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CLINICAL RESEARCH
Vascular medicine

Statin therapy and long-term adverse limb outcomes in patients with peripheral artery disease: insights from the REACH registry

Dharam J. Kumbhani[1]*, Ph. Gabriel Steg[2,3,4,5], Christopher P. Cannon[6,7], Kim A. Eagle[8], Sidney C. Smith Jr[9], Shinya Goto[10], E. Magnus Ohman[11], Yedid Elbez[2,3,4], Piyamitr Sritara[12], Iris Baumgartner[13], Subhash Banerjee[1], Mark A. Creager[6], and Deepak L. Bhatt[6,7,14], on Behalf of the REACH Registry Investigators†

[1]Division of Cardiology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-9047, USA; [2]Université Paris-Diderot, Sorbonne-Paris Cité, Paris, France; [3]INSERM U-1148, Paris, France; [4]Département Hospitalo-Universitaire FIRE, Hôpital Bichat, Assistance Publique-Hôpitaux de Paris, Paris, France; [5]NHLI Imperial College, ICMS, Royal Brompton Hospital, London, UK; [6]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [7]TIMI Study Group, Boston, MA, USA; [8]University of Michigan Cardiovascular Center, Ann Arbor, MI, USA; [9]Center for Cardiovascular Science and Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [10]Department of Medicine, Tokai University School of Medicine, Isehara, Japan; [11]Division of Cardiology, Duke University, Durham, NC, USA; [12]Faculty of Medicine, Department of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [13]Swiss Cardiovascular Center Bern, University Hospital Bern, Switzerland; and [14]VA Boston Healthcare System, Boston, MA, USA

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Aims Due to a high burden of systemic cardiovascular events, current guidelines recommend the use of statins in all patients with peripheral artery disease (PAD). We sought to study the impact of statin use on limb prognosis in patients with symptomatic PAD enrolled in the international REACH registry.

Methods Statin use was assessed at study enrolment, as well as a time-varying covariate. Rates of the primary adverse limb outcome (worsening claudication/new episode of critical limb ischaemia, new percutaneous/surgical revascularization, or amputation) at 4 years and the composite of cardiovascular death/myocardial infarction/stroke were compared among statin users vs. non-users.

Results A total of 5861 patients with symptomatic PAD were included. Statin use at baseline was 62.2%. Patients who were on statins had a significantly lower risk of the primary adverse limb outcome at 4 years when compared with those who were not taking statins [22.0 vs. 26.2%; hazard ratio (HR), 0.82; 95% confidence interval (CI), 0.72–0.92; $P = 0.0013$]. Results were similar when statin use was considered as a time-dependent variable ($P = 0.018$) and on propensity analysis ($P < 0.0001$). The composite of cardiovascular death/myocardial infarction/stroke was similarly reduced (HR, 0.83; 95% CI, 0.73–0.96; $P = 0.01$).

Conclusion Among patients with PAD in the REACH registry, statin use was associated with an ~18% lower rate of adverse limb outcomes, including worsening symptoms, peripheral revascularization, and ischaemic amputations. These findings suggest that statin therapy not only reduces the risk of adverse cardiovascular events, but also favourably affects limb prognosis in patients with PAD.

Keywords Statins • Peripheral vascular disease • Claudication • Morbidity • Registry

Introduction

Lower extremity peripheral artery disease (PAD) affects nearly one-fifth of all adults older than 55 years of age, with increased prevalence in high-risk subgroups such as those with diabetes, renal insufficiency, and smoking.[1–4] Patients with PAD have high rates of systemic event rates such as myocardial infarction, stroke, and death, with higher rates in symptomatic patients.[5–12] These can be as high as five-fold

*Corresponding author. Tel: +1 214 645 7508, Fax: +1 214 645 7573, Email: dharam@post.harvard.edu

† A complete list of the REACH Registry Investigators appears in *JAMA* 2006; **295**: 180–189.

for cardiovascular mortality and three-fold for all-cause mortality after adjustment for known Framingham risk factors.[5] In a pre-specified subgroup analysis of the Heart Protection Study (HPS) in patients with known PAD, simvastatin use was associated with a 20–25% reduction in major adverse cardiovascular events when compared with placebo.[8] Accordingly, current guidelines for secondary prevention and risk reduction in patients with PAD strongly recommend lipid-lowering therapy with a statin to achieve a goal low-density lipoprotein (LDL) level of $\leq$100 mg/dL in low-risk patients and $\leq$70 mg/dL in high-risk patients.[13,14] However, patients with PAD also have a high incidence of adverse limb outcomes. This can be as a high as a 25% annual risk of limb amputation in patients with advanced disease.[15] The association between statin use and limb outcomes in patients with PAD is unclear.

Since a randomized controlled trial would be unethical given the known salutary effects of statins on cardiovascular outcomes, we decided to investigate this hypothesis further in the large international Reduction of Atherothrombosis for Continued Health (REACH) Registry.

Methods

Study population

The methods of the REACH Registry have been published previously.[16–20] Briefly, 69 055 patients at least 45 years old with $\geq$3 risk factors for atherosclerosis and patients with established coronary, cerebrovascular, or PAD were enrolled between 2003 and 2004. The multiple risk factors category consisted of diabetes, diabetic nephropathy, symptomatic or asymptomatic ankle-brachial index $\leq$0.9, asymptomatic carotid stenosis of $\geq$70%, carotid intima media thickness at least two times that at adjacent sites, systolic blood pressure $\geq$150 mmHg despite treatment, hypercholesterolaemia treated with medication, current smoking of $\geq$15 cigarettes per day, and age $\geq$65 years for men or $\geq$70 years for women. These patients were assessed annually at years 1 through 4, and follow-up was completed in 2008. For the purpose of this analysis, we restricted the data set to patients with documented symptomatic PAD who had complete 4-year follow-up information (*Figure 1*). Documented symptomatic PAD consisted of current intermittent claudication with an ankle-brachial index of $<$0.9 and/or a history of intermittent claudication together with a previous intervention, such as angioplasty, stenting, atherectomy, peripheral arterial bypass grafting, or other vascular interventions, including amputations.

Ascertainment of exposure variables

Data relating to statin use were ascertained based on physicians' report on the standardized international case report form at each study visit. Information regarding the use of other medications, systolic and diastolic blood pressure, and fasting glucose and cholesterol levels was also obtained at each visit.

Ascertainment of outcomes

The primary outcome of interest was worsening PAD, which was a composite of worsening claudication/new episode of critical limb ischaemia (CLI), new lower extremity percutaneous or surgical revascularization, or amputation. Individual components of this composite endpoint were also studied. Endpoints were not adjudicated, but based on physician reporting at the time of follow-up. Subsequent lower extremity revascularization had to be chart-documented.

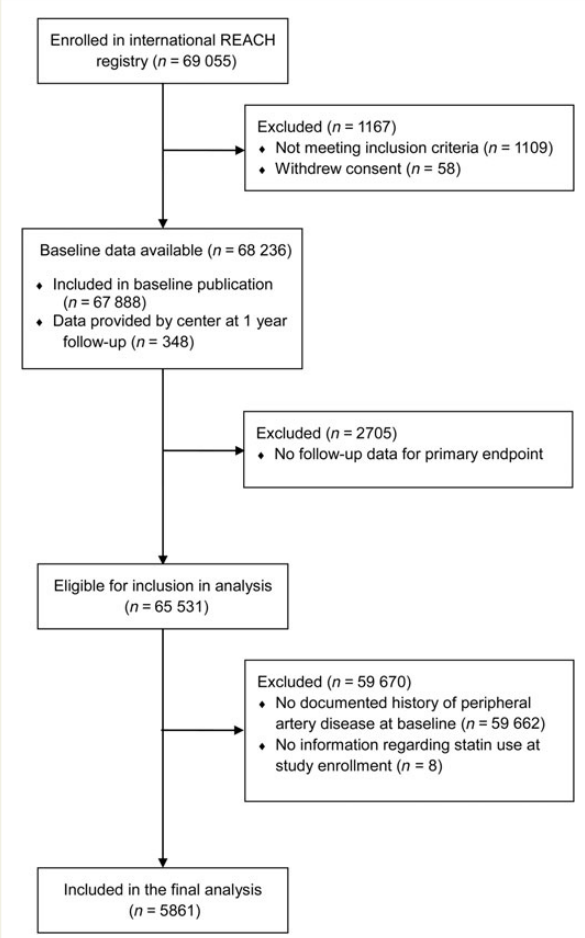

Figure 1 CONSORT flow diagram of study participants.

The key systemic/secondary outcome was a composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke over 4 years. Other endpoints studied were all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke (see Supplementary material online, *Methods* for definitions).[16]

Role of physician subspeciality

We compared statin non-usage rates by the subspeciality of the physician enrolling a given patient into the REACH registry: general or internal medicine/family practice vs. cardiology vs. angiology vs. vascular surgery vs. others. Physician subspeciality was self-reported.

Statistical analysis

The mean (standard deviation) and percentages are reported for continuous and categorical variables, respectively. Cumulative incidence rates were obtained using the Kaplan–Meier approach. Multivariate Cox regression analyses were conducted, with time to adverse limb events (worsening claudication/new episode of CLI, new percutaneous or surgical revascularization, or amputation), and systemic events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) as the outcome variables, and statin use as the primary independent variable. We also assessed extended Cox models where statin use was

included as a time-varying covariate, which meant that statin use could differ at any of the five visits (baseline, years 1–4). Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated. Other variables included in these models have all been shown to be significant independent predictors of the primary systemic outcome at 4 years in a prior analysis.[20] These include: gender, age, current smoker, history of diabetes, aspirin use, body mass index <20 (calculated as weight in kilograms divided by height in metres squared), timing of ischaemic event (≤1 or >1 year), polyvascular disease vs. single vascular disease, congestive heart failure, atrial fibrillation/flutter, and Eastern Europe, Middle East, or Japan vs. other regions. Geographic regions were collapsed into higher (Eastern Europe and Middle East) and lower (Japan/Australia) risk locations. Interaction terms for diabetes mellitus, smoking, gender, and atherosclerosis in other distributions were individually tested.

Under conditions of competing risks, the Cox regression models can produce misleading results,[21] so a competing risk analysis was performed using the *%CIF* macro in SAS.[22] We compared the overall cumulative incidence of adverse limb outcomes (adverse limb outcome before and after cardiovascular death/myocardial infarction/stroke) stratified by statin use. Differences in curves were tested using Gray's[23] test for equality of cumulative incidence functions.

Propensity analysis

To further account for significant differences in baseline characteristics between statin-users and non-users, we conducted a propensity analysis. Propensity scores for all patients were first estimated using a non-parsimonious multivariable logistic regression model, with the dependent variable of statin use at enrolment, and 15 baseline characteristics (including presence of CAD and cerebrovascular disease) entered as covariates. Propensity analysis was then conducted using inverse probability of treatment weights (IPTW), wherein individuals are weighted by the inverse probability of receiving the treatment that they actually received. To avoid bias from very large weights, the mean weight was calculated and utilized to normalize the weights, which were then introduced in a weighted least squares regression model along with other predictor covariates. The IPTW method is inclusive of all subjects in a study; therefore, no loss of sample occurs as in other conditioning methods, i.e. matching, stratification.[24,25]

Missing values for covariates were not imputed. For the time-varying analysis, a large number of patients did not have statin use information at years 3 and 4 (values missing for 21.8% at year 3, and 32.1% at year 4). For this analysis, imputations were performed as follows: if year 3 or year 4 information was missing (either, not both), then the single available value was assumed for both years. If information was missing for both years, the last available statin use information from year 2 was carried forward.

All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA). All *P*-values were two-tailed, with statistical significance set at 0.05. All CIs were calculated at the 95% level.

Results

A total of 5861 patients with established PAD were included, of which 2492 (42.5%) had a history of or current intermittent claudication only (ABI value < 0.9 without prior revascularization), 3085 (52.6%) had undergone prior lower extremity arterial revascularization (angioplasty/stenting/bypass graft), and 800 (13.6%) had undergone prior leg amputation at any level. Among these patients, 48.6% had concomitant coronary artery disease (CAD), 22.4% had cerebrovascular disease, 58.7% had polyvascular disease, and 12.3% had established disease in all three territories. Overall statin use in this patient population was 62.2% (74.5% in patients with concomitant CAD and in 64.0% patients with concomitant cerebrovascular disease) (*Figure 2*). Approximately two-thirds of these patients (65.0%) were enrolled by primary care or family practice physicians, 15.0% by vascular surgeons, 7.0% by cardiologists, 5.3% by angiologists, and 7.8% by others (*Figure 3*). Baseline characteristics of the study population based on statin use are demonstrated in *Table 1*. Patients who were not on statins at the time of enrolment were more likely to be older, male, and have experienced a PAD event (symptom/procedure) within the preceding year. Conversely, patients who were on statins were more likely to have multiple

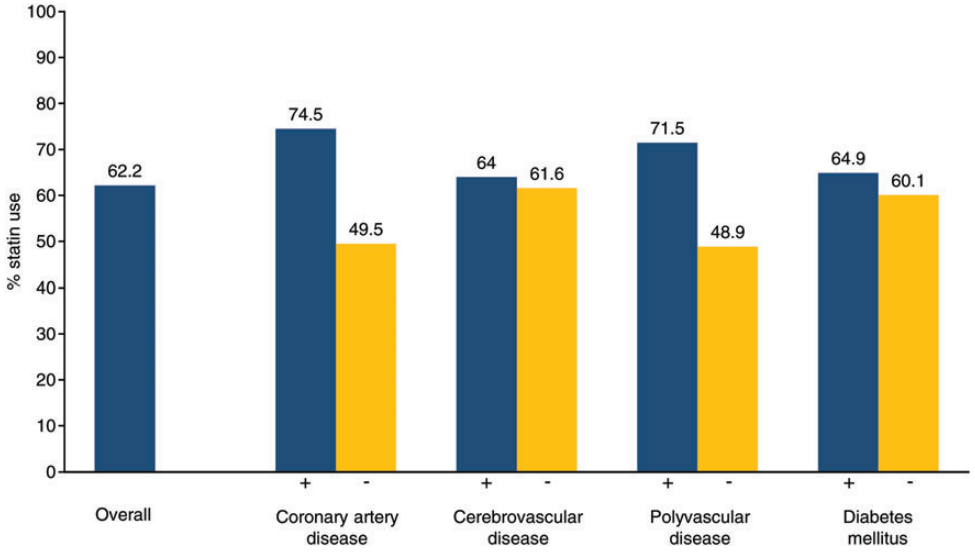

Figure 2 Proportion of patients on statins at enrolment.

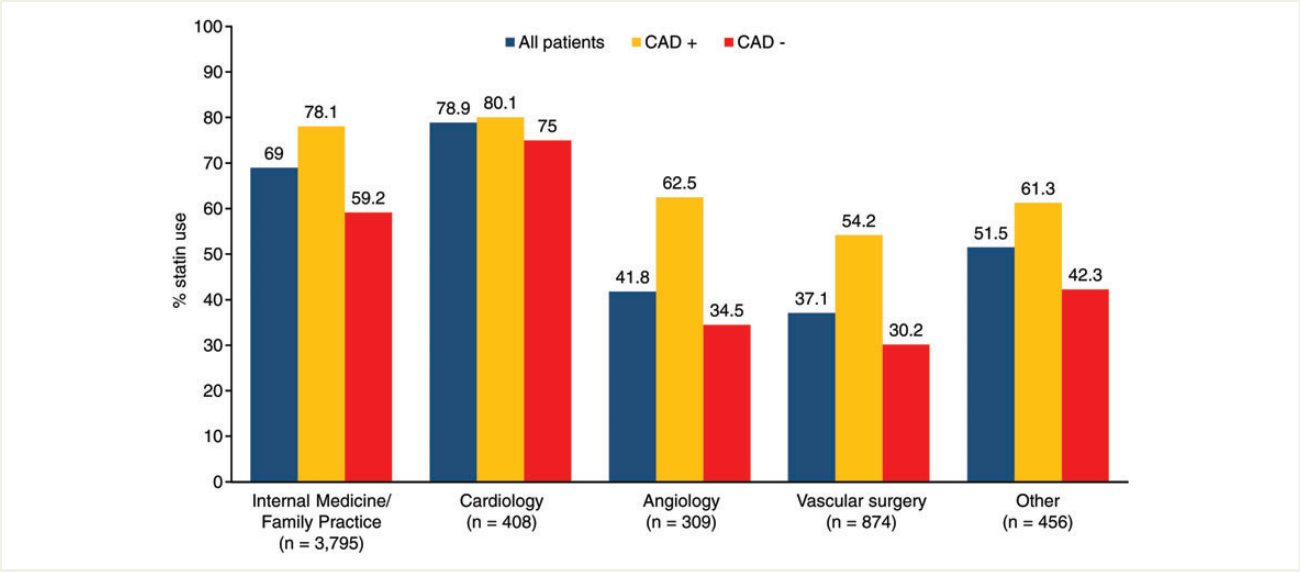

Figure 3 Proportion of patients on statins at enrolment based on enrolling investigator's subspecialty. Also reported are proportions based on the presence of concomitant CAD or not. CAD indicates coronary artery disease.

comorbidities including diabetes, hypercholesterolaemia, obesity, heart failure, CAD, and polyvascular disease; they were also more likely to be current smokers.

Statin use and adverse limb outcomes

A total of 1207 new adverse limb events occurred over 4 years (incidence = 23.6%), including 999 new revascularization procedures and 222 new ischaemic amputations. On multivariate analysis, the composite adverse limb outcome was lower in patients who were on statins at study enrolment when compared with those who were not on statins (22.0 vs. 26.2%; HR, 0.82; 95% CI, 0.72–0.92; $P = 0.0013$). The individual components of the primary endpoint, including worsening claudication or new critical limb ischaemia (14.7 vs. 18.2%; HR, 0.82; 95% CI, 0.70–0.95; $P = 0.0087$), new lower extremity percutaneous/surgical revascularization (18.2 vs. 21.7%; HR, 0.83; 95% CI, 0.72–0.95; $P = 0.0079$), and new ischaemic amputation (3.8 vs. 5.6%; HR, 0.64; 95% CI, 0.48–0.86; $P = 0.0027$) were all higher in patients who were not on statins. Time-varying analysis and the propensity analysis demonstrated similar results (*Table 2*). A separate analysis was performed in all patients with PAD in the REACH registry, not just in those with available 4-year data (7994 patients with available baseline and statin use information). Results were quantitatively similar (HR, 0.85, 95% CI 0.75–0.98; $P = 0.023$). On competing risk analysis, the cumulative incidence of the adverse limb outcome remained significantly lower in patients who were on statins at study enrolment (21.1 vs. 25.1%; $P = 0.0007$).

On subgroup analysis, overall results were similar in those with stable claudication only at baseline vs. those with lower extremity revascularization procedures or amputations. None of interaction terms tested attained statistical significance (*Figure 4*).

Statin use and systemic events

Over a follow-up period of 4 years, patients who were on statins demonstrated a 17% lower risk of the primary systemic endpoint of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke on multivariate analysis (19.6 vs. 20.3%; HR, 0.83; 95% CI, 0.73–0.96; $P = 0.01$). Other endpoints including all-cause mortality (17.3 vs. 19.7%; HR, 0.83; 95% CI, 0.72–0.96, $P = 0.014$), cardiovascular mortality (11.4 vs. 12.4%; HR, 0.84; 95% CI, 0.70–1.00; $P = 0.05$), and non-fatal stroke (6.0% vs. 6.8%; HR, 0.74, 95% CI 0.57–0.95; $P = 0.016$) were all similarly higher in patients who were not on statins at study enrolment. No difference was noted in the rates of non-fatal myocardial infarction (HR, 0.85; 95% CI, 0.63–1.14; $P = 0.28$) or non-cardiovascular mortality (HR, 0.83; 95% CI, 0.65–1.06; $P = 0.13$). Time-varying Cox models and the propensity analysis noted similar results (*Table 2*). Cumulative incidence curves for the primary adverse limb outcome and for the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke are demonstrated in Supplementary material online, *Figures S1* and *S2*.

Discussion

The results of our analysis of 5861 patients with established symptomatic PAD in the international REACH registry indicate that the use of statins in these patients is low (~62%). As has been reported before,[26] CAD remains an important modulator of statin use: more than 50% of patients without CAD were not on statins. Our results indicate that patients who are on statins have an ~18% lower long-term risk of adverse limb outcomes when compared with those patients who were not on statins. Both lower extremity revascularization procedures and need for ischaemic amputations were decreased in patients who were on statins. To our knowledge, this

Table 1 Baseline characteristics of the study population

Characteristic	On statins ($n = 3643$)	Not on statins ($n = 2218$)	*P*-value
Socio-demographic			
Age (years)	68.2 (9.5)	70.0 (10.0)	<0.0001
Men	71.4	74.6	0.0084
Region			<0.0001
North America/Latin America/Western Europe/Asia	84.8	69.7	
Eastern Europe/Middle East	9.7	11.7	
Japan/Australia	5.5	18.8	
Comorbidities			
Diabetes mellitus	44.6	39.7	0.0002
Hypercholesterolaemia	94.3	15.6	<0.0001
Hypertension	83.8	73.7	<0.0001
Obesity (BMI $\geq$ 30 kg/m^2)	24.8	16.7	<0.0001
Current smoker	53.3	47.7	<0.0001
Heart failure	17.3	12.0	<0.0001
Atrial fibrillation	10.2	10.6	0.65
Extent of vascular disease			
Coronary artery disease	58.2	32.7	<0.0001
Cerebrovascular disease	23.1	21.3	0.11
Polyvascular disease	67.6	44.2	<0.0001
PAD event within past year	38.1	46.1	<0.0001
Baseline ABI value	0.72 (0.18)	0.70 (0.19)	0.01
Qualifying PAD diagnosis			
ABI < 0.9	89.4	91.5	0.0089
Prior revascularization	54.0	50.4	0.0076
Prior amputation	13.2	14.3	0.23
Enrolling investigator speciality/subspeciality			
Primary care/family practice	72.2	53.1	<0.0001
Cardiology	8.9	3.9	<0.0001
Angiologist	3.6	8.1	<0.0001
Vascular surgeon	8.9	24.9	<0.0001
Other	6.5	10.0	<0.0001
Laboratory values			
Serum creatinine (mg/dL)	1.1 (0.8)	1.1 (0.7)	0.74
Fasting blood glucose (mg/dL)	121.9 (45.6)	119.2 (48.5)	0.83
Fasting total cholesterol (mg/dL)	197.5 (57.2)	202.0 (44.9)	0.0042
Fasting triglycerides (mg/dL)	172.7 (102.3)	152.4 (96.1)	<0.0001
Medication history			
Aspirin	66.3	51.2	<0.0001
ACE inhibitor	49.5	33.9	<0.0001
ARB	21.6	18.0	0.0009
β-Blocker	45.3	26.2	<0.0001
Diuretic	47.2	33.8	<0.0001
Calcium-channel blocker	38.3	35.3	0.022
Nitrate/other antianginal medication	26.7	17.0	<0.0001
Other antihypertensive	10.1	8.4	0.029
NSAIDs	10.9	7.6	<0.0001

Numbers represent mean (standard deviation) for continuous variables, and % for binary or categorical variables. *P*-values were obtained with Student's *t*-test for continuous variables, and χ^2 test for categorical variables.
ABI, ankle brachial index; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; NSAID, non-steroidal anti-inflammatory drug.

Table 2 Adjusted multivariate hazard ratios for 4-year systemic and adverse limb outcomes in patients who were on statins vs. those who were not on statins

Endpoint	Multivariate adjusted model for statin non-use at baseline ($n = 5861$), HR (95% CI); *P*-value	Multivariate adjusted model for time-varying statin use ($n = 5006$), HR (95% CI); *P*-value	IPTW weighted[a] multivariate adjusted model ($n = 5642$), HR (95% CI); *P*-value
Adverse limb outcomes			
Worsening PAD[b]	0.82 (0.72–0.92); $P = 0.0013$	0.85 (0.75–0.97); $P = 0.018$	0.79 (0.71–0.89); $P < 0.0001$
Worsening claudication or new CLI	0.82 (0.70–0.95); $P = 0.0087$	0.84 (0.72–0.99); $P = 0.037$	0.78 (0.68–0.90); $P = 0.0005$
New revascularization procedure	0.83 (0.72–0.95); $P = 0.0079$	0.90 (0.77–1.04); $P = 0.14$	0.79 (0.69–0.90); $P = 0.0003$
New amputation	0.64 (0.48–0.86); $P = 0.0027$	0.60 (0.44–0.82); $P = 0.0014$	0.57 (0.43–0.74); $P < 0.0001$
Systemic outcomes			
CV death/MI/stroke	0.83 (0.73–0.96); $P = 0.01$	0.79 (0.67–0.93); $P = 0.0038$	0.85 (0.75–0.96); $P = 0.0071$
All-cause mortality	0.83 (0.72–0.96); $P = 0.014$	0.79 (0.65–0.94); $P = 0.0098$	0.96 (0.84–1.09); $P = 0.50$
CV mortality	0.84 (0.70–1.00); $P = 0.05$	0.78 (0.61–0.98); $P = 0.034$	0.90 (0.77–1.06); $P = 0.21$
Non-fatal MI	0.85 (0.63–1.14); $P = 0.28$	0.80 (0.58–1.11); $P = 0.18$	0.67 (0.52–0.87); $P = 0.002$
Non-fatal stroke	0.74 (0.57–0.95); $P = 0.016$	0.75 (0.57–0.97); $P = 0.029$	0.73 (0.59–0.92); $P = 0.006$

CI, confidence intervals; CLI, critical limb ischaemia; CV, cardiovascular; HR, hazard ratio; IPTW, inverse probability of treatment weights; MI, myocardial infarction; PAD, peripheral artery disease.
[a]For propensity analysis.
[b]Worsening claudication/new development of critical limb ischaemia, new percutaneous or surgical intervention, or amputation.

is one of the largest cohort studies in stable outpatients with PAD, and one of the first to demonstrate an association between statin use and limb prognosis. Given the high morbidity and mortality associated with limb procedures, especially amputations,[27] our findings are thus of potential public health importance. Also, consistent with data from randomized controlled trials such as HPS,[8] our study indicates an ~20% lower rate of systemic cardiovascular events associated with statin use.

The benefit of statin therapy on adverse limb outcomes is not clearly defined.[1,28] Mohler *et al.*[29] randomized 354 patients with intermittent claudication to atorvastatin or placebo, and noted improvements in pain-free walking distance at 12 months. Similar functional improvements have been reported in other single-centre observational studies.[30–32] In a retrospective review of 1357 patients undergoing lower extremity revascularization procedures, Ardati *et al.*[10] reported that non-usage of both statin and aspirin was associated with a 55% lower rate in the need for further interventions including ischaemic amputations at 6 months, although the individual contribution of statin non-use was not reported. In the HPS subanalysis, simvastatin use was associated with a 20% lower rate in the need for non-coronary revascularization procedures, including carotid procedures. No differences were noted in rates of amputation.[8] Thus, in addition to being one of the first study to report on the association between statin use and adverse limb outcomes, our study extends the statin–PAD association in several important ways. Given the large sample size, we report an associated lower rate not only in the composite adverse limb outcome of worsening symptoms or development of critical limb ischaemia, need for lower extremity revascularizations, and ischaemic amputations, but also in each of these outcomes individually. While worsening claudication and need for revascularization procedures can sometimes be subjective (i.e. patient and provider-dependent), the requirement of an ischaemic amputation is a fairly objective outcome. We also report that the beneficial associations of statins on limb outcomes are apparent in patients across the full spectrum of symptomatic PAD: from patients with intermittent claudication alone to those who had undergone lower extremity revascularizations to those with prior amputations.

Another interesting observation in our registry is differences in statin use based on enrolling physician subspeciality. Patients were most likely to be on statins if enrolled by a cardiologist, and least likely if enrolled by a vascular surgeon. This discrepancy was most marked in patients without established CAD. Although differences in the utilization of evidence-based therapies between cardiologists and internal medicine or general practice physicians have been documented for patients with CAD,[33,34] there are very few studies investigating the role of the physician subspeciality and secondary prevention in patients with PAD.[35] Although physician awareness is likely part of the problem,[2] further research is urgently needed to explore reasons for differences in secondary prevention medication use based on physician subspeciality.

One might wonder whether a unique form of unmeasured confounding known as 'healthy user effect' could be operational here—the lower risk of adverse outcomes associated with statin use may be a surrogate marker for overall healthy behaviour such as healthy eating and regular exercise. However, this is unlikely for the following reasons. Patients in the current study who were on statins had more comorbidities and a higher severity of illness than

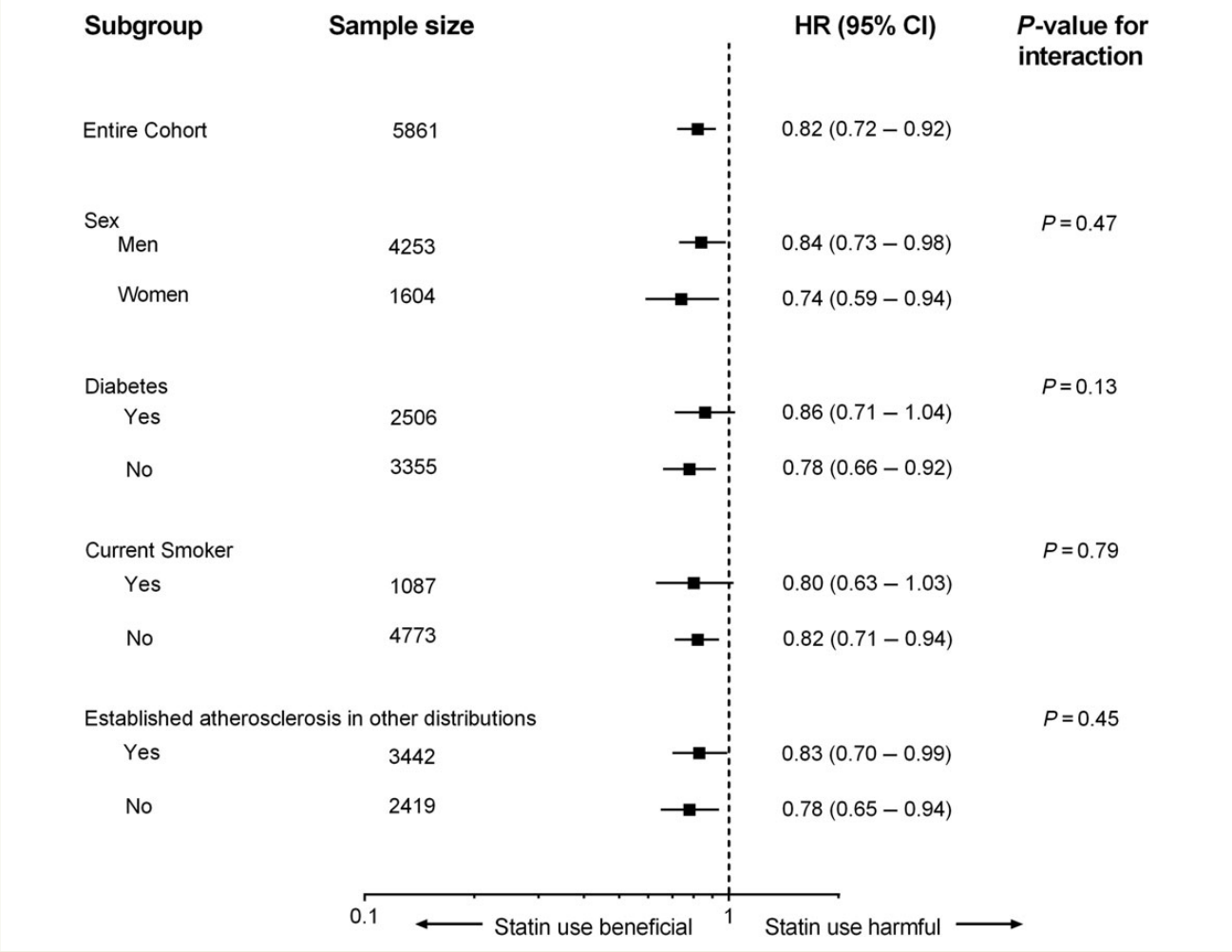

Figure 4 Subgroup analysis of the effect of statin use on the composite adverse limb outcome at 4 years. CI, confidence intervals; HR, hazard ratio.

statin non-users, arguing against a healthy user effect in the current analysis. If anything, these differences would bias the results towards the null, and the beneficial association with statin use may be even larger. Secondly, we did not observe a significant difference in non-cardiovascular mortality between statin users and non-users in the current study. Finally, the impact of a 'healthy user' effect in similar settings itself has been recently disputed.[36]

Other limitations of the REACH data are those inherent to registries such as selection bias and the presence of unmeasured confounders.[37] The two groups of patients were also fairly dissimilar. We attempted to mitigate this problem using advanced statistical methods to the extent possible. Results were fairly concordant between the three different methodologies, including on the propensity analysis. Medication use was assessed by patient self-report using detailed questionnaires/case report forms without external validation. Although other measures such as pharmacy prescription refills and electronic medication monitors can be more accurate, patient self-report has been shown to be the most useful method in the clinical setting;[38] the use of questionnaires also has good correlation with various electronic measures.[39] Information regarding dose, potency of statin used, and side effects and contraindications to their use was also not available. Finally, this analysis is unable to separate statin non-usage due to physician non-prescription from patient non-adherence. The former is a more surmountable problem and may be alleviated by systems-based interventions, as have been instituted for acute myocardial infarction and heart failure.[40]

Conclusion

Our analysis of a large international cohort of patients with established PAD indicates that the use of statins remains suboptimal, especially in patients without coexisting CAD. Patients who were taking statins had a significantly lower risk of adverse limb and systemic cardiovascular outcomes at 4 years. It is imperative to identify barriers to patient and physician compliance with statin use across the entire spectrum of PAD patients. In addition, future research should focus on identifying a possible dose–response relationship between statin use and limb outcomes, and also whether different LDL cholesterol targets may be necessary to prevent progressive PAD vs. progressive cardiovascular outcomes in these patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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CARDIOVASCULAR FLASHLIGHT

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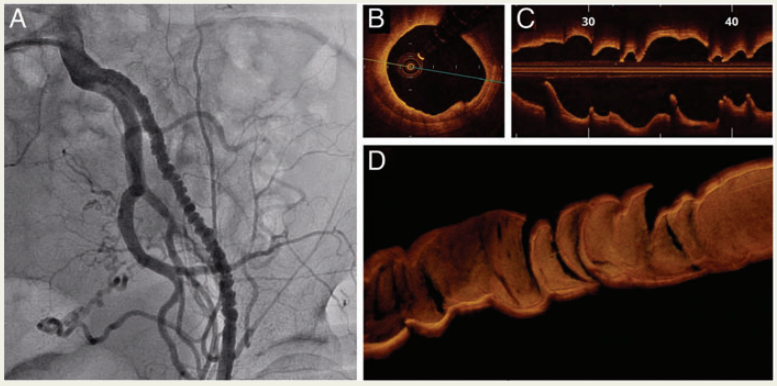
Optical coherence tomography images of iliac artery fibromuscular dysplasia

Akiko Tanaka*, Kenji Suzuki, Naoto Inoue, and Taiichiro Meguro

Cardiovascular Center, Sendai Kousei Hospital, 4-15 Hirosemachi, Aoba-ku, Sendai, Miyagi 980-0873, Japan

* Corresponding author. Tel: +81 222226181, Fax: +81 222670856, Email: akihende@yahoo.co.jp



A 47-year-old woman with a history of hypertension and cerebral infarction presented with intermittent claudication. No pulse was palpable in the bi-lateral dorsalis pedis, and peripheral arterial disease was suspected. The ankle-brachial index was 0.83 in the right leg and 0.76 in the left. Duplex sonography revealed severe stenosis in the bilateral external iliac artery (EIA) and renal artery. The EIA had the characteristic 'string of beads' appearance in angiography (*Panel A*), which was diagnosed as fibromuscular dysplasia (FMD). Endovascular therapy was performed for the EIA. There was a 30 mmHg pressure gradient in the FMD lesion. Optical coherence tomography (OCT) images revealed shrinkage of the media and mild thickness in the intima (*Panels B* and *C*), while three-dimensional OCT images showed a 'haustra coli'-like appearance (*Panel D*). After balloon angioplasty, the vessel was well dilated and claudication disappeared.