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Statins Have a Dose-Dependent Effect on Amputation and Survival in Peripheral Artery Disease Patients.

Running Title: *Arya et al.; Statin Intensity Peripheral Artery Disease*

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Abstract

Background—Statin dose guidelines for Peripheral Artery Disease (PAD) patients are largely based on coronary artery disease and stroke data. The aim of this study is to determine the effect of statin intensity on PAD outcomes of amputation and mortality.

Methods—Using an observational cohort study design and a validated algorithm we identified incident PAD patients (2003-2014) in the national Veterans Affairs data. Highest statin intensity exposure [high intensity vs low- moderate intensity vs antiplatelet therapy but no statin use (AP only)] was determined within one year of diagnosis of PAD. Outcomes of interest were lower extremity amputations and death. The association of statin intensity with incident amputation and mortality was assessed with Kaplan Meier plots, Cox proportional hazards modeling, propensity score (PS) matched analysis as well as sensitivity and subgroup analyses to reduce confounding.

Results—In 155,647 patients with incident PAD, more than a quarter (28%) were not on statin. Use of high intensity statins was lowest in patients with PAD only (6.4%) as compared to comorbid coronary/carotid disease (18.4%). Incident amputation and mortality risk declined significantly with any statin use compared to AP only group. In adjusted Cox models, the high intensity statin users were associated with lower amputation risk and mortality as compared to AP only users [HR 0.67; 95% CI (0.61, 0.74) and HR 0.74; 95% CI (0.70, 0.77), respectively]. Low-moderate intensity statins also had significant reductions in risk of amputation and mortality [HR amputation 0.81 (0.75, 0.86), HR death 0.83 (0.81, 0.86)] as compared to no statins (AP only) but effect size was significantly weaker than the high intensity statins ($p<0.001$). The association of high intensity statins with lower amputation and death risk remained significant and robust in PS matched, sensitivity and subgroup analyses.

Conclusions—Statins, especially high intensity formulations, are underutilized in PAD patients. This is the first population based study to show that high intensity statin use at time of PAD diagnosis is associated with a significant reduction in limb loss and mortality compared to low-moderate intensity statin users as well as patients treated only with antiplatelet medications but not with statins.

Key Words: peripheral artery disease, statins, high intensity statins, amputations, vascular medicine, mortality, propensity score, veterans health.

Clinical Perspective

What is new?

- Our study shows that use of high intensity statins early in PAD diagnosis is better in terms of decreasing risk of amputation and death in PAD patients.
- Use of low and moderate intensity statins also have beneficial effects for limb loss and mortality compared to no use of statins.
- There is still considerable underutilization and recognition of the role of secondary prevention using statins in PAD patients especially in those without coronary disease.

What are the clinical implications?

- Upon diagnosis of PAD, a patient should be started on the highest intensity of statin that can be tolerated much like coronary artery disease (CAD) to reduce their lifetime risk of amputation and death.
- Emphasis needs to be laid on early diagnosis and treatment of PAD especially in the absence of CAD by all providers including primary care physicians, cardiologists, vascular specialists etc.

Introduction

Peripheral artery disease (PAD) is a highly prevalent atherosclerotic syndrome affecting 8 to 12 million individuals in the United States and is associated with significant disability, morbidity and mortality[1, 2]. The prevalence is 15-20% in individuals over 65 years[3]. There are 148,000 major amputations done annually in the United States due to PAD[4]. Annual mortality (8.2%) is higher among patients with PAD than after a myocardial infarction (6.3%)[5]. Despite the significant limb and cardiovascular outcomes in PAD, there is poor risk factor modification relative to other atherosclerotic diseases like coronary artery disease (CAD) or stroke[6-15].

In 2013, the American Heart Association/ American College of Cardiology (AHA/ACC) guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults recommended that all patients with clinically apparent atherosclerotic cardiovascular disease should be initiated on high-intensity statins [3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors] [16]. The guidelines cited that the level of evidence for PAD was low. The Heart Protection Study is the only RCT to include a large number of PAD patients and showed a reduction in the rate of first major vascular and peripheral vascular events in a subcohort of Simvastatin treated PAD patients [17, 18]. PAD remains an understudied disease population[19] and most data or risk estimates are obtained from sub-cohorts of CAD patients or isolated from population group estimates[5, 20, 21].

Given the lack of evidence supporting use of high intensity statins in PAD patients, the objective of our study was to determine the effect of statin intensity (based on 2013 ACC/AHA guidelines) on PAD outcomes of amputation and mortality. We also sought to evaluate the variation in prescription of statin intensity over time and by presence of comorbid atherosclerotic disease conditions in a large PAD cohort.

Methods

This study was approved by the Emory University IRB and Atlanta VAMC Research and Development Committee. Informed consent was waived for a retrospective cohort study design with no human subject contact and minimal privacy risks. The data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure since they contain subject identifiers. However, the analytical approach is described in sufficient detail in the manuscript to allow researchers with VA data access to reproduce and replicate results.

Sample and Database

Incident PAD patients were identified from the national Veterans Health Administration (VHA) data using a validated algorithm[22] [ICD-9 diagnosis code for PAD + any one of three criteria: 1.) Two ankle brachial indices (ABIs) in 14 months, 2.) 2 visits to vascular surgeon/clinic in 14 months, or 3.) any PAD procedure code] from 2003-2014 and who did not have previous PAD diagnosis code in their medical record in 3 years (2000-2002) [N=155,647][23].

Study Exposure and Outcome

The exposure was defined as the highest statin dose used/prescribed to a veteran around their PAD diagnosis date (six months before and after). The statin dose/intensity was defined by the 2013 ACC/AHA guidelines (eTable 1). Low and moderate intensity statins were combined into one category because less than 4% subjects were on low intensity statins. Since the Simvastatin 80mg dose is not part of the 2013 ACC/AHA guidelines and is no longer prescribed in the VHA pharmacy due to concerns of myotoxicity[24], we excluded it from the main Cox models and propensity matched analyses but included it in a sensitivity analysis.

The outcomes of interest were (1) incident amputation (mid/hind-foot, below and above knee amputations) and (2) death after PAD diagnosis during follow-up (ICD-9 diagnosis codes and procedure codes in eTable 2). The follow-up continued through outcome occurrence or December 31, 2015 (whereupon the subject was censored). Patients with prior amputations were included in the analysis but incident amputation was defined as the first amputation after PAD diagnosis. Long-term survival of the cohort of patients was extracted from the VA vital status file.

Covariates

A comprehensive list of patient covariates was abstracted from the database; all variables were measured as close as possible to the PAD diagnosis date with a 6-month limit on either side. Covariates included demographics (age at PAD diagnosis, sex, race), socioeconomic status (SES) as defined by median household income of the patient's most recent residential zip code tabulation area (ZCTA), body mass index (BMI), smoking (current vs. former vs. never smoker, classified using a validated method for text based health factors[25]), antiplatelet drug use (aspirin, clopidogrel, other), cilostazol use, patient co-morbidities [diabetes (DM), hypertension (HTN), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), atrial fibrillation (AF), carotid artery stenosis (CAS), chronic kidney disease or end stage renal disease (CKD/ESRD), and depression] (eTable 2), laboratory values [total cholesterol, high density lipoprotein (HDL), low-density lipoprotein (LDL), hemoglobin A1c and serum creatinine], PAD severity (claudication vs. rest pain vs. ulceration/gangrene vs. not specified), and diagnosis year. All variables were abstracted from the national Veterans Affairs (VA) Corporate Data Warehouse and VA Medical SAS administrative databases.

Statistical Analysis

Demographic and clinical variables were assessed for the entire cohort and stratified by statin use (none vs. low-moderate intensity vs. high intensity). Continuous variables were expressed as means (± standard deviations (SD)) or as medians (± interquartile ranges (IQR)) if they were not normally distributed. These were compared using the Kruskal-Wallis test. Discrete variables were compared using χ^2 tests for proportions. Proportions of missing data were also calculated and compared in the cohort to determine whether data were missing at random (eTable 3). We explored the distribution of statin use over time by 3-year periods and among patients with other atherosclerotic diseases for the full cohort [N=155,647].

For the main analysis comparing statin intensity with outcomes of amputation and mortality, we did a 3 level comparison: high dose statin users (N=19,301), low-moderate dose (N=60,338) statin users and those not taking statins but following another guideline-directed therapy [antiplatelet drugs including aspirin and clopidogrel, as the "active comparator group"] (N=28,351) to reduce healthy user bias [patients who initiate a medication (i.e. statin in our study) may do better than those who don't due to their healthy behavior rather than the effect of the medication]. Unadjusted associations for statin intensity and risk of death and amputation were obtained using Kaplan-Meier curves over entire study period accounting for censoring. Subjects were censored on December 31, 2015 in the mortality curves and upon death or December 31, 2015 in the amputation curves. Cox proportional hazards regression models were then constructed to calculate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for amputation and death by statin intensity categories with the referent as the "active comparator" group on antiplatelet medications but no statins (AP only). The Cox proportional hazard models for amputations were cause specific to account for competing risk of death in follow-up. The

models adjusted for listed covariates in Table 1 except cholesterol levels as statin use would impact these measurements and therefore they function as mediating variables.

We then performed **propensity score (PS) matched analysis** to further control for possible confounding in two sub analyses. (1) We calculated 3-level propensity scores comparing low-moderate and high intensity statin users to the active comparator group (AP only) to address confounding by indication. Propensity scores were calculated with logistic regression using all covariates listed in Table 1 except cholesterol (impacted by statin use), HbA1c (large proportion missing data) and excluding antiplatelet use as a predictor. For this we used a validated SAS macro to execute a 1:1:1 match using a caliper of 0.6 times the standard deviation of the logit of the propensity score, generating AP only, low-moderate intensity statin and high statin intensity trios matched on propensity scores[26]. Pre-match histograms of scores were compared to ensure sufficient overlap for matching, and post-match balance was assessed using pairwise standardized differences in eTable 4. Cox models stratified on matched trio and adjusting for all propensity score covariates were run to calculate hazard ratios for low-moderate intensity statin vs AP only group and high intensity statin vs. AP only group. Tests for trend from AP only to low-moderate to high intensity statin were also performed. Despite strong observed post-match balance, we additionally adjusted for all propensity score covariates to guard against a mis-specified score[27]. (2) We made low-moderate intensity statin users as the active comparator to further control for a healthy user bias and provide more closely matched controls. Propensity scores were calculated to match high intensity statin subjects to those taking low-moderate intensity statins in a 2- level analysis[27]. A validated SAS macro was used to execute a 1:1 nearest neighbor matching algorithm with a caliper of 0.2 times the standard deviation of the logit of the propensity scores. Pre-match histograms of scores were compared to

ensure sufficient overlap for matching, and post-match covariate balance was assessed in eTable 5 using standardized differences. Cox models stratified by matched set were then constructed to calculate adjusted HRs among these matched pairs.

The effects of excluding simvastatin 80 mg were evaluated in a sensitivity analysis. Subgroup analysis was done for age, gender, diabetes status, CAD status, and race. All variables were found to meet the proportional hazards assumption via log-log survival curves for amputation and mortality. Wald confidence limits were constructed for all hazard ratios and an additional test for trend was run to compare the low-moderate and high statin groups.

The statistical analysis was done using SAS version 9.4 (SAS Institute, Cary, NC). Two-sided p-values < 0.05 were considered statistically significant.

Results

Statin use in veterans with PAD

Our cohort consisted of 155,647 veterans with incident clinical PAD with a median follow up of 5.9 years. The majority of the cohort was male (97.9%) with a mean age: 66.7 years (SD 9.9). The demographics of the full cohort and each analytic group are listed in Table 1. More than a quarter of patients (N=45,503, 28.0%) were not on any statin medication at the time of PAD identification. Of these, 28,351 (18.2%) were on antiplatelet medications but not on statins and served as the active comparator in our subsequent analyses. About 60,338 (38.8%) patients were on low-moderate intensity statins and 19,301 (12.4%) were on high intensity statins at the time of PAD diagnosis. There were a substantial number of veterans (20.9%) on Simvastatin 80mg. We stratified study subjects by use of statins over time (Figure 1a) and found that the use of Simvastatin 80 mg declined dramatically in the most recent study time period (2012-2014) while

the use of other high intensity statins rose during the same interval. Interestingly, the number of patients not on statins remained steady (25-30%) from the 2006-2008 interval till the most recent study interval (2012-2014). We investigated statin use in patients by concurrent clinical atherosclerotic comorbidities [coronary artery disease (CAD) or carotid artery stenosis (CAS)] (Figure 1b). Patients with PAD alone were much more likely to not be prescribed statins (42%) as compared to those with PAD and a concomitant diagnosis of CAS (34.9%), CAD (17.6%), or both (15.7%). Having a diagnosis of concomitant CAD/carotid disease with PAD also was associated with a higher likelihood of being on a high intensity statin as compared to those with PAD only (18.4% vs 6.4%).

Unadjusted associations of statin intensity with amputation and mortality

There were 10,824 amputations and 63,287 deaths identified during follow up. The median time to outcome was 0.98 yrs for amputation and 3.6 years for mortality. Figure 2 provides the KM analysis demonstrating any statin medication use (high-intensity as well as low- moderate intensity statin) at the time of PAD diagnosis having better overall survival and amputation-free survival compared to the active comparator (AP only) group while accounting for censoring over time. The crude incidence rate of amputation and mortality in PAD patients were 0.04 amputations per 1000 person yrs and 0.16 deaths/1000 person yrs for high intensity statin users respectively, 0.03 amputations and 0.2 deaths/ 1000 person yrs for low- moderate intensity statins respectively as compared to 0.04 amputations and 0.21 deaths/1000 person yrs for the active comparator group respectively. The unadjusted risks using Cox proportional hazards modeling showed use of low-moderate intensity statins at the time of PAD diagnosis having a 7% decrease in mortality in PAD patients [HR 0.93, 95% CI (0.90, 0.95)] while high intensity statins had a 18% decreased risk of death [HR 0.82, 95% CI (0.79, 0.85)] compared to the AP

only group. Similarly, use of statins was associated with lower amputation risk in the PAD cohort: Low-moderate intensity [HR 0.80, 95% CI (0.75, 0.84)] and high intensity statins [HR 0.85, 95% CI (0.79, 0.91)] as compared to the active comparator group (AP only).

Adjusted associations of statin intensity with amputation and mortality

To better delineate the effect of statin intensity on mortality and amputation risk in PAD we adjusted for a host of confounders. We determined age, presence of CAD and year of diagnosis of PAD to be the most important confounders that may affect use of statin as well as the outcomes of interest. We adjusted for these three variables using Cox proportional hazards modeling (Table 2, adjusted model 1); we found low-moderate intensity statins still had a significant reduction in mortality and amputation risk respectively [HR 0.83, 95% CI (0.81, 0.85)] and HR 0.76, 95% CI (0.72, 0.80)] as compared to AP only use while high intensity statins had a more significant benefit for both outcomes with a 30% risk reduction in mortality [HR 0.70, 95% CI (0.67, 0.73)] and 39% risk reduction in amputation risk [HR 0.61, 95% CI (0.56- 0.66)] as compared to AP only group.

In a more comprehensive Cox model [Table 2, adjusted model 2 and eTable 6], we further adjusted Model 1 for additional confounders like race, sex, SES, BMI, serum creatinine, comorbidities [DM, HTN, CHF, COPD, AF, CAS, depression and CKD/ESRD], antiplatelet medications, cilostazol and PAD severity. The hazard of death was 17% lower for low-moderate [HR 0.83, 95% CI (0.81-0.86)] and 26% lower for high intensity statins [HR 0.74, 95% CI (0.70-0.77)], compared to AP only active comparator group. The risk of amputation was similarly lower: 19% [HR 0.81, 95% CI (0.75-0.86)] for low-moderate intensity statin users and 33% [HR 0.67, 95% CI (0.61-0.74)] lower for high intensity statin users versus AP only group. The hazard ratios for those on high intensity statins were also statistically significantly lower than those on

low-moderate intensity statins for both death and amputation, demonstrating a protective dose-response relationship (test for trend p<0.001).

Propensity score matched analyses

We found similar results in a PS matched analysis whether performing a 3-level or a 2-level matched analysis (Table 3, eTables 4 and 5) with regards to improved survival and decreased amputations with high-intensity statin use in crude and adjusted PS matched models. In a 3-level comparison, 30,780 patients were matched in a 1:1:1 high intensity statin, low- moderate intensity statin and active comparator group (AP only). A statistically significant reduction in amputation risk [crude HR 0.69 (0.61, 0.76), adjusted HR 0.60 (0.52, 0.69)] and an almost 30% reduction in all-cause mortality [crude HR 0.72 (0.68, 0.76), adjusted HR 0.70 (0.66, 0.75)] was observed for high-intensity statin users compared to those not on statins but taking antiplatelet medications. A modest but statistically significant reduction of ~20% in amputations [crude HR 0.84 (0.75, 0.93), adjusted HR 0.80 (0.70, 0.91)] and mortality [crude HR 0.83 (0.79, 0.88), adjusted HR 0.80 (0.75, 0.85)] was seen for low-moderate intensity statin users as compared to the AP only group. Using low-moderate intensity statins as the active comparator in a 2 level PS matched analysis, we found a statistically significant reduction of ~20% in amputation risk [crude HR 0.82 (0.74, 0.90), adjusted HR 0.78 (0.68, 0.89)] and 15% reduction in mortality risk [crude HR 0.86 (0.82, 0.91), adjusted HR 0.85 (0.80, 0.90)] for users of high intensity statins.

Sensitivity Analyses

The a priori hypothesis and methodology for our analysis sought to compare outcomes PAD patients using statins classified by intensity in the 2013 AHA/ACC lipid guidelines. However, 21% of the PAD cohort was on simvastatin 80 mg, mostly in the earlier years of the cohort. Therefore, we also ran Cox models as a sensitivity analysis to test whether inclusion of

simvastatin 80 mg changed the effect of the statin intensity association with death and amputations. The use of simvastatin 80 mg had a similar risk lowering effect on death and amputations overall for the PAD cohort as with any statin therapy compared to AP only group while the association of high and low-moderate intensity statins remained significant with similar effect sizes as the main model in terms of lower amputation and mortality risk (eTable 7).

Subgroup Analysis

The 2013 AHA/ACC lipid guidelines are mostly applicable to patients 75 years or less in age and there is less evidence for statin use in PAD for older patients, blacks, women and patients with diabetes. Furthermore, CAD was a main indication for patients already on statins at the time of PAD diagnosis. Therefore, we performed subgroup analysis to explore the association of statin intensity and amputations and mortality in the cohort stratified by age, gender, diabetes status, comorbid CAD (at PAD diagnosis) and race (Figure 3). Individuals on low-moderate intensity and high intensity statins had similar reduction in amputation and mortality risk regardless of their age categorization. Patients older than 75 years of age had comparable risk reduction in mortality (HR 0.5) versus those 75 years or younger (HR 0.73) when using high-intensity statins versus being on antiplatelet medications only but no statins. In terms of limb loss, patients older than 75 years had a much lower risk of amputation (HR 0.61) as compared to those 75 years or younger (HR 0.70) when taking high intensity statins versus only antiplatelet medication and no statin. The number of female PAD patients (n=1799) was small in the Cox model thus leading to wide confidence intervals in our estimates. Women still had a significant reduction in mortality while on high intensity statins [HR 0.72, 95% CI 0.53-0.98] but the association of statin use with amputation risk was not significant with point estimate greater than 1 [HR 1.09]. Patients with diabetes and those without diabetes both showed significant risk reduction with statin use in a

dose response fashion similar to the entire cohort, though the effect of high-intensity statins on mortality and amputation was magnified among patients without diabetes (mortality HR 0.68 vs. 0.76 in no-DM vs. DM, amputation HR 0.52 vs. 0.75 in no-DM vs. DM). Similarly, PAD patients with or without comorbid CAD had a lower risk for amputations [With CAD: HR 0.66 (High) vs 0.81 (Low-Mod); Without CAD: HR 0.73 (High) vs 0.79 (Low-Mod)] and mortality [With CAD: HR 0.73 (High) vs 0.85 (Low-Mod); Without CAD: HR 0.72 (High) vs 0.84 (Low-Mod)] with statin use in a dose-dependent fashion compared to AP only group. Finally, when stratified by race, the effect of statin use was still significant for white and black PAD patients with similar reductions in mortality and amputation risk as the entire cohort.

Discussion

Our study is the largest and first of its kind to examine the effect of statin use and intensity on mortality and amputation risk in a large cohort of PAD patients. We confirmed low prescription of statins for PAD patients as compared to those with other well-known atherosclerotic disease processes such as CAD or carotid disease. We found an inverse dose response relationship of statin intensity on death and amputation risk with patients on high intensity statins. Our adjusted analyses showed almost 30% reduction in risk of death and 30-40% reduction in risk of major amputation in high intensity statin users as compared to those not on statins but on another guideline directed therapy i.e. antiplatelet medications. Low-moderate intensity statins also had a favorable association with reduced limb loss and mortality but not to the same degree as high-intensity statins. These findings were robust to adjustment for potential confounding by indication and possible healthy user bias in propensity matched, sensitivity and subgroup analyses using active comparator groups.

The association of high intensity statins with risk reduction of cardiovascular endpoints in the coronary[28-31] and carotid beds[32, 33] is well known. However, there are no randomized clinical trials or observational studies in PAD to compare high versus low- moderate intensity statins for PAD outcomes. The Heart Protection Study (HPS) is the only RCT that included a large subcohort of PAD patients (N=6748 with PAD, out of 20,536) conducted in the United Kingdom. They had a larger proportion of women (26%) and lower prevalence of smokers (21%), patients with diabetes (23%) and hypertension (43%) as compared to our cohort. The study showed simvastatin 40 mg had a 17% reduced incidence of CV death, 25% reduction in MI, coronary revascularization, and stroke and a 16% reduction in peripheral vascular events (non-coronary revascularization, aneurysm repairs, major amputations or PAD deaths)[18]. In our sensitivity analysis we found that patients on Simvastatin 80 mg did have 16% lower all-cause mortality and 22% lower risk of amputation as compared to those only on antiplatelet medication and no statin while patients on high intensity statins had larger reductions in amputation (32%) and mortality (26%) risk compared to Simvastatin 80 mg as well as the estimates from the HPS study. Observational studies have shown that use of any statins in PAD patients is associated with lower mortality and cardiovascular events[34, 35]. A particularly important, but often understudied outcome in PAD patients, is limb-related outcomes. Observational studies have shown statin use to be associated with increased walking performance in claudicants[36, 37], reduced risk of amputation or revascularization[18, 38] and improved patency of lower extremity vein bypass grafts[39, 40]. Our study confirms the association of statin use with decreased amputation rates and further highlights the incremental benefit of using high intensity statins rather than low- moderate intensity in eligible patients to improve limb salvage. Postulated mechanisms of this overall benefit of statins include lipid lowering as well as pleiotropic effects

of statins on atherosclerotic plaque[18, 34, 41]. Clinical studies on femoral plaque characteristics have reported high-dose of statins to predominantly improve plaque composition or cause plaque regression, leading to a more stable phenotype in PAD[42, 43].

Recent studies have shown that PAD patients are less likely to receive medical management including statin therapy[6-15], antiplatelet therapy[6, 8, 10-13, 15], glycemic control[9, 11, 15], hypertension control[8-12, 15] and exercise[6] as compared to patients with CAD. The reasons cited include lack of awareness of PAD by providers[6, 7, 9, 11, 12, 15] and patients[14, 44], lesser perceived risk in PAD[6, 9, 11, 14, 15], differences in subspecialists managing PAD[6, 14], practice setting (university versus private)[8], racial disparity[8], lack of regulatory mandates/performance measures[9, 10, 13, 15], advanced disease at diagnosis[11] and lack of insurance coverage of PAD rehabilitation[14]. Our findings show the lack of appropriate statin use in a PAD cohort --more than a quarter of the patients did not take statin therapy throughout the study interval. Furthermore, a large percentage of PAD patients were on low-moderate intensity statins instead of high intensity statins as recommended.

The AHA/ACC lipid guidelines were published in 2013 and we examined the temporal trends in statin intensity. We found that the percentage of patients not on statins persisted in the 25%-30% range throughout the study interval 2003 to 2014. An encouraging trend toward greater use of high intensity statins, 4% in 2003-2005 up to 28% in 2012-2014 was observed. The under-treatment of PAD is further magnified when co-morbidities that require high intensity statins are considered. In patients with concurrent diagnosis of PAD with either CAD or carotid stenosis, the use of statins in general and high intensity statins was much higher in our cohort while patients with only PAD as their sole atherosclerotic disease process, about 42% were not on any statin medication and only 5.8% were on high intensity statins. Treatment with two or

more preventative therapies (including aspirin, statin, and/or hypertensive control) is associated with a 65% reduced risk of all-cause mortality in individuals with PAD who do not have previously established cardiovascular disease[12]. This further amplifies the need for education and dissemination of the latest evidence and guidelines amongst primary care/ specialist providers caring for PAD as well as development of performance measures to promote use of high intensity statins in PAD.

Patients on high intensity statins maybe be inherently different compared to those not on any statins based on indication for medication use, patient compliance or adherence to treatment. Therefore, we tested our hypothesis in multiple ways. We first compared statin users to antiplatelet users but not on statins as "healthy users" (active comparators). Furthermore, we confirmed the association of reduced limb loss and death with high intensity statin use in a propensity matched analysis where we alternated the comparison groups between high intensity versus low-moderate intensity vs AP only groups as well as limiting the analysis to only high versus low-moderate intensity statin groups to provide a highly matched control group. Additionally, we did sensitivity analysis where addition of simvastatin 80 mg cohort did not alter the effect sizes or direction of risk for amputations and mortality with statin intensity. The findings also remained significant in their graded (high vs low-moderate vs AP only) association of PAD outcomes with statin intensity in each subgroup analysis for age, race, presence of comorbid DM and CAD accounting for differences in indication of statin use. The consistent finding of reduced PAD adverse events with use of high intensity statins in our study should prompt further investigation into mechanisms, further observational studies, clinical trials and consensus guidelines for medical management of PAD.

Our study has several limitations. We only assessed the prevalent statin use within the first year of diagnosis of PAD. Patients could have been started later on appropriate statin therapy. However, our study could be interpreted as indicating that timely initiation of statin or being on a statin already at the time of PAD diagnosis is associated with substantial reduction in death and amputations. We could not separate the statin "initiators" from the "users" given the high occurrence of comorbid CAD or other atherosclerotic disease processes that would need statin therapy. However, we did find in our subgroup analysis, that non-CAD patients had a similar risk reduction on amputation and death suggesting that possible statin "initiation" for non CAD patients has similar effects. This is an observational study using administrative data, the data sources are from clinical care records, and the analysis may be susceptible to residual confounding. We have made a significant effort to account for accurate PAD diagnosis as well as performing a comprehensive Cox model. Additionally, careful handling of missing data and performance of sensitivity and PS matched analyses were done to minimize and investigate the possibility of bias. The adherence and patient compliance with prescribed statin dose was not measured in the study hence, we did not do a time varying covariate analysis. This should be looked into further in future studies. We conjecture that patient compliance may show more benefit with adherence to high intensity statin use. Our study is based on VHA data and it is overwhelmingly comprised of male patients with high prevalence of smoking. Results may differ in a non-VA population.

In conclusion, our study shows an associated benefit between patients on high intensity statins before or early upon diagnosis of PAD to have a lower lifetime risk of death and amputations. Low-moderate intensity statins also reduce the risk of limb loss and mortality as compared to patients on antiplatelet medications but no statin therapy and may have an important

role in patients intolerant of high-intensity statins. Further work is needed to quantify the risk benefit with patient medication adherence, the effect of statin intensity on disease severity of PAD as well as implementation of strategies to increase statin use in PAD patients.

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Table 1. Demographics and clinical data of full cohort and stratifications by exposure (Statin intensity at diagnosis of PAD) for N = 155,647 incident PAD diagnoses from 2003-2014.

	All patients	Exposure groups*		
		No Statin, With Antiplatelet (AP only)	Low-moderate intensity	High-intensity
PAD patients in study, No.	155,647	28,351	60,338	19,301
Age, Mean (SD), years	66.7 (9.9)	67.0 (10.6)	67.1 (9.7)	65.6 (8.2)
Sex, % Male	97.9	98.0	98.1	97.8
Race, %				
White	82.6	81.1	84.2	82.5
Black	16.1	17.8	14.6	16.3
Other	1.3	1.2	1.3	1.3
Smoking, %				
Current	29	48.9	28.8	29.4
Former	26.4	37.8	27.5	27.1
Never	8.8	13.3	8.9	8.6
Unknown	35.8		34.8	34.9
BMI, Mean (SD), kg/m2	28.6 (6.2)	27.4 (6.2)	28.6 (6.0)	29.8 (6.1)
Laboratory				
Total Cholesterol, Mean (SD), mg/dL	168.6 (45.2)	172.5 (43.1)	169.6 (44.9)	169.5 (50.2)
LDL Cholesterol, Mean (SD), mg/dL	97.1 (36.3)	100.8 (34.1)	98.4 (36.7)	96.6 (39.9)
HDL Cholesterol, Mean (SD), mg/dL	40.6 (13.4)	42.0 (15.3)	40.5 (13.0)	39.9 (12.2)
HbA1c, Median (IQR), percent	6.5 (5.8-7.6)	6.2 (5.7-7.3)	6.5 (5.8-7.5)	6.7 (6.0-8.0)
Creatinine, Median (IQR), mg/dL	1.1 (0.9-1.4)	1.1 (0.9-1.3)	1.1 (0.9-1.4)	1.1 (0.9-1.4)
Comorbidities, %				
Diabetes	45.5	36.1	46.7	56.7
Hypertension	84.2	78.7	86.6	90.0
CAD	46.3	31.2	47.5	66.8
CHF	16.4	12.8	16.8	21.8
COPD	8.5	8.6	8.6	8.6
AF	12.0	11.0	12.8	12.7
Carotid Disease	63.8	61.0	65.7	69.7
Depression	16.0	14.9	15.5	20.0
CKD or ESRD	7.4	7.0	7.2	6.9
Antiplatelet Therapy, %				
None	20.7	0	17.2	9.7
Prasugrel	<0.1	<0.1	<0.1	<0.1
Dipyridamole	0.9	0.9	1.0	0.8
Clopidogrel	4.1	5.2	4.3	3.9
Aspirin	74.4	93.9	77.6	85.7
Cilostazol, %	7.99	7.6	8.4	9.3
Median Household Income of Residential Zip Code, %				
<=$25,000	3.3	3.9	3.1	2.8

$25,001-$40,000	27.6	28.8	27.2	26.5
$40,001-$75,000	59.4	58.3	59.9	60.9
$75,001+	9.8	9.2	9.8	9.8
PAD severity, %				
Not Specified	68.5	66.3	68.8	66.0
Claudication	20.2	19.9	20.3	23.0
Rest Pain	3.9	4.5	3.9	4.2
Ulceration/Gangrene	7.3	9.3	7.0	6.8

Abbreviations: PAD, Peripheral Artieral Disease; VHA, Veterans Health Administration; SD, standard deviation; IQR, interquartile range; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, Hemoglobin A1c; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CKD, chronic kidney disease; ESRD, end stage renal disease; mg, milligram; dL, deciliter.

*p for comparisons across 3-level exposure categories <0.0001 except for sex, COPD, CKD (p>0.05)

Table 2. Cox proportional hazard model results for effect of statin intensity on mortality and amputations comparing high intensity statin use and low-moderate intensity statin use to an active comparator group (use of antiplatelet medication but no statin) in incident peripheral arterial disease cohort (PAD); N=90,257.

	Mortality HR (95% CI)	Amputation HR (95% CI)
Unadjusted model*		
Antiplatelet only- No statin	Ref.	Ref.
Low-Moderate intensity statin	0.92 (0.90 , 0.95)	0.79 (0.75 , 0.83)
High intensity statin	0.82 (0.79 , 0.85)	0.84 (0.78 , 0.90)
Adjusted model 1†		
Antiplatelet only- No statin	Ref.	Ref.
Low-Moderate intensity statin	0.83 (0.81 , 0.85)	0.76 (0.72 , 0.80)
High intensity statin	0.70 (0.67 , 0.73)	0.61 (0.56 , 0.66)
Adjusted model 2‡		
Antiplatelet only- No statin	Ref.	Ref.
Low-Moderate intensity statin	0.83 (0.81 , 0.86)	0.81 (0.75 , 0.86)
High intensity statin	0.74 (0.70 , 0.77)	0.67 (0.61 , 0.74)

Abbreviations: HR, hazard ratio; CI, confidence interval; CAD: coronary artery disease

*Model excludes subjects taking simvastatin 80 as that is not part of ACC/AHA 2013 lipid guidelines.

†Model 1 adjusted for age at cohort entry, PAD diagnosis year and CAD.

‡Model 2 adjusted for age at cohort entry, PAD diagnosis year race, sex, socio-economic status, body mass index, comorbidities [Diabetes mellitus, hypertension, congestive heart failure, chronic obstructive pulmonary disease, atrial fibrillation, carotid disease, depression, chronic kidney disease and end stage renal disease], antiplatelet medications, cilostazol, PAD severity (not specified vs. claudication vs. rest pain vs. ulceration/gangrene) and serum creatinine.

p-value for High vs. Low-Moderate statin use <0.001 in unadjusted, adjusted model 1, and fully adjusted model 2.

Table 3. Propensity score matched analysis results for effect of statin intensity on mortality and amputations in incident peripheral arterial disease cohort (PAD) in a 3 level analysis [high intensity statin, low-moderate intensity statin and an active comparator group (use of antiplatelet medication but no statin] and a 2 level analysis [High intensity statin vs low-moderate intensity statin use].

	Mortality HR (95% CI)	**Amputation HR (95% CI)**
3-level Propensity Score Matched Analysis (N= 30,780)		
Propensity Score Matched Model, Crude		
Antiplatelet only- No statin	Ref.	Ref.
Low-Moderate intensity statin	0.83 (0.79 , 0.88)	0.84 (0.75 , 0.93)
High intensity statin	0.72 (0.68 , 0.76)	0.69 (0.61 , 0.76)
Propensity Score Matched Model, Adjusted		
Antiplatelet only- No statin	Ref.	Ref.
Low-Moderate intensity statin	0.80 (0.75 , 0.85)	0.80 (0.70 , 0.91)
High intensity statin	0.70 (0.66 , 0.75)	0.60 (0.52 , 0.69)
2-level propensity matched analysis (N=30,418)		
Propensity Score Matched Model, Crude		
Low-Moderate intensity statin	Ref.	Ref.
High intensity statin	0.86 (0.82 , 0.91)	0.82 (0.74 , 0.90)
Propensity Score Matched Model, Adjusted		
Low-Moderate intensity statin	Ref.	Ref.
High intensity statin	0.85 (0.80 , 0.90)	0.78 (0.68 , 0.89)

HR: hazard ratio; CI: Confidence interval

Figure Legends

Figure 1. Statin use in the cohort by intensity

(A) Percent of all incident PAD patients categorized by initiation of Statin therapy and intensity, within each 3-year time period

(B) Statin Use Categories Stratified by Presence of Non-PAD Statin Indications.

Abbreviations: CAS: Coronary Artery Stenosis; CAD: Coronary Artery Disease; PAD: Peripheral Arterial Disease.

Figure 2. Kaplan-Meier curves of (A) mortality and (B) amputation

N = 107,990 patients taking a low-moderate or high-dose statin or no statin and an antiplatelet medication. Subjects were censored on December 31, 2015.

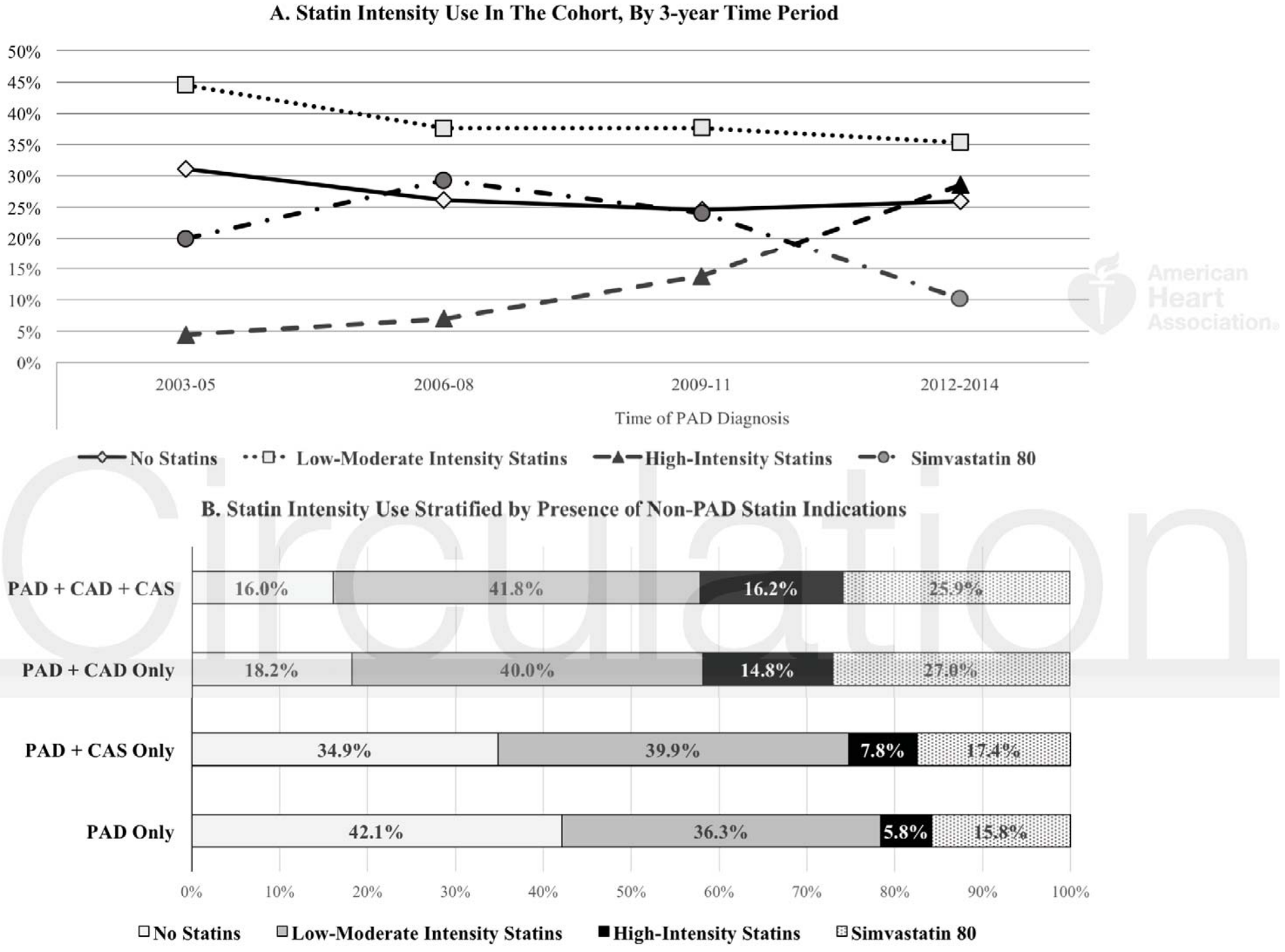
Figure 3. Subgroup analysis – adjusted Hazard ratios (HR) for (A) mortality and (B) amputations, by age, gender, diabetes status, CAD status, and race.

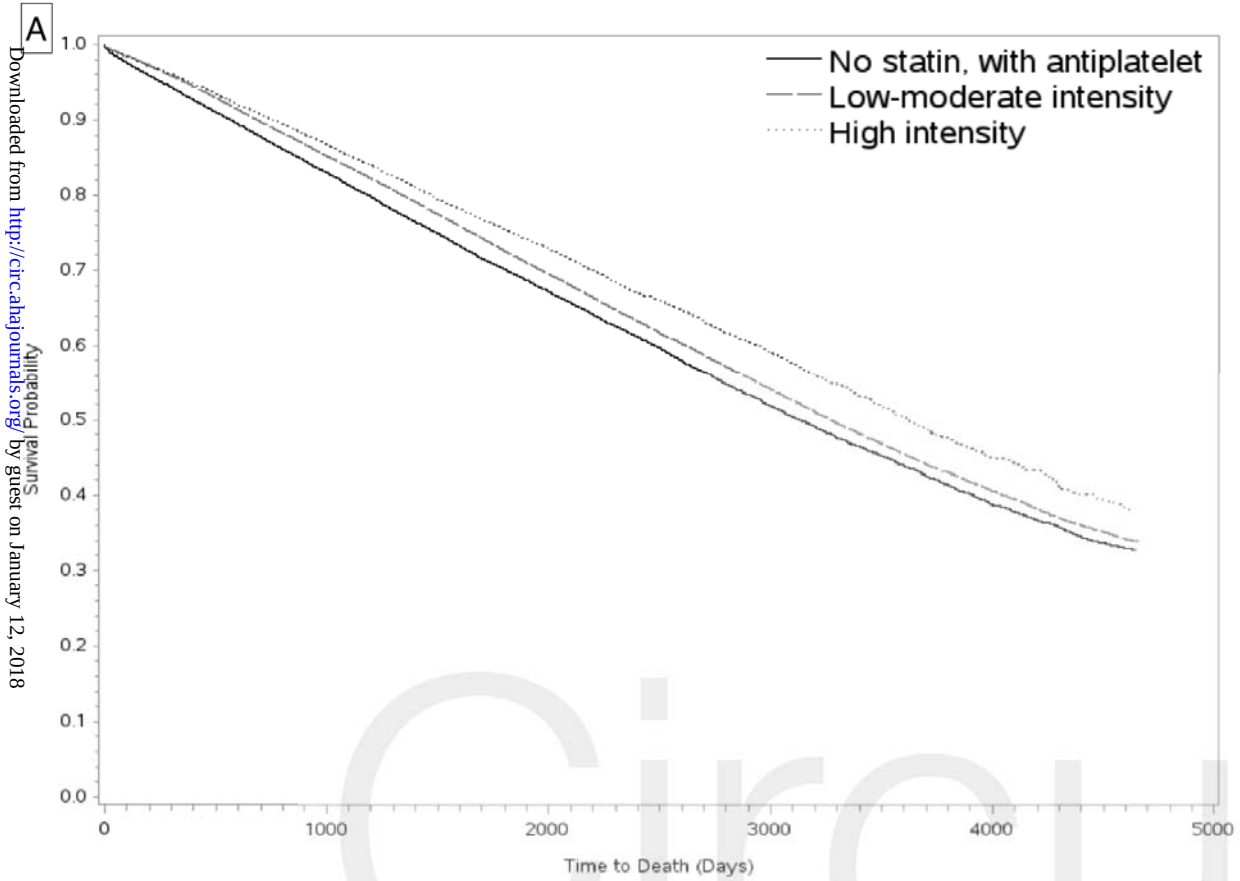
Stratified Cox proportional hazards models for effect of statin intensity on mortality and amputations in PAD patients stratified by age, gender, diabetes status, CAD status, and race.

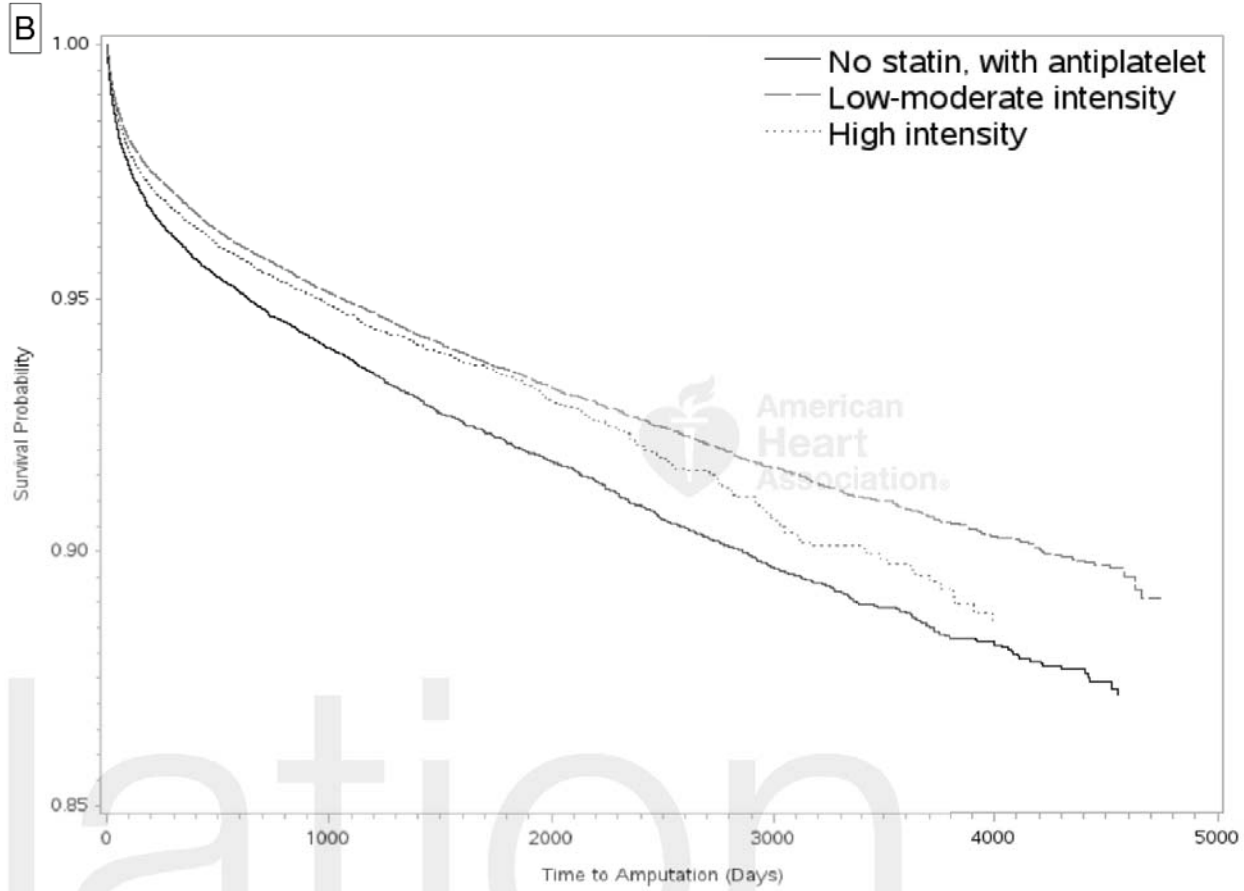
Abbreviations: DM: Diabetes Mellitus; CAD: Coronary Artery Disease.

Referent group is “None”: active comparator group on antiplatelet medications but no statins.

HR for High Intensity statin shown as black triangles and low- moderate intensity statins as gray squares.



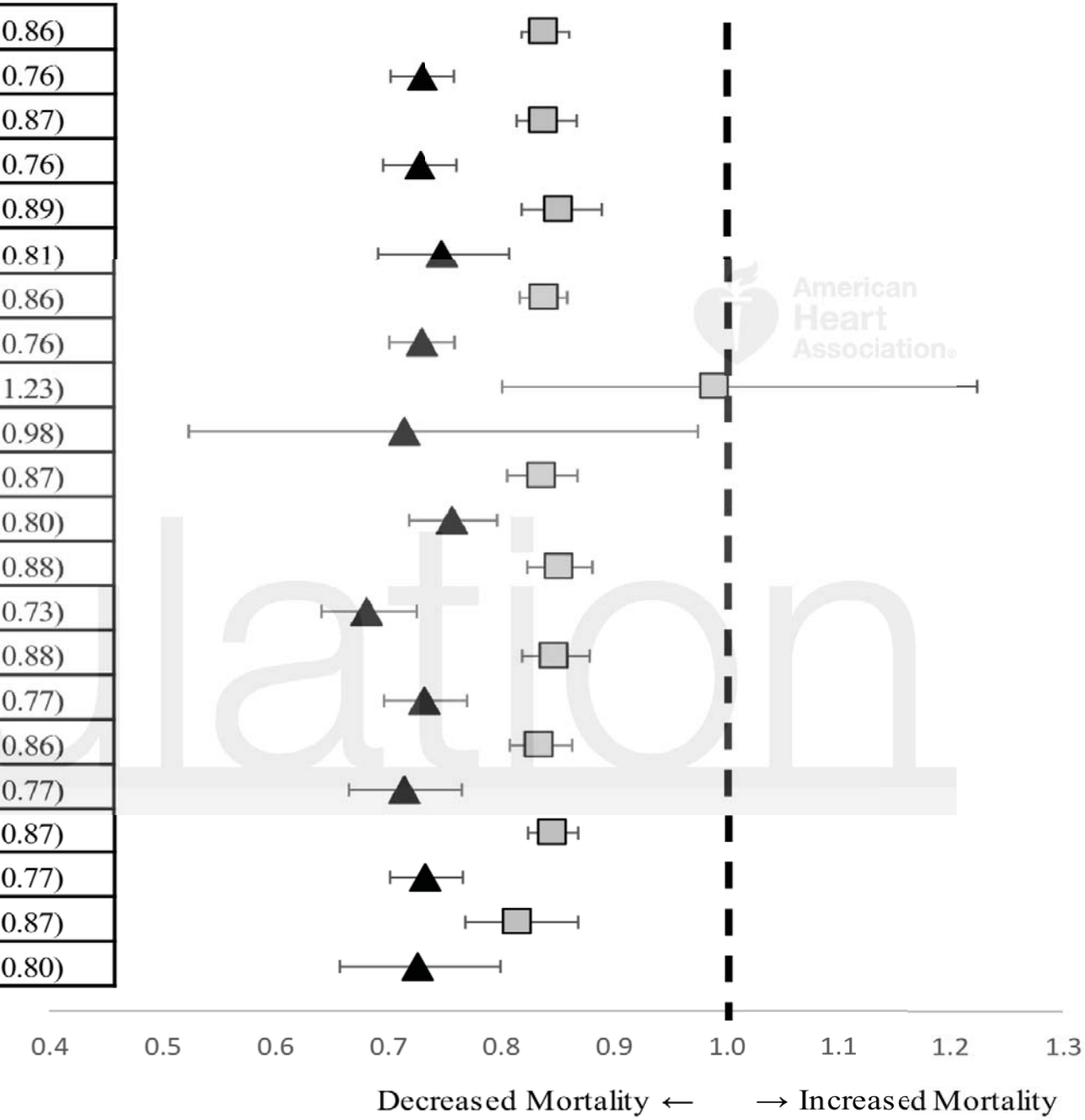




A

Mortality HR and 95% Confidence Intervals

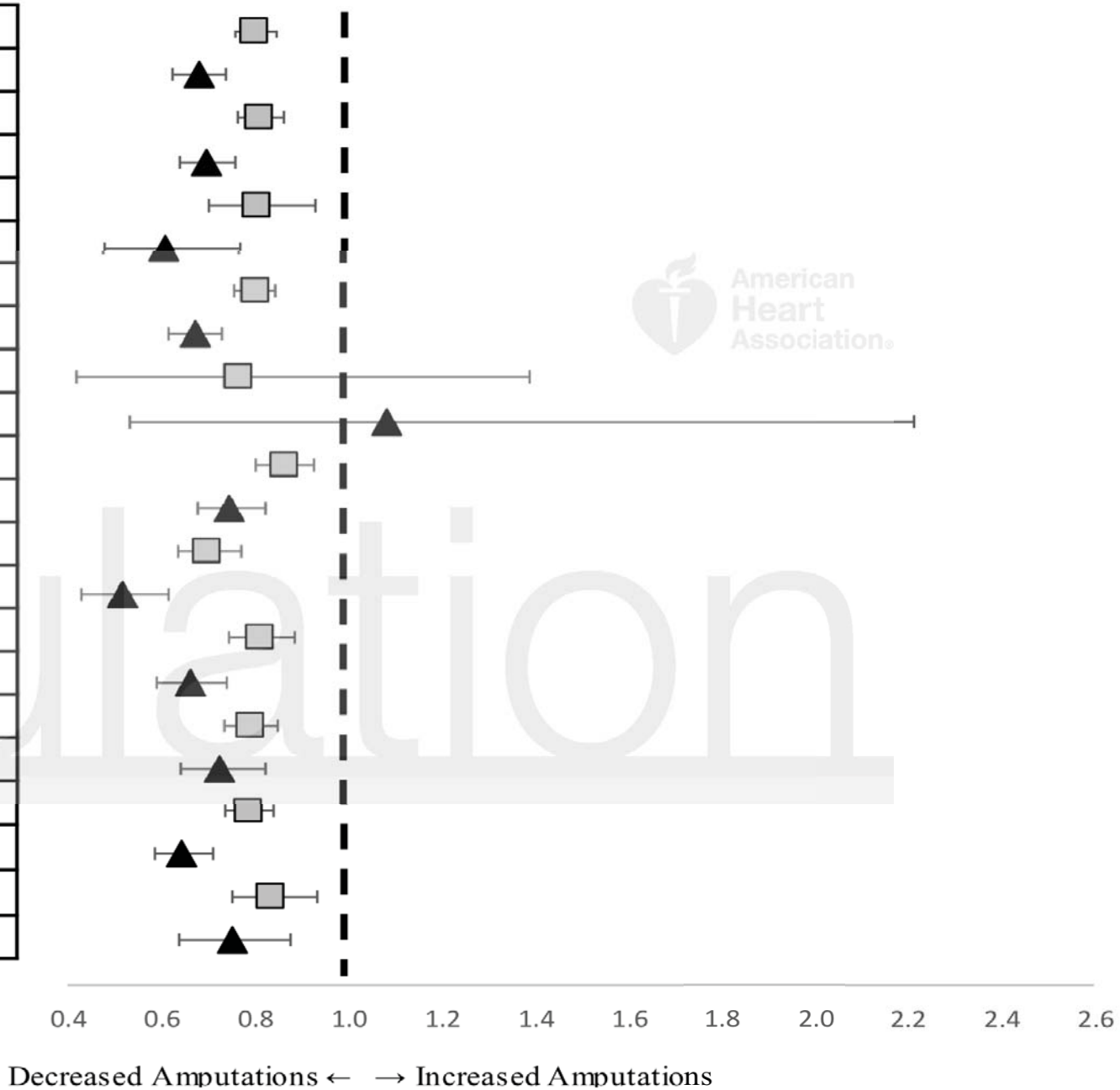
All (N=90,257)	Low-Medium vs. None	0.84 (0.82, 0.86)
	High vs. None	0.73 (0.70, 0.76)
<75 years (N=71,327)	Low-Medium vs. None	0.84 (0.82, 0.87)
	High vs. None	0.73 (0.70, 0.76)
>= 75 years (N=18,930)	Low-Medium vs. None	0.85 (0.82, 0.89)
	High vs. None	0.75 (0.69, 0.81)
Male (N=88,458)	Low-Medium vs. None	0.84 (0.82, 0.86)
	High vs. None	0.73 (0.70, 0.76)
Female (N=1,799)	Low-Medium vs. None	0.99 (0.80, 1.23)
	High vs. None	0.72 (0.53, 0.98)
DM (N=41,652)	Low-Medium vs. None	0.84 (0.81, 0.87)
	High vs. None	0.76 (0.72, 0.80)
No DM (N=48,605)	Low-Medium vs. None	0.85 (0.82, 0.88)
	High vs. None	0.68 (0.64, 0.73)
CAD (N=42,743)	Low-Medium vs. None	0.85 (0.82, 0.88)
	High vs. None	0.73 (0.70, 0.77)
No CAD (N=47,514)	Low-Medium vs. None	0.84 (0.81, 0.86)
	High vs. None	0.72 (0.67, 0.77)
Whites (N=74,883)	Low-Medium vs. None	0.85 (0.82, 0.87)
	High vs. None	0.73 (0.70, 0.77)
Blacks (N=14,279)	Low-Medium vs. None	0.82 (0.77, 0.87)
	High vs. None	0.73 (0.66, 0.80)



B

Amputation HR and 95% Confidence Intervals

All (N=90,257)	Low-Medium vs. None	0.80 (0.76, 0.85)
	High vs. None	0.68 (0.62, 0.73)
<75 years (N=71,327)	Low-Medium vs. None	0.81 (0.76, 0.86)
	High vs. None	0.70 (0.64, 0.76)
>= 75 years (N=18,930)	Low-Medium vs. None	0.81 (0.70, 0.93)
	High vs. None	0.61 (0.48, 0.77)
Male (N=88,458)	Low-Medium vs. None	0.80 (0.76, 0.85)
	High vs. None	0.67 (0.62, 0.73)
Female (N=1,799)	Low-Medium vs. None	0.77 (0.42, 1.39)
	High vs. None	1.09 (0.53, 2.22)
DM (N=41,652)	Low-Medium vs. None	0.86 (0.81, 0.93)
	High vs. None	0.75 (0.68, 0.82)
No DM (N=48,605)	Low-Medium vs. None	0.70 (0.64, 0.77)
	High vs. None	0.52 (0.43, 0.62)
CAD (N=42,743)	Low-Medium vs. None	0.81 (0.74, 0.89)
	High vs. None	0.66 (0.59, 0.74)
No CAD (N=47,514)	Low-Medium vs. None	0.79 (0.74, 0.85)
	High vs. None	0.73 (0.64, 0.83)
Whites (N=74,883)	Low-Medium vs. None	0.79 (0.74, 0.84)
	High vs. None	0.65 (0.59, 0.71)
Blacks (N=14,279)	Low-Medium vs. None	0.84 (0.75, 0.93)
	High vs. None	0.75 (0.64, 0.88)



Statins Have a Dose-Dependent Effect on Amputation and Survival in Peripheral Artery Disease Patients

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SUPPLEMENTAL MATERIAL

eTable1. Statin intensity as defined by the 2013 AHA/ ACC lipid guidelines

High Intensity Statins	**Moderate Intensity Statins**	**Low Intensity Statins**
Atorvastatin 40–80 mg Rosuvastatin 20 -40 mg	Atorvastatin 10 -20 mg Rosuvastatin 5-10 mg Simvastatin 20–40 mg Pravastatin 40 -80 mg Lovastatin 40 mg Fluvastatin XL 80 mg Fluvastatin 40 mg bid Pitavastatin 2–4 mg	Simvastatin 10 mg Pravastatin 10–20 mg Lovastatin 20 mg Fluvastatin 20–40 mg Pitavastatin 1 mg

eTable 2. ICD-9 diagnosis and CPT codes used to define comorbidities and amputations.

Comorbid condition	**Codes used**
Hypertension	ICD9 diagnosis codes: 401.0 - 406
Coronary Artery Disease (CAD)	ICD9 diagnosis codes: 410.0 or 414.9 ICD9 ProcedureCode:36.xx
Depression	ICD9 diagnosis codes: 29383,2960,29621,29622,29623,29624,29625,29626,29630,29631,29632,29633,29634,29635,29636,3004,311
Atrial Fibrillation	ICD9 diagnosis codes: 427.31 or 427.32
Carotid artery stenosis	ICD9 diagnosis codes: 433.00 - 433.91,433.1, 433.10, 433.3, 433.30, 433.11, 433.31, 433.9 ,433.90, 433.91, 435.8 ,435.9, 784.94, 368.12, 434.91 ,436 ,342, 368.11, 368.44, 362.84, 435 ,437, 443.21, 900.01, 781.4, V12.54, 784.5 ,780.4, 780.2 ,368.9, 781.3, 447.1, 447.9, V72.81,v72.83, v72.84, 362.xx ICD9 Procedure Code: 00.63,38.12 CPT Code: 37215,37216,37217,0075T,35301
Congestive Heart Failure (CHF)	ICD9 diagnosis codes: 428.0 - 428.9
Chronic Obstructive Pulmonary Disease (COPD)	ICD9 diagnosis codes: 490,491.0, 491.1, 491.2, 491.20, 491.21, 491.22, 491.8, 491.9, 492.0, 492.8, 494, 494.0, 494.1, 496, 493.00, 493.01, 493.02, 493.10, 493.11, 493.12, 493.20, 493.21, 493.22, 493.81, 493.82, 494.90, 493.90, 493.92
Chronic Kidney Disease/End Stage Renal Disease (CKD/ESRD)	ICD9 diagnosis codes: 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.12, 404.13, 404.92, 404.93,585.5,585.6, V45.11, V45.12, V56.0, V56.1, V56.2, V56.32, V56.9,996.73 ICD9 Procedure Code: 38.95
Amputation	ICD9 Procedure Code: 84.10, 84.12, 84.13, 84.14, 84.15,84.16, 84.17, 84.18, 84.19 CPT Code: 27290, 27295, 27590, 27591,27592,27598, 27880, 27881,27882, 27888, 27889, 28800,28805

eTable 3. Comparison of missing and non-missing demographics and baseline covariates. Stratified by no vs. any missing data, and observations included in and excluded from the Cox proportional hazards models due to missing data.

Variable	All	No Missing Data	Any Missing Data*	Included in Cox models (missing nothing or only HbA1c, smoking, and/or cholesterol)	Excluded from Cox models (missing something other than HbA1c, smoking, and/or cholesterol) †
PAD patients in study, No.	155,647	48,557	107,090	129,157	26,490
Age, Mean (SD), years	66.66 (9.85)	65.68 (9.09	67.11 (10.14)	66.41 (9.74)	67.89 (10.27)
Sex, % Male	97.92	98.07	97.85	97.93	97.88
Race, %					
White	82.6	82.01	82.9	82.53	83.21
Black	16.14	16.57	15.92	16.24	15.25
Other	1.26	1.41	1.18	1.23	1.55
Smoking, %					
Current	45.17	39.78	42.08	45.21	44.98
Former	41.1	45.48	43.4	41.31	39.96
Never	13.73	14.74	14.52	13.48	15.06
BMI, Mean (SD), kg/m2	28.61 (6.19)	29.59 (6.36)	28.12 (6.05)	28.64 (6.20)	28.38 (6.11)
Laboratory					
Total Cholsterol, Mean (SD), mg/dL	168.55 (45.22)	165.13 (45.67)	170.36 (44.87)	168.52 (45.38)	168.71 (44.30)
LDL Cholesterol, Mean (SD), mg/dL	97.05 (36.28)	93.78 (36.18)	98.84 (36.21)	97.01 (36.36)	97.31 (35.88)
HDL Cholesterol, Mean (SD), mg/dL	40.63 (13.42)	39.35 (12.82)	41.32 (13.69)	40.56 (13.40)	41.02 (13.51)
HbA1c, Median (IQR), percent	6.50 (5.80-7.60)	6.40 (5.80-7.60)	6.50 (5.90-7.60)	6.50 (5.80-7.60)	6.50 (5.80-7.60)
Creatinine, Median (IQR), mg/dL	1.10 (0.90-1.40)	1.10 (0.90-1.40)	1.10 (0.90-1.40)	1.10 (0.90-1.40)	1.10 (0.90-1.40)
Comorbidities, %					

Diabetes	45.52	66.86	35.84	46.1	42.68
Hypertension	84.22	88.87	82.11	85.02	80.28
CAD	46.25	52.03	43.63	47.1	42.13
CHF	16.4	20.32	14.62	16.87	14.12
COPD	8.53	8.94	8.35	8.82	7.09
AF	12.01	13.01	11.56	12.26	10.8
Carotid Disease	63.79	68..82	61.51	65.07	57.55
Depression	15.99	18.57	14.83	16.52	13.41
CKD or ESRD	7.37	9.18	6.54	7.6	6.25
Antiplatelet Therapy, %					
None	20.65	16.16	22.68	19.64	25.56
Prasugrel	0.02	0.01	0.03	0.02	0.02
Dipyridamole	0.86	0.89	0.85	0.85	0.94
Clopidogrel	4.07	3.78	4.2	4	4.42
Aspirin	74.4	79.16	72.23	75.49	69.06
Cilostazol, %	7.99	8.43	7.79	8.06	7.67
Median Household Income of Residential Zip Code, %					
<=$25,000	3.29	3.29	3.29	3.31	3.17
$25,001-$40,000	27.56	27.35	27.66	27.68	26.89
$40,001-$75,000	59.36	59.68	59.21	59.27	59.87
$75,001+	9.79	9.69	9.84	9.74	10.06
PAD severity, %					
Not Specified	68.54	66.93	69.26	68.39	69.25
Claudication	20.2	19.56	20.49	20.1	20.66
Rest Pain	3.94	4.36	3.75	4.05	3.42
Ulceration/Gangrene	7.32	9.14	6.5	7.46	6.66
Diagnosis Year, %					
2003	9.3	5.98	10.81	8.84	11.59
2004	8.47	6.46	9.38	8.26	9.49
2005	8.32	7.06	8.89	8.3	8.42
2006	8.5	7.73	8.85	8.41	8.95
2007	8.25	8.51	8.13	8.23	8.33
2008	8.81	9.5	8.5	8.92	8.3
2009	9.11	9.96	8.73	9.23	8.52
2010	9.11	10.17	8.63	9.29	8.24
2011	8.77	10.2	8.13	8.88	8.25
2012	7.99	9.34	7.37	8.09	7.47
2013	7.86	8.99	7.34	7.95	7.42
2014	5.51	6.09	5.25	5.61	5.01
Statins, %					

No	27.95	20.51	31.33	26.89	33.13
Low	3.21	3.2	3.21	3.18	3.37
Medium	35.56	37.35	34.74	35.96	33.59
High	12.4	16.35	10.61	12.84	10.25
Simvastatin 80	20.88	22.6	20.11	21.13	19.67
Mortality, %	40.66	38.28	41.74	39.7	45.35
Amputation, %	6.95	9.13	5.97	7.24	5.57

Abbreviations: PAD, Peripheral Artieral Disease; VHA, Veterans Health Administration; SD, standard deviation; IQR, interquartile range; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, Hemoglobin A1c; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CKD, chronic kidney disease; ESRD, end stage renal disease; mg, milligram; dL, deciliter.

[*]p for no vs. any missing data <0.001 for all variables except sex (p=0.0046) and median household income (p=0.3660)

[†]p for included vs. excluded in Cox model <0.001 for all variables except cilostazol and income (p=0.03); and sex, total cholesterol, LDL cholesterol, HbA1c, creatinine, (all p>0.05)

eTable 4. Demographics and clinical data of matched Antiplatelet - No statin (AP only) to Low-moderate intensity statin to High intensity statin trios (3 level propensity matched analysis).

Variable	Antiplatelet- No statin (AP only)	Low-Moderate Intensity Statin	High Intensity Statin	Standardized Difference		
				AP only vs. Low-Moderate	Low-Moderate vs. High	High vs. AP only
PAD patients in study, No.	10,260	10,260	10,260			
Age, Mean (SD), years	66.12 (9.83)	65.65 (9.23)	65.86 (8.44)	-0.05	-0.02	-0.03
Sex, % Male	97.71	97.8	97.68	-0.01	0.01	0.00
Race, %[a]						
White	82.47	81.49	81.84	0.03	-0.01	-0.02
Black	16.14	17.19	16.83			
Other	1.39	1.32	1.33			
Smoking, %[*]						
Current	29.53	30.88	31.06	-0.03	0.00	0.03
Former	26.21	26.01	25.89			
Never	8.92	8.54	8.55			
Missing	35.34	34.57	34.5			
BMI, Mean (SD), kg/m2	29.07 (6.70)	28.86 (6.18)	29.02 (5.69)	-0.03	-0.03	-0.01
Creatinine, Median (IQR), mg/dL	1.08 (0.90-1.36)	1.10 (0.90-1.39)	1.10 (0.90-1.40)	-0.01	-0.01	0.00
Comorbidities, %						
Diabetes	49.77	49.28	50.55	0.01	-0.03	0.02
Hypertension	87.26	87.7	87.53	-0.01	0.01	0.01
CAD	52.83	54.04	53.36	-0.02	0.01	0.01
CHF	17.53	18.89	18.27	-0.04	0.02	0.02
COPD	8.66	9.17	8.86	-0.02	0.01	0.01
AF	12.52	12.63	12.94	0.00	-0.01	0.01
Carotid Disease	67.85	68.35	67.39	-0.01	0.02	-0.01
Depression	18.56	18.85	18.01	-0.01	0.02	-0.01
CKD or ESRD	7.64	7.18	7.57	0.02	-0.01	0.00
Cilostazol, %	8.72	8.75	8.6	0.00	0.01	0.00
Median Household Income of Residential Zip Code, %[*]						
<=$25,000	3.02	3.6	3.11			
$25,001-$40,000	27.42	27.47	27.19			
$40,001-$75,000	59.99	59.89	60.04	0.00	0.00	0.00

$75,001+	9.57	9.04	9.66			
PAD severity, %[*]						
Not Specified	66.9	66.15	66.3			
Claudication	21.18	21.87	21.52	-0.02	0.01	0.01
Rest Pain	4.29	4.05	4.37			
Ulceration/Gangrene	7.63	7.92	7.82			
Diagnosis Year, %[*]						
2003	3.62	3.27	3.39			
2004	3.73	3.88	4.44			
2005	4.27	4.53	4.62			
2006	5.57	5.4	4.93			
2007	6.01	6.04	5.2			
2008	7.39	7.62	8.37			
2009	9.27	9.7	10.14			
2010	10.44	10.97	10.48			
2011	11.8	13.08	11.48			
2012	13.33	12.84	12.11			
2013	13.9	13.83	13.96			
2014	10.67	8.83	10.88	0.06	-0.07	0.01

Abbreviations: PAD, Peripheral Arterial Disease; VHA, Veterans Health Administration; SD, standard deviation; IQR, interquartile range; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, Hemoglobin A1c; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CKD, chronic kidney disease; ESRD, end stage renal disease; mg, milligram; dL, deciliter.

[*]All categorical variables with 3+ levels were dichotomized for calculation of standard differences. The line on which the difference appears indicates the first level, while all others indicate the second.

eTable 5. Demographics and clinical data of matched High intensity statin to Low-moderate intensity statin pairs (2 level propensity matched analysis).

Variable	**Low-Moderate Intensity Statin**	**High Intensity Statin**	**Std. Difference**
PAD patients in study, No.	15,209	15,209	
Age, Mean (SD), years	65.60 (8.93)	65.66 (8.17)	0.01
Sex, % Male	97.68	97.76	0.01
Race, %[*]			
White	82.37	82.58	0.01
Black	16.37	16.11	
Other	1.26	1.32	
Smoking, %[*]			
Current	29.29	29.78	0.01
Former	27.37	27.36	
Never	8.74	8.72	
Missing	34.6	34.14	
BMI, Mean (SD), kg/m2	29.72 (6.51)	29.62 (5.97)	-0.02
Creatinine, Median (IQR), mg/dL	1.10 (0.90-1.40)	1.10 (0.90-1.40)	-0.01
Comorbidities, %			
Diabetes	56.09	55.61	-0.01
Hypertension	90.03	89.94	0.00
CAD	64.73	64.52	0.00
CHF	21.29	21.45	0.00
COPD	8.98	8.84	0.00
AF	13.18	13.23	0.00
Carotid Disease	70.12	70.2	0.00
Depression	19.84	19.84	0.00
CKD or ESRD	7.38	7.19	-0.01
Antiplatelet Therapy, %[*]			
None	11.17	10.05	-0.04
Prasugrel	0.03	0.03	
Dipyridamole	0.84	0.83	
Clopidogrel	4.47	3.59	
Aspirin	83.5	85.51	
Cilostazol, %	8.88	9.07	0.01
Median Household Income of Residential Zip Code, %[*]			
<=$25,000	2.79	2.84	
$25,001-$40,000	26.87	26.83	
$40,001-$75,000	60.58	60.56	0.00
$75,001+	9.76	9.77	
PAD severity, %[*]			

Not Specified	66.68	66.27	
Claudication	21.91	22.27	0.01
Rest Pain	4.23	4.25	
Ulceration/Gangrene	7.17	7.21	
*Diagnosis Year, %**			
2003	2.11	2.29	
2004	2.7	3	
2005	3.19	3.2	
2006	3.58	3.54	
2007	4.44	4.02	
2008	6.22	7.04	
2009	8.3	9.19	
2010	11.23	10.2	
2011	14.74	12.44	
2012	15.85	14.33	
2013	16.31	16.78	
2014	11.32	13.96	0.08

Abbreviations: PAD, Peripheral Arterial Disease; VHA, Veterans Health Administration; SD, standard deviation; IQR, interquartile range; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, Hemoglobin A1c; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CKD, chronic kidney disease; ESRD, end stage renal disease; mg, milligram; dL, deciliter, Std: standardized.

*All categorical variables with 3+ levels were dichotomized for calculation of standard differences. The line on which the difference appears indicates the first level, while all others indicate the second.

eTable 6. Primary model: Full results of Cox proportional hazard model for effect of statin intensity on mortality and amputations comparing high intensity statin use and low-moderate intensity statin use to an active comparator group (use of antiplatelet medication but no statin) in incident peripheral arterial disease cohort (PAD) [N=90,257]*.

Variable	**Death**	**Amputation**
	HR (95% CI)	**HR (95% CI)**
Statins (Ref. = Antiplatelet only, No statin)		
Low-Moderate Intensity	0.83 (0.81 , 0.86)	0.81 (0.75 , 0.86)
High Intensity	0.74 (0.70 , 0.77)	0.67 (0.61 , 0.74)
Age (1-year increase)	1.05 (1.05 , 1.05)	0.98 (0.97 , 0.98)
Sex (Ref. = Male)	0.85 (0.76 , 0.95)	0.45 (0.33 , 0.60)
Race (Ref. = White)		
Black	0.86 (0.82 , 0.89)	1.43 (1.33 , 1.54)
Other	0.91 (0.81 , 1.03)	1.19 (0.93 , 1.53)
Smoking (Ref. = Never)		
Current	1.31 (1.26 , 1.37)	0.95 (0.86 , 1.04)
Former	1.05 (1.01 , 1.09)	0.91 (0.83 , 0.99)
Unknown	0.97 (0.97 , 0.97)	0.97 (0.96 , 0.97)
BMI (1 kg/m2 increase)	1.11 (1.09 , 1.12)	1.02 (0.99 , 1.04)
Creatinine (1 mg/dL increase)	1.37 (1.33 , 1.40)	2.45 (2.28 , 2.63)
Comorbidities (Ref. = No)		
Diabetes	1.13 (1.09 , 1.18)	1.30 (1.17 , 1.44)
Hypertension	1.21 (1.18 , 1.25)	1.04 (0.98 , 1.11)
CAD	1.88 (1.82 , 1.95)	1.45 (1.34 , 1.56)
CHF	1.36 (1.30 , 1.41)	0.90 (0.80 , 1.01)
COPD	1.39 (1.34 , 1.44)	1.13 (1.03 , 1.24)
AF	1.11 (1.07 , 1.14)	1.21 (1.13 , 1.30)
Carotid Disease	1.18 (1.14 , 1.23)	1.10 (1.02 , 1.18)
Depression	1.49 (1.41 , 1.58)	1.56 (1.39 , 1.76)
CKD or ESRD	0.93 (0.89 , 0.99)	0.77 (0.67 , 0.88)
Cilostazol (Ref. No)	1.11 (1.06 , 1.17)	1.08 (0.96 , 1.22)
Income (Household) Quartile of Residential Zip Code (Ref. = $75,001+)		
<=$25,000	1.07 (1.02 , 1.12)	1.02 (0.91 , 1.13)
$25,001-$40,000	1.34 (1.23 , 1.45)	1.19 (1.00 , 1.41)
$40,001-$75,000	1.02 (0.98 , 1.06)	1.36 (1.22 , 1.50)
PAD Severity (Ref. = Claudication)		
Not Specified	1.12 (1.04 , 1.20)	2.37 (2.02 , 2.77)
Rest Pain	1.69 (1.60 , 1.78)	9.45 (8.49 , 10.53)
Ulceration/Gangrene	1.03 (1.03 , 1.04)	1.08 (1.07 , 1.09)
Diagnosis Year (1-Year increase)	1.67 (0.45 , 6.17)	1.29 (0.10 , 15.94)

Abbreviations: PAD, Peripheral Artieral Disease; VHA, Veterans Health Administration; SD, standard deviation; IQR, interquartile range; BMI, body mass index; HbA1c, Hemoglobin A1c; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CKD, chronic kidney disease; ESRD, end stage renal disease; mg, milligram; dL, deciliter.

[*]p for High vs. Low-Moderate statin use <0.001

eTable 7. Sensitivity analysis: Full results of Cox proportional hazards model for effect of statin intensity on death and amputations in incident PAD patients comparing high intensity statin use, low-moderate intensity statin use and simvastatin 80mg user patients to an active comparator group (use of antiplatelet medication but no statin) in incident peripheral arterial disease cohort (PAD) [N=117,151].

Variable	**Death**	**Amputation**
	HR (95% CI)	**HR (95% CI)**
Statins (Ref. = Antiplatelet only- No statin)		
Low-Moderate	0.84 (0.82 , 0.86)	0.80 (0.76 , 0.85)
High	0.74 (0.71 , 0.76)	0.68 (0.62 , 0.73)
Simvastatin 80 mg	0.84 (0.82 , 0.87)	0.78 (0.73 , 0.83)
Age (1-year increase)	1.05 (1.05 , 1.05)	0.97 (0.97 , 0.98)
Sex (Ref. = Male)	0.85 (0.78 , 0.92)	0.48 (0.39 , 0.59)
Race (Ref. = White)		
Black	0.85 (0.82 , 0.87)	1.40 (1.33 , 1.48)
Other	0.87 (0.80 , 0.95)	1.11 (0.92 , 1.32)
Smoking (Ref. = Never)		
Current	1.29 (1.25 , 1.34)	0.92 (0.85 , 1.00)
Former	1.05 (1.01 , 1.09)	0.90 (0.84 , 0.97)
Unknown	1.14 (1.10 , 1.18)	0.89 (0.83 , 0.96)
BMI (1 kg/m2 increase)	0.97 (0.97 , 0.97)	0.96 (0.96 , 0.97)
Creatinine (1 mg/dL increase)	1.10 (1.09 , 1.11)	1.02 (1.00 , 1.03)
Comorbidities (Ref. = No)		
Diabetes	1.37 (1.34 , 1.40)	2.58 (2.45 , 2.72)
Hypertension	1.11 (1.08 , 1.14)	1.26 (1.17 , 1.36)
CAD	1.17 (1.15 , 1.20)	1.02 (0.98 , 1.07)
CHF	1.90 (1.85 , 1.94)	1.51 (1.43 , 1.60)
COPD	1.35 (1.31 , 1.39)	0.91 (0.84 , 0.99)
AF	1.42 (1.38 , 1.45)	1.23 (1.15 , 1.31)
Carotid Disease	1.08 (1.06 , 1.10)	1.19 (1.13 , 1.25)
Depression	1.17 (1.14 , 1.20)	1.11 (1.05 , 1.17)
CKD or ESRD	1.51 (1.46 , 1.57)	1.61 (1.48 , 1.75)
Cilostazol (Ref. No)	0.92 (0.88 , 0.95)	0.73 (0.66 , 0.81)
Income (Household) Quartile of Residential Zip Code (Ref. = $75,001+)		
<=$25,000	1.16 (1.12 , 1.20)	1.12 (1.03 , 1.22)
$25,001-$40,000	1.08 (1.05 , 1.12)	1.03 (0.95 , 1.12)
$40,001-$75,000	1.33 (1.25 , 1.41)	1.13 (0.99 , 1.28)
PAD Severity (Ref. = Claudication)		
Not Specified	1.01 (0.98 , 1.04)	1.27 (1.18 , 1.36)
Rest Pain	1.16 (1.10 , 1.23)	2.39 (2.12 , 2.68)
Ulceration/Gangrene	1.71 (1.65 , 1.78)	9.17 (8.49 , 9.90)

Diagnosis Year (1-Year increase)	1.03 (1.03 , 1.03)	1.07 (1.07 , 1.08)

Abbreviations: VHA, Veterans Health Administration; SD, standard deviation; IQR, interquartile range; BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, Hemoglobin A1c; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; CKD, chronic kidney disease; ESRD, end stage renal disease; mg, milligram; dL, decilitre