (HR: 0.82; 95% CI, 0.56–1.21). The propensity model demonstrated balance in adjusted variables, with no significant difference in the pooled odds of statin prescribing after propensity weighting for all measured covariates, including other medication use. After propensity adjustment for baseline characteristics, comorbidities, and medications, HI statin therapy was associated with significantly improved survival (adjusted HR: 0.52; 95% CI, 0.33–0.81; *P*=0. 004) and reduced MACE (adjusted HR: 0.58; 95% CI, 0.37–0.92; *P*=0.02) (Figure 1). Rates of AFS (adjusted HR: 0.77; 95% CI, 0.51–1.15; *P*=0.2) and MALE (adjusted HR: 0.92; 95% CI, 0.56–1.49; *P*=0.7) did not differ significantly between the 2 groups (Figure 2). In a subgroup analysis of patients with CLI, HI statin therapy was associated with improved survival and reduced MACE, with point estimates similar to that of the overall cohort (Table 4). For claudicants, the subgroup analysis did not detect a statistically significant difference in MACE and survival. Rates of AFS and MALE were similar for patients treated with HI and LMI statin therapy.

Trends in Statin Prescribing

The majority of patients in this study were treated with LMI statin therapy. Between 2006 and 2013, >70% of patients prescribed statins were treated with LMI agents. The percentage of patients treated with HI versus LMI statins was not significantly different by year and did not increase over time (Figure 3). At 2 years, patients on HI were more likely to remain on statin therapy than those taking LMI (66% versus 54%, *P*=0.017).

Discussion

Statins are recommended for all patients with PAD, and recent guidelines suggest use of HI statins based on the recognition that patients with PAD have a high risk of cardiovascular mortality. To our knowledge, this study is the first comparing HI and LMI statin therapy in patients with PAD undergoing peripheral angiography and/or intervention. We found that HI statin therapy was associated with a significant reduction in overall mortality and MACE compared with LMI statin therapy in this population. These results were present in both unadjusted and adjusted models, suggesting an independent benefit of HI statin therapy among patients with PAD. In addition, we reported the prevalence of HI statin use in a population of patients with PAD referred for angiography and/or endovascular intervention.

Improved Survival and Reduced MACE With HI Statin Therapy

The results of this study suggest that HI statin therapy provides a mortality benefit over LMI statin therapy in patients with PAD. This effect was accompanied by a significant

Table 3. Three-Year Outcome Rates With Unadjusted and Adjusted HRs

	Unadjusted			IPTW Adjusted		
Variable	HI Statin (n=124)	LMI Statin (n=505)	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Death	26 (21)	136 (27)	0.64 (0.42–0.97)	0.04	0.53 (0.34–0.83)	0.004
MACE	25 (20)	125 (25)	0.69 (0.44–1.06)	0.09	0.58 (0.37–0.92)	0.02
MALE	20 (16)	84 (17)	0.91 (0.46–1.49)	0.7	0.94 (0.57–1.58)	0.8
Amputation	10 (8)	46 (9)	0.81 (0.41–1.60)	0.5	0.92 (0.44–1.94)	0.8

Values are represented as n (%). CI indicates confidence interval; HI, high intensity; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LMI, low or moderate intensity; MACE, major adverse cardiovascular events (myocardial infarction, cerebrovascular accident, or death); MALE, major adverse limb events (amputation, target lesion revascularization).

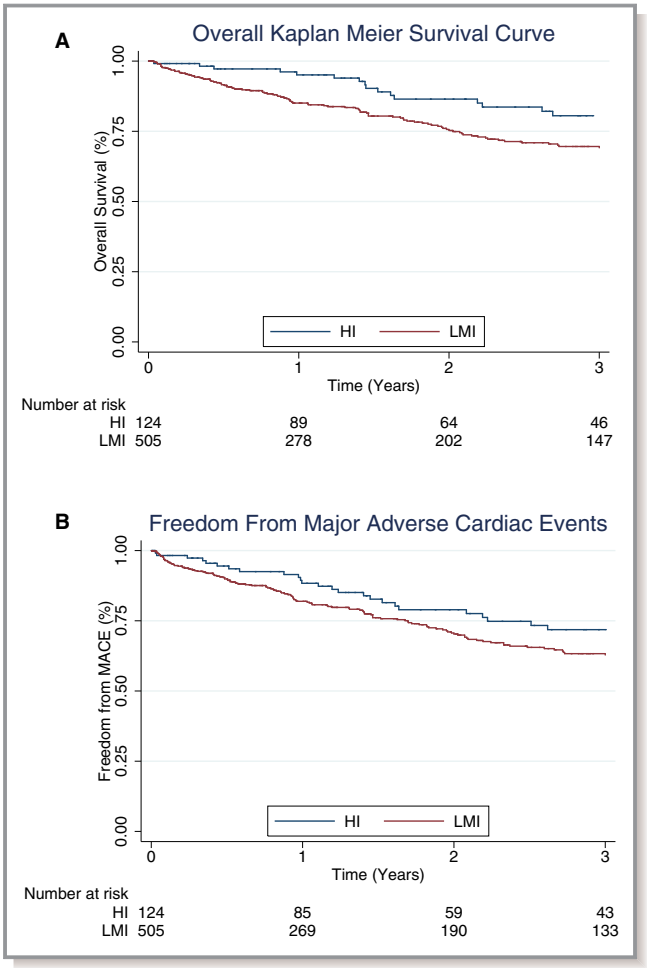

Figure 1. Survival and MACE rates associated with HI and LMI statin use. Kaplan–Meier curves to 3 years demonstrating survival (A) and MACE rates (B) in patients with peripheral artery disease treated with HI and LMI statin therapy. HI indicates high intensity; LMI, low or moderate intensity; MACE, major adverse cardiovascular events.

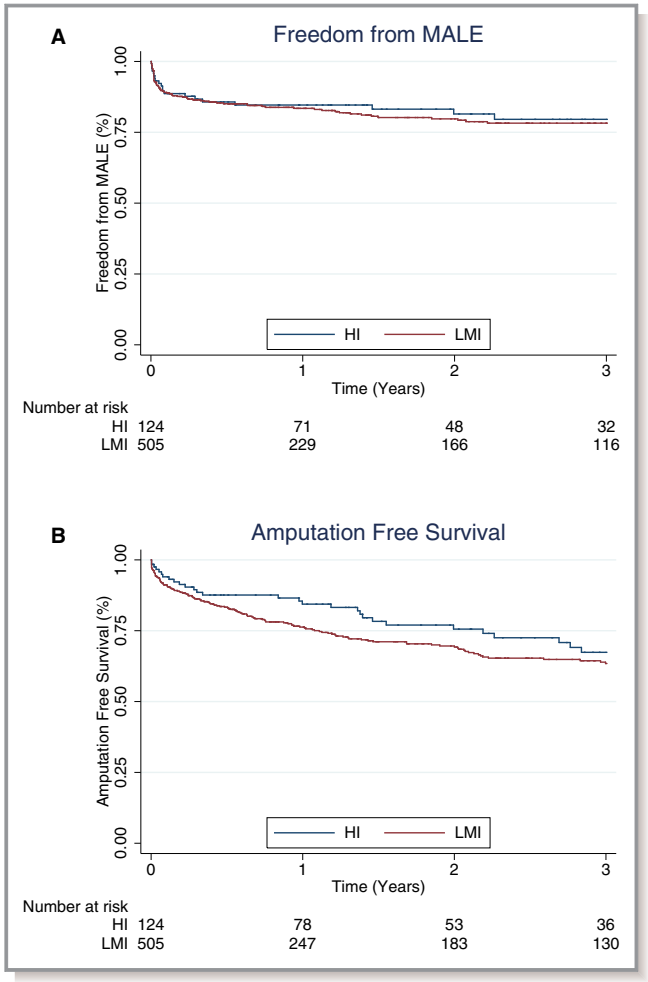

Figure 2. Amputation-free survival and freedom from MALE rates associated with HI and LMI statin use. Kaplan–Meier curves to 3 years demonstrating no significant difference in freedom from MALE (A) or amputation-free survival (B) among patients treated with HI and LMI statin therapy. HI indicates high intensity; LMI, low or moderate intensity; MALE, major adverse limb events.

reduction in MACE and is consistent with the results of several large randomized controlled trials demonstrating reduced mortality and secondary ischemic events in patients with atherosclerosis of the coronary and cerebral vasculature treated with HI statin therapy.[13–15,18]

The benefit of lowering LDL in preventing MACE has been well described, particularly among patients with coronary atherosclerosis. HI statins exert potent LDL-lowering effects and may mediate additional benefits through pleiotropic mechanisms leading to atherosclerotic regression and plaque stabilization.[19,20] Indeed, mechanistic studies have demonstrated that HI statin therapy (atorvastatin 80 mg daily) is associated with greater regression of carotid intima–media thickness and coronary atherosclerosis compared with moderate-intensity therapy (eg pravastatin 40 mg daily, simvastatin 40 mg daily).[21–23] Several large clinical trials have demonstrated rapid reductions in event rates among patients with CAD treated with HI statin therapy independent of baseline lipid profiles.[14,15] Consistent with this, we observed significant improvement in overall mortality and reduction of MACE with HI statin therapy despite similar baseline LDL levels between groups. This finding likely reflects a pleiotropic effect of HI statin therapy leading to atherosclerotic regression, plaque stabilization, and fewer atherothrombotic events among patients with PAD, as lipid values were not significantly different between the 2 groups. Furthermore, reductions in MACE and mortality were observed despite a higher prevalence of proximal left anterior descending and multivessel CAD among those prescribed HI statins.

As a manifestation of systemic atherosclerosis, PAD is associated with a high risk of adverse cardiovascular events such as stroke and myocardial infarction.[24] Statin therapy has been shown to mitigate this risk among patients with PAD across a broad spectrum of disease severity. The Heart

Table 4. Outcomes by Subgroup Analysis

Variable	HI Statin (n=74)	LMI Statin (n=237)	Unadjusted		IPTW	
			HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Claudication						
Death	9 (12)	28 (12)	0.88 (0.42–1.87)	0.747	0.72 (0.32–1.61)	0.426
MACE	14 (19)	37 (16)	1.16 (0.53–2.52)	0.711	1.05 (0.46–2.39)	0.901
MALE	3 (4)	12 (5)	0.77 (0.22–2.76)	0.7	0.67 (0.17–2.6)	0.561
Amputation	1 (1)	2 (1)	1.46 (0.13–16.07)	0.76	1.14 (0.09–14.5)	0.921
Critical limb ischemia						
Death	17 (35)	107 (40)	0.69 (0.41–1.14)	0.149	0.53 (0.31–0.91)	0.021
MACE	22 (45)	115 (43)	0.7 (0.41–1.18)	0.178	0.54 (0.3–0.97)	0.039
MALE	17 (35)	72 (27)	1.2 (0.71–2.04)	0.494	1.21 (0.7–2.08)	0.493
Amputation	9 (18)	44 (17)	0.98 (0.48–2)	0.945	1.1 (0.52–2.36)	0.8

Values are represented as n (%). HI indicates high intensity; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LMI, low moderate intensity; MACE, major adverse cardiovascular events; MALE, major adverse limb events.

Protection Study included 6748 patients with symptomatic PAD and demonstrated 22% relative risk reduction in vascular events among patients prescribed simvastatin compared with placebo.[5] Similarly, Feringa et al demonstrated reduced cardiac and all-cause mortality among patients with symptomatic PAD prescribed statins, an effect that was most pronounced among patients receiving HI statin therapy and that was independent of LDL lowering.[6] The REACH registry included 5861 patients with symptomatic PAD and demonstrated significant reductions in MACE and adverse limb outcomes such as amputation among patients treated with statins.[9] Recently, data have also emerged supporting the use of statins in patients with CLI. In a retrospective study of 646 patients undergoing endovascular therapy for CLI, Aiello et al found that statin therapy was associated with significant improvements in overall mortality, primary and secondary

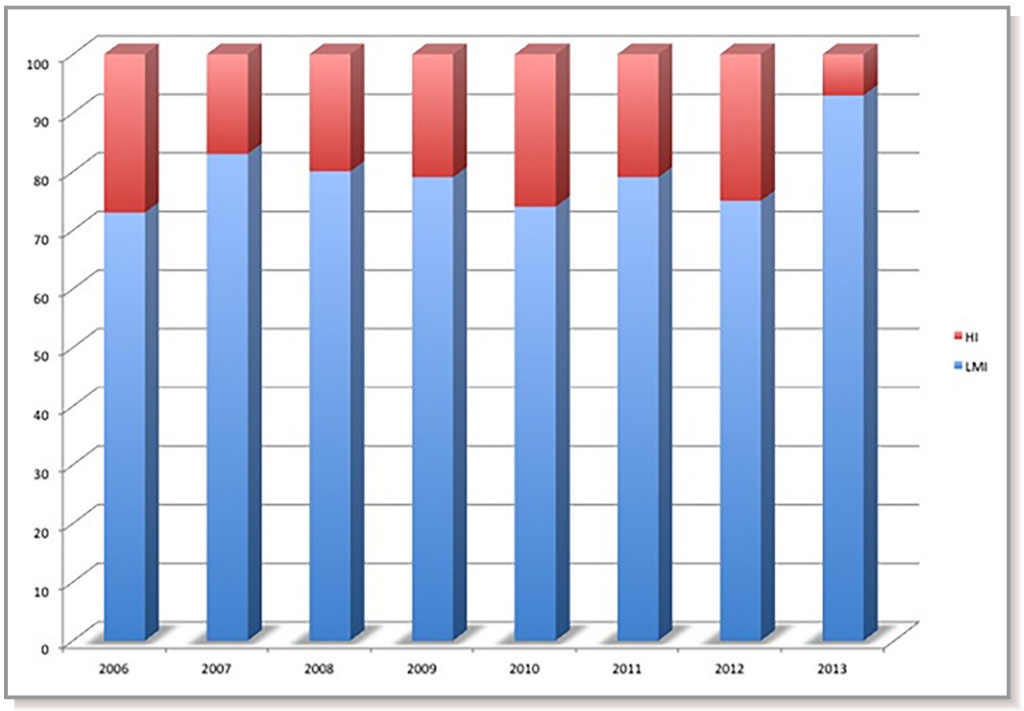

Figure 3. HI vs LMI statin prescriptions between 2006 and 2013. Graph illustrating a prevalence of LMI statin use that persisted throughout the study period. HI indicates high intensity; LMI, low or moderate intensity.

patency, and limb salvage at 24 months.[7] Similarly, Westin et al reported lower rates of major adverse cardiovascular and cerebrovascular events and reduced mortality among patients with CLI treated with statins.[8]

Despite this preponderance of evidence demonstrating superior clinical outcomes in patients with PAD treated with statins, little is known about the relative effects of statin intensity in this population. In patients with coronary atherosclerosis, HI statin therapy has consistently been shown to confer greater protection in terms of MACE and mortality. The PROVE-IT TIMI 22 investigators demonstrated that among patients with CAD and recent acute coronary syndrome, intensive statin therapy with atorvastatin 80 mg was superior to standard therapy with pravastatin 40 mg nightly in reducing all-cause mortality and MACE.[14] In patients with stable CAD, high-dose atorvastatin (80 mg) was shown to reduce cardiovascular death, nonfatal myocardial infarction, and fatal or nonfatal stroke compared with low-dose atorvastatin (10 mg).[13]

Recently, the IDEAL study compared the effect of HI versus moderate-intensity statin therapy among patients with recent myocardial infarction.[25] In a subgroup analysis of patients with PAD, HI statin therapy was associated with a reduction in overall cardiovascular and coronary events and lower rates of coronary revascularization. Similarly, a recent study by Rodriguez et al included 509 766 patients with atherosclerotic cardiovascular disease, including PAD, and found that HI statin therapy was associated with a survival advantage compared with moderate-intensity statin therapy.[26] Our study expands on these findings by including only patients with clinically significant PAD referred for angiography or endovascular intervention, a selected population with a greater likelihood of having advanced PAD compared with those identified through screening or with non–lifestyle-limiting claudication. Multiple studies have demonstrated a strong correlation in overall cardiovascular risk and disease severity in PAD.[3,8,27] Our study highlights the potential for HI statin therapy to mitigate this risk among patients with more advanced PAD requiring angiography and/or endovascular intervention.

MALE and AFS

Rates of MALE and AFS did not differ significantly between patients treated with HI and LMI statin therapy. Two prior studies demonstrating improved limb salvage and AFS with statin therapy included patients with CLI exclusively and did not stratify outcomes based on statin intensity.[7,8] It is possible that statin therapy, regardless of intensity and through pleiotropic mechanisms, improves limb-specific outcomes in populations with a high prevalence of infrapopliteal disease, such as those with CLI.

In our study, nearly half of patients presented with claudication. Although statin therapy in these patients reduces MACE, patients with claudication alone are unlikely to undergo amputation. Consequently, our study is likely underpowered to detect a significant difference in MALE and AFS. Regardless, our findings have implications for the broader PAD population, which stands to derive significant benefit in terms of overall mortality and reduced MACE from HI statin use.

Prevalence of HI Statin Use Among Patients With PAD

Our study provides insight into the use of HI statins among patients with PAD. Overall cardiovascular risk reduction is a primary objective in the treatment of patients with PAD, and medical therapy with an antiplatelet agent and statin is indicated in all patients with PAD who do not have contraindications to these medications. The use of statins is a core performance measure for the treatment of patients with PAD and is supported by a class 1 recommendation in ACC/AHA guidelines.[28] Nonetheless, studies have demonstrated that nearly half of patients with PAD alone do not receive statin therapy.[11] In our study, in which a majority of patients had concomitant CAD, 68.9% were prescribed a statin. This is slightly lower than reported rates of statin use in patients with CAD alone, which range from 70% to 78%.[29,30] Importantly, only a minority of patients in our study (13.6%) were treated with guideline-directed HI statin therapy These patients were more likely to have multivessel CAD and to remain on statin therapy at 2 years. To our knowledge, this study is the first to stratify the prevalence of statin therapy by drug intensity in patients with PAD and identifies areas for future clinical improvement.

Limitations

This study has several limitations. First, we reported outcomes from a single tertiary care center. Consequently, our findings (eg, statin prescriptions) are representative of the practice patterns only at this institution; however, this institution includes a dedicated vascular center that focuses on the treatment of patients with PAD. In addition, our data are derived from statin prescriptions and do not necessarily reflect adherence to statin therapy. There was substantial heterogeneity among the statins used in this study, and follow-up LDL levels are not available for our cohort, limiting our understanding of whether the improvement in overall mortality was driven primarily by LDL reduction or an alternative mechanism. Clinical information regarding symptom improvement following intervention is not available. Finally, the retrospective nature of this study allows for the description of associations and does not prove a causal relationship between high-potency statin use and improved survival; however, the propensity model demonstrated

excellent covariate balance, suggesting an independent effect of HI statin therapy based on measured covariates.

Conclusions

This study is the first to compare the relative effects and outcomes of HI versus LMI statin therapy in patients with PAD undergoing peripheral angiography and/or intervention. Our data support current guideline recommendations by demonstrating improved survival in patients with PAD treated with HI statins compared with LMI statins. Consistent with previously published reports, our study suggests that many patients with PAD do not receive statin therapy, and even fewer receive HI statin therapy. These findings highlight a need for ongoing education to raise awareness among providers and patients alike about the benefits of statin therapy in PAD. Future studies are needed to confirm these findings and to determine whether the overall mortality benefit observed with HI statin therapy is results from reduced MACE, MALE, or both.

Disclosures

Ehrin Armstrong reports being a consultant for Abbott Vascular, Boston Scientific, Cardiovascular Systems, Medtronic, and Spectranetics. Laird reports being a consultant or advisory board member for: Bard Peripheral Vascular, Boston Scientific, Medtronic, and Abbott Vascular. He receives research support from WL Gore. All other authors report no conflicts of interest related to this study.

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Supplemental Material

Table S1. Standardized mean difference calculation for covariates before and after propensity weighting

VARIABLE	Before IPTW SMD	After IPTW SMD
Age, years	0.1067	0.163
Sex (female)	0.01601	0.0037
BMI (kg/m2)	0.03545	0.061
Current/former smoker (%)	0.08086	0.074
Diabetes (%)	0.10509	0.00813
CHF (%)	0.04288	0.00376
Ejection Fraction (%)	0.05637	0.00598
CVA/TIA (%)	0.02718	0.0265
HTN (%)	0.04684	0.04618
ESRD (%)	0.01774	0.05824
Creatinine (mg/dL)	0.07816	0.101
CAD (%)	0.2	0.02731
Aspirin (%)	0.35	0.29
DAPT (%)	0.278	0.2446
ACE/ARB (%)	0.07987	0.06763
Beta Blocker (%)	0.226	0.02142
Total Cholesterol (mg/dL)	0.00237	0.024
LDL (mg/dL)	0.0209	0.0486
HDL (mg/dL)	0.019	0.04702
Triglycerides (mg/dL)	0.0503	0.1227
Procedure Type (Dx vs Tx)	0.16386	0.149
Presentation	0.2097	0.19378

SMD = standardized mean deviation; BMI = body mass index; CHF = congestive heart failure; CVA = cerebrovascular accident; TIA = transient ischemic attack; HTN = hypertension; ESRD = end stage renal disease; CAD = coronary artery disease; DAPT = dual antiplatelet therapy; ACE= angiotensin converting enzyme; ARB = angiotensin receptor blocker; LDL = low density lipoprotein; HDL = high density lipoprotein; Dx = diagnostic; Tx = therapeutic