Statin use and lower extremity amputation risk in nonelderly diabetic patients

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Objective: **To examine the association between use of statin and nonstatin cholesterol-lowering medications and risk of nontraumatic major lower extremity amputations (LEAs) and treatment failure (LEA or death).**

Methods: **A retrospective cohort of patients with Type I and Type 2 diabetes mellitus (diabetes) was followed for 5 years between 2004 and 2008. The follow-up exposure duration was divided into 90-day periods. Use of cholesterol-lowering agents, diabetic medications, hemoglobin A1c, body mass index, and systolic and diastolic blood pressures were observed in each period. Demographic factors were observed at baseline. Major risk factors of LEA including peripheral neuropathy, peripheral artery disease, and foot ulcers were observed at baseline and were updated for each period. LEA and deaths were assessed in each period and their hazard ratios (HRs) were estimated. The study took place in the U.S. Department of Veterans Affairs Healthcare system, and the subjects consisted of cholesterol drug-naïve patients with Type I or II diabetes who were treated in the U.S. Department of Veterans Affairs Healthcare system in 2003 and were <65 years old at the end of follow-up.**

Results: **Of 83,953 patients in the study cohort, 217 (0.3%) patients experienced a major LEA and 11,716 (14.0%) patients experienced an LEA or death (treatment failure) after a mean follow-up of 4.6 years. Compared with patients who did not use cholesterol-lowering agents, statin users were 35% to 43% less likely to experience an LEA (HR, 0.65; 95% confidence interval [CI], 0.42-0.99) and a treatment failure (HR, 0.57; 95% CI, 0.54-0.60). Users of other cholesterol-lowering medications were not significantly different in LEA risk (HR, 0.95; 95% CI, 0.35-2.60) but had a 41% lower risk of treatment failure (HR, 0.59; 95% CI, 0.51-0.68).**

Conclusions: **This is the first study to report a significant association between statin use and diminished amputation risk among patients with diabetes. In this nonrandomized cohort, beneficial effects of statin therapy were similar to that seen in large-scale clinical trial experience. For LEA risk, those given nonstatins did not have a statistically significant benefit and its effect on LEA risk was much smaller compared with statins. Unanswered questions to be explored in future studies include a comparison of statins of moderate vs high potency in those with high risk of coronary heart disease and an exploration of whether the effects seen in this study are simply effects of cholesterol-lowering or possibly pleiotropic effects. (J Vasc Surg 2013;58:1578-85.)**

Diabetes elevates the risk of limb loss, adverse cardiovascular events, and death.[1] Aggressive management of dyslipidemia is a cornerstone of risk-factor modification in diabetes.[2] Current Adult Treatment Panel (ATP) III guidelines define diabetes as a coronary heart disease risk equivalent and mandate a low-density lipoprotein cholesterol (LDL-C) goal of <100 mg/dL for all individuals with diabetes[3] and an optional goal of LDL-C <70 mg/dL for very high-risk individuals.[2]

While there is trial evidence that LDL-C-lowering therapy reduces cardiovascular risk in patients with diabetes, its effect on vascular health has not been clearly evaluated.[4] The landmark Heart Protection Study, which included 5963 patients with diabetes, demonstrated a significant 22% reduction in cardiovascular events and revascularizations among subjects with diabetes randomized to simvastatin 40 mg but failed to show a significant reduction in lower extremity amputations (LEAs).[4] The Cholesterol Treatment Trialists evaluated 18,686 individuals with diabetes from 14 randomized trials of statin therapy.[5] Although there was a significant reduction in vascular mortality in patients assigned to statins, the association between LEA and statin use was not reported.

Given the current lack of evidence on the effect of statins on amputation risk, our large nontrial population of individuals in the VA healthcare system with diabetes provides a unique opportunity to evaluate the association of statin and nonstatin cholesterol-lowering medication

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use with LEA and amputation-free survival over 5 years of follow-up. Our objective was to examine how cholesterol-lowering medications among new users are associated with 5-year amputation risk and amputation-free survival.

METHODS

Research design. We used a retrospective cohort comprised of nonelderly (<65 years of age) diabetic patients who were not using cholesterol-lowering medications at baseline. We used inpatient and outpatient data sets for fiscal years 2002 and 2003 (October 2001 to September 2003; all years in this study are fiscal years) to identify patients who were treated for diabetes in the U.S. Department of Veterans Affairs (VA) healthcare system. An annual inpatient data set contains patient records for all hospitalizations that occurred during each fiscal year in all VA medical centers across the country. For each hospital stay, patient conditions using up to 10 International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes and all procedures performed are recorded using ICD-9 procedure codes. The outpatient data set contains "encounter" level data for all visits to VA hospital-based and community-based outpatient clinics each year. An encounter is a patient seen at a "clinic stop," a concept analogous to a revenue center in the private sector. A patient can have several encounters during an outpatient care visit. Each encounter contains up to 10 patient diagnoses in ICD-9 codes and up to 20 procedures in Current Procedural Technology, Version 4 codes.

We identified an individual as having diabetes if he or she had a prescription of diabetes medication in 2003 and/or two or more inpatient or outpatient care episodes with a diagnosis of diabetes (detected by an ICD-9-CM diagnostic code 250.xx) in 2002 to 2003.[6]

Because VA beneficiaries may also be entitled to receive health care from Medicare providers, we limited our study cohort to those aged <65 years at the end of follow-up (September 30, 2008) so that they would not be eligible for Medicare benefits on account of age before the end of follow-up. At the time of this study, we did not have access to Medicare data, and diagnoses made by Medicare providers were not observable in this study.

We additionally excluded all patients who died before October 1, 2004 (the index date from when the follow-up started), who had a history of any LEA before the index date, and who were new users of, or new enrollees in, the VA healthcare system in 2003. New users and/or new enrollees were excluded because baseline comorbidities were not observable.

Identification of amputation and mortality. The goal of treatment for patients with diabetic complications in the lower extremities is amputation-free survival. As our main outcomes, we used LEA and treatment failure defined as an LEA or death. We identified all major (ankle or above) LEAs between 2004 and 2008 by searching both inpatient and outpatient data. The procedure codes in the ICD-9-CM or CPT used to identify LEAs are shown in the Supplementary Table I (online only). Deaths were identified by the VA Vital Status file, which contains deaths for the VA beneficiaries up to April 2009. Any death before the end of follow-up was identified as a competing risk for amputation and as an event for the treatment failure. The VA Vital Status file has over 98% sensitivity and 97% specificity compared with the National Death Index.[7]

Cholesterol-lowering medications. We divided the 5-year follow-up into 90-day periods and observed cholesterol-lowering medications used during each period. A 90-day period was chosen because a large number of prescriptions for diabetic medications are filled for 90 days in the VA. The VA pharmacy prescription-level data were searched to identify all cholesterol-lowering agents dispensed to patients during each period. Medications were grouped according to their drug classes into statins (simvastatin, atorvastatin, fluvastatin, lovastatin, pravastatin, and rosuvastatin), fibrates (bezafibrate, ciprofibrate, clofibrate, gemfibrozil, and fenofibrate), nicotinic acid (niacin), bile acid sequestrants (cholestyramine, colesevelam, and colestipol), and cholesterol absorption inhibitors (ezetimibe). Days of supply filled for each class of medications were separately tallied from the dispensing date, and oversupply for a period was rolled over to the next. We defined a patient as a user of a class of medications if the patient had at least 30 days' supply of medications in the same class during each period. We likewise identified patients who had at least 30-day supply of any cholesterol-lowering medication in 2003 and excluded them from the study cohort.

Potential confounders. Other risk factors of LEA and death were identified either at baseline or during each period from various sources that may potentially confound the association between cholesterol-lowering medication use and outcome. Demographic factors, including patient age, gender, race/ethnicity, marital status, and coexisting conditions, were obtained from inpatient and outpatient records in 2003. We identified some coexisting conditions in 2003 for which statins may be contraindicated and their new diagnoses during each period.

Other major risk factors of LEA or mortality include coronary artery disease (CAD), peripheral artery disease (PAD), peripheral neuropathy, foot ulcers, osteomyelitis, and history of vascular procedures. These were detected by ICD-9-CM codes in the inpatient and outpatient records for 2003 and were updated for each period. The specific codes for identifying these conditions are listed in Supplementary Table II (online only).

Diabetes duration was estimated as the number of years a person had been treated for diabetes on October 1, 2003 in the VA healthcare system and was identified by searching the VA inpatient and outpatient records from 1997, the first year these data sets are available for research. Hemoglobin A1c and all cholesterol and blood pressure measures were obtained at baseline and updated for each period. The non-high-density lipoprotein cholesterol (non-HDL-C) level was computed as the total cholesterol minus high-density lipoprotein cholesterol (HDL-C). Non-HDL-C levels have the advantage of being calculable in the

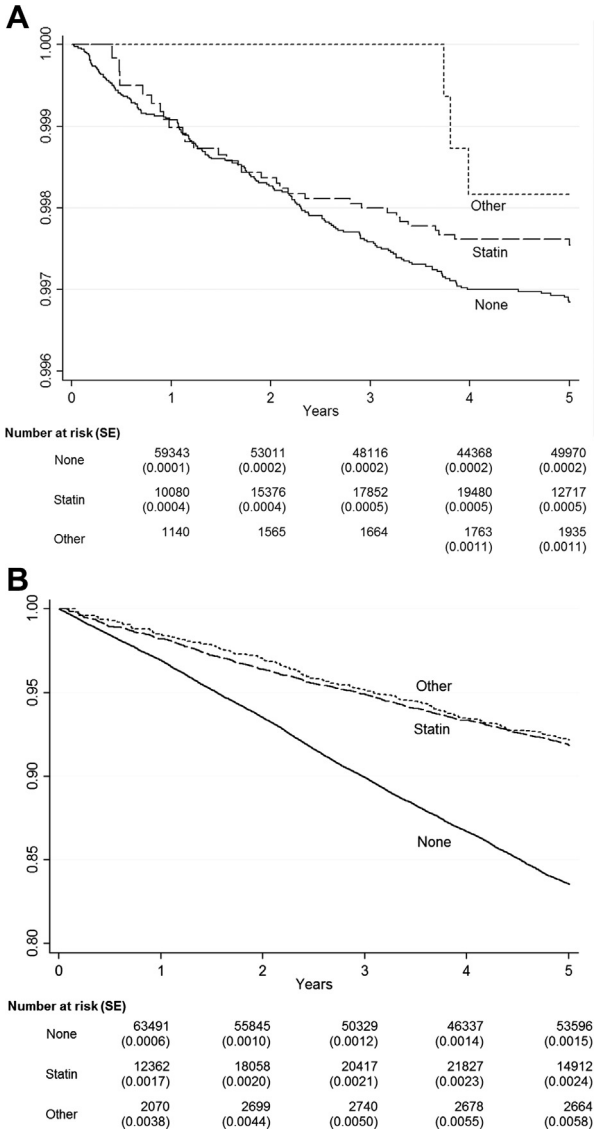

Fig 1. Kaplan-Meier survival curves for **(A)** lower extremity amputation (LEA) and **(B)** treatment failure. This figure shows Kaplan-Meier survival curves for three treatment groups (None, Statin, and Other) over 5 years of follow-up for LEA and treatment failure. *None,* No cholesterol-lowering medications; *Other,* cholesterol-lowering medications other than statins; *SE,* standard error; *Statin,* statins alone.

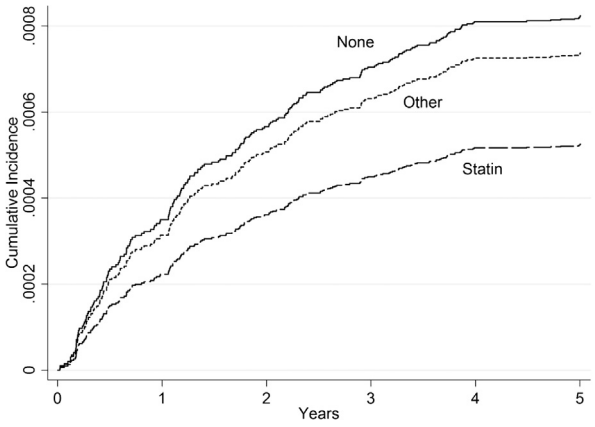

Fig 2. Cumulative incidence function curves for lower extremity amputation (LEA) after adjusting for competing risks. This figure shows cumulative incidence function curves for three treatment groups (None, Statin, and Other) over 5 years of follow-up for LEA, adjusting for death as a competing risk. *None,* No cholesterol-lowering medications; *Other,* cholesterol-lowering medications other than statins; *Statin,* statins alone.

nonfasting state and include LDL-C. Moreover, in a large-scale clinical trial of patients with diabetes, non-HDL-C was shown to be a strong and independent predictor of cardiovascular endpoints.[8]

We also obtained all height and weight measures taken during visits to the VA hospitals or clinics in 2003 and in each period. For all period-specific measures, when a measure is not observed in a period, we used the last observation carried forward method to impute the missing values from the previous period, assuming that the last observed values did not change until the next measurement.[9] When multiple measures were available from the same period, we used the average of all available values.

Statistical analysis. Our primary outcomes were major LEAs and deaths identified during a 5-year follow-up. Time to our primary outcomes were compared between four groups of patients according to cholesterol-lowering therapies they used: "nonusers" who were not treated with any cholesterol-lowering medications, "statin users" who were treated with statins alone, "nonstatin users" who were treated with cholesterol-lowering medications other than statins, and "both users" who were treated with both statins and nonstatin agents. We analyzed the time to the first major LEA using a competing risk regression,[10] adjusting for death as a competing risk. Time to the first LEA or death was analyzed using a Cox regression. Both models included baseline patient characteristics (age, race, marital status, diabetes duration >7 years at baseline) and time-varying covariates such as diabetes control (A1c), diabetic medication use, body mass index (BMI), and comorbidities (CAD, PAD, foot ulcers, osteomyelitis, diabetic neuropathy, and history of vascular procedures) in each person-period. Patient gender was not included in the final regression models because it was not significant in both models, and a reliable estimate for LEA risk was not available due to a small number of events for females.

We graphically compared survival estimates by therapy groups using Kaplan-Meier survival curves (Fig 1). The number of patients at risk and standard errors of the estimates at each major time point were provided below the graphs. Note that none of the patients were taking any cholesterol-lowering medications at baseline and so the numbers for Year 0 are not provided. The curves for both statin and nonstatin users were mainly overlapping

Table I. Baseline characteristics of the study cohort

Measures	*No.*	*Mean (SD)*	*Percentiles*				
			5%	*25%*	*Median*	*75%*	*95%*
Age, years	83,593	52.3 (6.1)	40.0	49.0	54.0	57.0	59.0
Cholesterol levels, mg/dL							
LDL-C	48,276	104.1 (34.1)	48.2	83.3	104.0	125.0	159.4
non-HDL-C	55,751	140.6 (38.4)	82.7	115.0	138.0	163.0	207.5
Total cholesterol	59,329	182.3 (40.0)	124.0	157.0	179.5	204.0	248.5
HDL-C	52,662	41.8 (14.5)	25.0	33.0	39.0	47.7	66.5
Triglycerides	52,783	200.4 (132.6)	80.0	114.0	162.0	241.7	447.0
Hemoglobin A1c, %	63,351	7.5 (1.8)	5.3	6.2	7.2	8.6	11.0
Blood pressure, mm Hg							
Systolic	53,117	137.0 (15.5)	113.3	126.8	136.0	146.0	164.0
Diastolic	53,102	79.4 (9.0)	65.0	73.5	79.3	85.0	94.3
BMI, kg/m^2	48,420	32.1 (6.8)	22.5	27.4	31.1	35.8	44.6

BMI, Body mass index; *LDL-C,* low-density lipoprotein cholesterol; *HDL-C,* high-density lipoprotein cholesterol; *SD,* standard deviation.

those for statin users and were not displayed. Because Kaplan-Meier curves are not appropriate in the presence of competing risks,[11] we also used the Cumulative Incidence Function curves to compare cumulative risk of major LEAs by four therapy groups, adjusting for deaths as a competing risk (Fig 2). The sample provides power >0.8 for a minimum detectable hazard ratio (HR) of 0.65 for LEAs and 0.95 for treatment failure between nonusers and statin users and of 0.41 for LEAs and 0.85 for treatment failure between nonusers and nonstatin agent users with alpha <.05 on a two-sided test. We use Stata/SE 12.1 (StataCorp LP, College Station, Tex) for statistical analysis. This study was approved by the institutional review board at the Hines VA Hospital, Hines, Illinois.

RESULTS

There were 83,593 cholesterol drug-naïve individuals in the study cohort, of whom 217 (0.3%) experienced a major LEA and 11,716 (14.0%) experienced a treatment failure during a mean follow-up of 4.6 years (median, 5 years).

Baseline characteristics are shown in Table I. Over half of those who had valid measures consistently did not meet ATP III goals[12] recommended for persons with diabetes in cholesterol levels (LDL-C ≥100 mg/dL, HDL-C <40 mg/dL), blood pressure (≥130/80 mm Hg), and BMI (BMI ≥30 kg/m^2).

Patient characteristics in Table II show that about 75% of the cohort were aged 50 years or older and 2.9% were 60 years or older at baseline. About 44% were non-Hispanic white and 24% non-Hispanic black. Hemoglobin A1c was measured for over 75% of the cohort in 2003, and 14% of all patients (19% with A1c measures) had an average A1c >9%. Twenty-one percent had diabetes for 7 years or longer at baseline. Fourteen percent were treated with insulin alone, 49% with oral medications alone, 13% with both insulin and oral medications, and the rest (23%) did not receive any pharmacological treatment for diabetes in 2003. Within this cohort, 11% had peripheral neuropathy, 10% CAD, 3% PAD, 0.12% history of vascular procedures, 2% foot ulcers, 0.3% osteomyelitis, 1.6% renal failure, and 6% liver disease at baseline.

Compared with patients who have never experienced an adverse outcome during follow-up, those who experienced a treatment failure were older (52 vs 55 years), had slightly higher A1c (7.50 vs 7.54 mg/dL), were less likely to be obese (36.0% vs 27.4%), but were more likely to have diabetes ≥7 years (19.7% vs 27.7%), CAD (8.5% vs 18.0%), PAD (2.1% vs 6.0%), foot ulcers (1.5% vs 4.8%), and osteomyelitis (0.3% vs 0.6%) at baseline.

When we compared baseline characteristics of patients between statin users and nonusers, we found that most factors significantly and positively associated with statin use were also factors that are usually associated with poor vascular health, including BMI >30 kg/m^2 (30.5% for nonusers vs 37.6% for statin users), A1c >9% (13.4% vs 15.3%), and PAD (2.4% vs 2.8%). However, at baseline, more patients had foot ulcers (2.2% vs 1.8%), osteomyelitis (0.18% vs 0.28%), and diabetes duration >7 years (21.4% vs 20.6%) among nonusers than statin users.

Fig 1 shows Kaplan-Meier survival curves for LEA and for the treatment failure by three therapy groups over 5 years. For LEAs, limb survival steadily decreased for both nonuser ("None") and statin ("Statin") groups until the 4th year and leveled off during the last year of follow-up. On the other hand, the nonstatin ("Other") group experienced most of the LEA events during the 3rd year. While the nonstatin group had the best survival of the three groups in these unadjusted Kaplan-Meier curves, the cumulative incidence function curves from the full-adjusted competing risk regression (Fig 2) shows that the statin group had the lowest cumulative incidence and the nonuser group had the highest cumulative incidence of LEA, with the nonstatin group resembling the nonuser group more than the statin group.

For the treatment failure, survival curves for the statin and nonstatin groups mostly overlapped each other, but they diverged from the nonuser group from the very beginning of follow-up with an ever-widening gap in survival throughout the entire follow-up.

Table II. Unadjusted rates of adverse outcomes by patient characteristics at baseline

	LEA, No. (%)	*LEA or death, No. (%)*	*No events, No. (%)*
All	217 (100)	11,716 (100)	71,877 (100)
Age, years			
<50	30 (13.8)	1805 (15.4)	19,626 (27.3)
50-54	60 (27.6)	3401 (29.0)	20,122 (28.0)
55-59	82 (37.8)	5566 (47.5)	30,642 (42.6)
60-64	41 (18.9)	944 (8.1)	1487 (2.1)
Gender			
Female	[a]	243 (2.1)	3412 (4.7)
Male	[a]	11,473 (97.9)	68,465 (95.3)
Race/ethnicity			
Non-Hispanic white	106 (48.8)	6341 (54.1)	30,333 (42.2)
Non-Hispanic black	75 (34.6)	3040 (25.9)	17,228 (24.0)
Other/unknown	36 (16.6)	2335 (19.9)	24,316 (33.8)
Marital status			
Not married	134 (61.8)	7069 (60.3)	35,015 (48.7)
Married	83 (38.2)	4647 (39.7)	36,862 (51.3)
Hemoglobin A1c, %			
<7	71 (32.7)	4005 (34.2)	25,033 (34.8)
7-9	50 (23.0)	3064 (26.2)	19,222 (26.7)
>9	58 (26.7)	1870 (16.0)	10,157 (14.1)
Unknown	38 (17.5)	2777 (23.7)	17,465 (24.3)
Diabetes duration, years			
<7	121 (55.8)	8474 (72.3)	57,739 (80.3)
7 or longer	96 (44.2)	3242 (27.7)	14,138 (19.7)
BMI, kg/m^2			
<25	33 (15.2)	1564 (13.3)	4835 (6.7)
25-29.9	32 (14.7)	1596 (13.6)	10,947 (15.2)
30 or higher	43 (19.8)	3208 (27.4)	25,898 (36.0)
Unknown	109 (50.2)	5348 (45.6)	30,197 (42.0)
Antihyperglycemic medications			
None	32 (14.7)	2133 (18.2)	17,280 (24.0)
Insulin alone	72 (33.2)	2719 (23.2)	8739 (12.2)
Oral medications alone	61 (28.1)	4498 (38.4)	36,982 (51.5)
Insulin and oral medications	52 (24.0)	2366 (20.2)	8876 (12.3)
Comorbidities			
Peripheral neuropathy	79 (36.4)	1872 (16.0)	7048 (9.8)
CAD	54 (24.9)	2111 (18.0)	6144 (8.5)
PAD	57 (26.3)	705 (6.0)	1477 (2.1)
History of vascular procedure	12 (5.5)	54 (0.5)	47 (0.1)
Foot ulcers	98 (45.2)	565 (4.8)	1061 (1.5)
Osteomyelitis	16 (7.4)	51 (0.4)	138 (0.2)
Congestive heart failure	26 (12.0)	945 (8.1)	1090 (1.5)
Hypertension	142 (65.4)	6935 (59.2)	37,564 (52.3)
Paralysis	10 (4.6)	223 (1.9)	465 (0.6)
Chronic lung diseases	32 (14.7)	1663 (14.2)	5398 (7.5)
Renal failure	38 (17.5)	937 (8.0)	1143 (1.6)
Liver disease	20 (9.2)	1756 (15.0)	3287 (4.6)

BMI, Body mass index; *CAD,* coronary artery disease; *LEA,* lower extremity amputation; *No events,* no LEA or death during follow-up; *PAD,* peripheral artery disease.
[a]Cell with a small number.

Table III characterizes cholesterol-lowering prescriptions filled over the follow-up period for individuals with LDL-C below and above 100 mg/dL. In this cholesterol drug-naïve cohort at baseline, patients were not treated with any cholesterol-lowering medications in 72% of all periods during the 5-year follow-up. Patients were treated with statins alone in 22% and by nonstatin medications alone or statin and nonstatin medications together in 3% and 2.7% of all periods, respectively. During periods when patients were not treated with any cholesterol-lowering medications, they had LDL-C ≥100 mg/dL for 38.3% of periods. In 71% of periods, patients received treatment consistent with ATP-III recommendations (LDL-C <100 mg/dL or treated with statins). Altogether, 44.2% of all patients in the cohort have never been treated with statins during follow-up. Among patients experiencing an LEA, only 32% were treated with statins, while 55.5% were treated with statins among those who did not experience an amputation (data not shown).

Table IV lists HRs by type of cholesterol-lowering therapy, adjusting for demographic factors, diabetes severity, and other confounders. Compared with those

Table III. Distribution of the cohort by cholesterol-lowering therapy and low-density lipoprotein cholesterol (*LDL-C*) level, all periods (N = 1,629,488)

		LDL-C level during period, % of therapy	
Therapy[a]	*% of all periods*[b]	*<100 mg/dL*	*≥100 mg/dL*
None	71.9	61.8	38.3
Statin	22.3	59.7	40.3
Nonstatin	3.0	55.1	44.9
Both	2.7	63.9	36.1
All patients	100	61.1	36.1

[a]*Both,* Used both statins and nonstatin classes of cholesterol-lowering medications; *Nonstatin,* used nonstatin classes of cholesterol-lowering medications alone; *None,* prescribed no cholesterol-lowering medications; *Statin,* used statins alone.
[b]Do not sum up to 100% due to rounding errors.

not receiving any cholesterol-lowering medications, users of statins alone were about 35% less likely to experience any LEA (HR, 0.65; 95% confidence interval [CI], 0.42-0.99; $P = .045$) and 43% less likely to experience a treatment failure (HR, 0.57; 95% CI, 0.54-0.60; $P < .001$). The LEA risk for nonstatin users was not significantly different (HR, 0.95; 95% CI, 0.35-2.60; $P = .915$) from that for nonusers, but they were 41% less likely to experience a treatment failure (HR, 0.59; 95% CI, 0.51-0.68; $P < .001$) than nonusers. Individuals on both statin and nonstatin agents were 50% less likely to experience a treatment failure (HR, 0.51; 95% CI, 0.43-0.59; $P < .001$).

DISCUSSION

Our results show that 0.3% of nonelderly patients with diabetes who did not use any cholesterol-lowering medications at baseline had a major amputation in the lower extremities, and 14% died during a 5-year follow-up. Within this cohort, patients who used statins had a 35% lower risk of an LEA, compared with those who were not treated with any cholesterol-lowering medications. The use of other classes of medications appears to be minimally, if at all, associated with lower risk of LEA, but our sample was not adequately powered to test statistical significance of this association. On the other hand, the use of any cholesterol-lowering medications (statins, nonstatin medications, or both) was associated with increased amputation-free survival over 5 years. These results imply that statin use may be associated with a decrease in amputation risk, but the use of nonstatin agents may not share in this protection against limb loss.

Since their introduction, statins have been used not only for LDL-C reduction but for improvement in survival in patients at high risk for cardiovascular events. Randomized controlled trials such as the Heart Protection Study,[13] Collaborative Atorvastatin Diabetes Study,[14] and Scandinavian Simvastatin Survival Study (4S)[15] provide strong clinical evidence that statin therapy is associated with a reduction in mortality both for primary and secondary prevention, particularly in patients with diabetes.

Statins have also been shown to modify disease burden and morbidity in patients with lower extremity occlusive disease. In the Regression Growth Evaluation Statin Study (REGRESS), pravastatin use was associated with decrease in atherosclerotic plaque burden, as assessed by ultrasound of the femoral artery.[16] In small cohorts, statin therapy has been demonstrated to increase walking time and distance[17] and delay functional decline.[18] The 4S study was the first randomized controlled trial to demonstrate an improvement in PAD symptoms. In the 153 subjects with PAD, simvastatin was associated with a 38% reduction in new or worsening intermittent claudication.[19] In patients with diabetes, peripheral neuropathy is an independent risk factor for LEA and increases the risk for foot ulcers and LEA multiplicatively in the presence of PAD.[20] Previous research has shown that statins are associated with improvement in microvascular function and peripheral neuropathy, independent of LDL-C lowering.[21] Despite accumulating evidence that statins have these beneficial effects on vascular health, clinical research until now has not clearly demonstrated beneficial effects of statins on amputation risk.[22]

Some propose that in addition to the proven benefits of LDL-C lowering on atherosclerotic cardiovascular disease (ASCVD) risk, pleiotropic effects of statins may explain other favorable results. In the Justification for the Use of Statins in Primary Prevention study, a primary prevention clinical trial, investigators showed benefit of those men ≥50 and women ≥ 60 years, both with high-sensitivity C-reactive protein >2 mg/L, randomized to rosuvastatin 20 mg/day as contrasted with placebo as regards the combined primary endpoint of ASCVD outcomes.[23] While this result is explained by the statin effects on lowering LDL-C levels, the 43% reduction in the risk of venous thromboembolism in those randomized to rosuvastatin in this trial is less convincingly assumed to be related to statin-induced LDL-C reduction.[24]

The role of nonstatin cholesterol-lowering medications in the maintenance of diabetic limb health is unclear. In our cohort, nonstatin cholesterol-lowering medications were associated with a nonsignificant decrease in amputation and a less robust, but significant, reduction in treatment failure. In comparison, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial evaluated the use of fenofibrate as monotherapy in 9795 subjects with type 2 diabetes.[25] Fenofibrate did not significantly reduce the risk of the primary outcome of coronary events or total mortality. It did reduce total cardiovascular events, mainly due to fewer nonfatal myocardial infarctions and revascularizations. Over the 5 years of follow-up, there was a significantly lower rate of minor amputations in the fenofibrate treated group but no significant difference in major amputations.[26] The benefit of fenofibrate to prevent minor amputation was strongest in subjects with known microvascular disease such as retinopathy and microalbuminuria. There was no strong association between amputation and

Table IV. Hazard ratios (*HRs*) and their 95% confidence intervals (*CIs*) of any lower-extremity amputation (*LEA*) or any LEA or death for users of different cholesterol-lowering medications compared with nonusers

	LEA		*LEA or death*	
	HR (95% CI)[a]	P *value*	*HR (95% CI)*	P *value*
Statin	0.645 (0.420-0.991)	.045	0.569 (0.537-0.602)	<.001
Nonstatin	0.946 (0.345-2.596)	.915	0.586 (0.508-0.676)	<.001
Both[b]	–	–	0.505 (0.433-0.589)	<.001

BMI, Body mass index; *CAD,* coronary artery disease; *PAD,* peripheral arterial disease.
Both models were adjusted for age, race/ethnicity, marital status, A1c, BMI, insulin use and/or oral antihyperglycemic medication use, history of vascular surgery, and comorbidities (foot ulcer, CAD, PAD, peripheral neuropathy, foot ulcers, and osteomyelitis). The LEA model was additionally adjusted for mortality as a competing risk.
[a]HRs for LEA were adjusted for deaths as competing risks.
[b]For LEA, a reliable estimate was not available for the "Both" group due to small number of events (n = 7).

known large vessel arterial occlusive disease. Patients in our cohort were treated with nonstatin agents for only 6% of all periods (3% with nonstatin agents alone and 2.7% with statins and nonstatins together) and, as such, our ability to draw inferences about users of nonstatin agents may be limited. Both our study and the FIELD study highlighted the unique pathology of the microvasculature in diabetes.

One must recognize the limitations inherent in the inclusion/exclusion criteria for this cohort study that may limit its broad generalizability. The study population is entirely persons with diabetes, disproportionately male, and limited to those who are nonelderly. It remains unclear if a similar benefit of statins is attributable to individuals with different characteristics. Given that this is a retrospective study, we were required to assume that statin prescriptions filled during each period implied actual use. We also could not entirely exclude the possibility that some statins were filled outside the VA and were not accounted for in our analysis. Finally, as in other retrospective studies, it was impossible for us to exclude all sources of confounding, especially one due to patient selection. When we compared baseline characteristics of patients between nonusers and statin users, we found that statin users did not necessarily have better vascular health at baseline than nonusers to the extent that patient selection alone could have explained the differences in event rates between our comparison groups. It is noteworthy that the rate of statin use in our cohort is surprisingly low. Even though we did not have information on contraindications to safe statin use, such as allergies and adverse side effects, it is worrisome that patients in our study cohort did not meet the LDL-C target (<100 mg/dL) for 36.1% of all periods during follow-up but were not treated with any cholesterol-lowering medication in 70.8% of these periods (Table III). Patients in general were treated with statins for 25% of all periods (22.3% with statins alone and 2.7% with both statins and other agents). Limited statin use in our cohort is not an exception, however. Under-utilization of statins and suboptimal LDL-C levels have been documented in other diabetic populations as well.[27] While this study supports a positive relationship between statin use and limb survival, our ability to draw an inference about the positive effect of statins on the micro- and macrovasculature is limited. Unfortunately, our clinical cohort remains incompletely characterized. In the literature, one-third of patients with diabetes have concomitant PAD.[28] Our cohort has a low reported rate of PAD (3% at baseline), which likely reflects broad underdiagnosis. Because ankle-brachial index measures were not available for use in this study, we could not verify accuracy of PAD based on the ICD-9-CM diagnostic coding in inpatient and outpatient administrative records.

In conclusion, this is the first study that demonstrated protective effects of statins in LEA. Even though we limited our sample to nonelderly diabetic patients, our large sample from observational data allowed us to observe a striking effect of statin therapy on LEA risk and amputation-free survival. Finally, we showed that there were a large number of patients with diabetes who were not treated for cholesterol lowering. These findings indicate an area where clinical practice may need improvement, and at the same time, offer an opportunity for a future study. While prospective clinical trial data support widespread use of statins in those with diabetes and ASCVD,[5] it is not known if statin therapy that titrates to ATP-III goal is superior to just initiating fixed-dose statin therapy in this high-risk population. A clinical trial that randomized those with diabetes and ASCVD to either an intensive treatment arm (using a maximally tolerated statin dosage to achieve an LDL-C <70 mg/dL) or merely a fixed moderate dose arm (such as simvastatin 40 mg/day or atorvastatin 10 mg/day) has the promise to provide useful information for the care of these patients. Given that moderate dose statins in the Collaborative Atorvastatin Diabetes Study (CARDS) trial had a beneficial effect on CVD outcomes, it is important to know if using high-dose potent statins with their attendant increase in statin-related side effects and possibly decreased adherence is worth the increased cost and effort.

The paper presents the findings and conclusions of the authors; it does not necessarily represent the Department of Veterans Affairs, Health Services Research and Development Service, or the National Institutes of Health.

The corresponding author had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

AUTHOR CONTRIBUTIONS

Conception and design: MS, WP
Analysis and interpretation: MS, NS, EO, WP, JM, TL
Data collection: MS, EO
Writing the article: MS, EO, JM, WP
Critical revision of the article: WP, NS, EO, JM, TL, EM
Final approval of the article: MS, WP, EO, JM, TL, EM, NS
Statistical analysis: MS, EO
Obtained funding: EM
Overall responsibility: MS, WP

REFERENCES

1. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med 1992;326:381-6.
2. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease). Circulation 2006;113:e463-654.
3. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143-421.
4. Collins R, Armitage J, Parish S, Sleigh P, Peto R. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003;361:2005-16.
5. Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, et al. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet 2008;371:117-25.
6. Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the Department of Veterans Affairs based on computerized patient data. Diabetes Care 2004;27(Suppl 2):B10-21.
7. Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. Popul Health Metr 2006;4:2.
8. Bittner V, Hardison R, Kelsey SF, Weiner BH, Jacobs AK, Sopko G. Non-high-density lipoprotein cholesterol levels predict five-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI). Circulation 2002;106:2537-42.
9. National Research Council of the National Academies. The Prevention and Treatment of Missing Data in Clinical Trials. Washington, DC: The National Academies Press; 2010.
10. Zhang X, Zhang MJ, Fine J. A proportional hazards regression model for the subdistribution with right-censored and left-truncated competing risks data. Stat Med 2011;30:1933-51.
11. Satagopan JM, Ben-Porat L, Berwick M, Robson M, Kutler D, Auerbach AD. A note on competing risks in survival data analysis. Br J Cancer 2004;91:1229-35.
12. Adult Treatment Panel III, National Institute of Health. Third Report of the National Cholesterol Education Program Expert Panel and Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; 2006. Available at: http://www.nhlbi.nih.gov/cholesterol/atp3full.pdf. Accessed July 25, 2013.
13. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360:7-22.
14. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HA, Livingstone SJ, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004;364:685-96.
15. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-9.
16. de Groot E, Jukema JW, Montauban van Swijndregt AD, Zwinderman AH, Ackerstaff RG, van der Steen AF, et al. B-mode ultrasound assessment of pravastatin treatment effect on carotid and femoral artery walls and its correlations with coronary arteriographic findings: a report of the Regression Growth Evaluation Statin Study (REGRESS). J Am Coll Cardiol 1998;31:1561-7.
17. McDermott MM, Guralnik JM, Greenland P, Pearce WH, Criqui MH, Liu K, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. Circulation 2003;107:757-61.
18. Giri J, McDermott MM, Greenland P, Guralnik JM, Criqui MH, Liu K, et al. Statin use and functional decline in patients with and without peripheral arterial disease. J Am Coll Cardiol 2006;47:998-1004.
19. Pedersen TR, Kjekshus J, Pyorala K, Olsson AG, Cook TJ, Musliner TA, et al. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). Am J Cardiol 1998;81:333-5.
20. Sohn MW, Stuck RM, Pinzur M, Lee TA, Budiman-Mak E. Lower-extremity amputation risk after charcot arthropathy and diabetic foot ulcer. Diabetes Care 2010;33:98-100.
21. Leiter LA. The prevention of diabetic microvascular complications of diabetes: is there a role for lipid lowering? Diabetes Res Clin Pract 2005;68(Suppl 2):S3-14.
22. Aikawa M. Effects of statin therapy on vascular dysfunction. Coron Artery Dis 2004;15:227-33.
23. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359:2195-207.
24. Glynn RJ, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. A randomized trial of rosuvastatin in the prevention of venous thromboembolism. N Engl J Med 2009;360:1851-61.
25. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 2005;366:1849-61.
26. Rajamani K, Colman PG, Li LP, Best JD, Voysey M, D'Emden MC, et al. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. Lancet 2009;373:1780-8.
27. Li M, Ong KL, Tse HF, Cheung BM. Utilization of lipid lowering medications among adults in the United States 1999-2006. Atherosclerosis 2010;208:456-60.
28. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al. Peripheral arterial disease detection, awareness, and treatment in primary care. JAMA 2001;286:1317-24.

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Additional material for this article may be found online at www.jvascsurg.org.

Supplementary Table I (online only). Procedure codes used to identify major amputations

Level	*ICD-9-CM codes*	*CPT-4 codes*
Ankle or leg	84.13 – 84.15	27880 – 27889
Knee or above	84.16 – 84.17	27590 – 27598

CPT, Current Procedural Terminology, Version 4; *ICD-9-CM,* International Classification of Diseases, Ninth Revision, Clinical Modification.

Supplementary Table II (online only). Comorbidities and their definitions in International Classification of Diseases, Ninth Revision, Clinical Modification (*ICD-9-CM*) codes

Coexisting condition	*ICD-9-CM codes*
Peripheral neuropathy	250.6, 355.x, 337.1, 357.2
CAD	410.xx-414.xx, 429.2
PAD	250.7, 443.9
History of vascular procedure	Procedure codes 39.25, 39.29, 39.49, 39.50, 39.90, or 00.40-00.48, 00.55, 00.60 used with 440.20-440.24 diagnostic codes
Foot ulcers	707.1x, 707.9
Osteomyelitis	730.06-730.09, 731.06-731.09, 732.06-732.09

CAD, Coronary artery disease; *PAD,* peripheral artery disease.
Diagnostic codes for all other comorbidities were obtained from http://www.hcup-us.ahrq.gov/reports/ComorbiditySoftwareDocumentationFinal.pdf.