HHS Public Access

Author manuscript

Am J Cardiol. Author manuscript; available in PMC 2015 November 12.

Published in final edited form as:

Am J Cardiol. 2010 May 1; 105(9): 1348–1352. doi:10.1016/j.amjcard.2009.12.054.

Comparison of Effects of Statin Use on Mortality in Patients With Peripheral Arterial Disease With Versus Without Elevated C-Reactive Protein and D-Dimer Levels

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Abstract

We determined whether statin use was associated with lower all-cause and cardiovascular disease (CVD) mortality in 579 participants with lower extremity peripheral arterial disease (PAD) according to the presence and absence of elevated C-reactive protein (CRP) and D-dimer levels. Statin use was determined at baseline and at each annual visit. The CRP and D-dimer levels were measured at baseline. The mean follow-up was 3.7 years. The analyses were adjusted for age, gender, race, co-morbidities, ankle brachial index, cholesterol, and other confounders. Of the 579 participants, 242 (42%) were taking a statin at baseline and 129 (22%) died during follow-up. Statin use was associated with lower all-cause mortality (hazard ratio 0.51, 95% confidence interval [CI] 0.30 to 0.86, p = 0.012) and CVD mortality (hazard ratio 0.36, 95% CI 0.14 to 0.89, p = 0.027) compared to statin nonuse. No statistically significant interaction was found for the baseline CRP or D-dimer level with the association of statin use and mortality. However, statin therapy was associated with significantly lower all-cause and total mortality only among participants with baseline CRP values greater than the median and not among those with CRP values less than the median (hazard ratio 0.44, 95% CI 0.23 to 0.88 vs hazard ratio 0.73, 95% CI 0.31 to 1.75 for all-cause mortality and hazard ratio 0.20, 95% CI 0.063 to 0.65 vs hazard ratio 0.59, 95% CI 0.093 to 3.79 for CVD mortality). In conclusion, among those with PAD, statin use was associated with lower all-cause and CVD mortality compared to no statin use. The favorable association of statin use with mortality was not influenced significantly by the baseline CRP or D-dimer level.

We studied the associations between statin use and all-cause and cardiovascular disease (CVD) mortality among patients with peripheral arterial disease (PAD) with high versus low levels of C-reactive protein (CRP) and D-dimer. Men and women with PAD have increased levels of circulating inflammatory biomarkers and D-dimer compared to those without

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Dr. Ridker is listed as a co-inventor on patents held by Brigham and Women's Hospital (Boston, Massachusetts) that relate to the use of inflammatory biomarkers in cardiovascular disease.

PAD.[1,2] Thus, patients with PAD are a potentially ideal cohort in which to study the associations between biomarker levels, statin therapy, and mortality. We hypothesized that favorable associations of statin use with mortality would be stronger in those with PAD and high levels of CRP and D-dimer than among those with low levels of CRP and D-dimer.

Methods

The present study was an observational, prospective study of participants with PAD in the Walking and Leg Circulation Study (WALCS) and WALCS II cohort studies.[3,4] The WALCS cohort was assembled from October 1998 to March 2000. The WALCS II cohort was assembled from November 2002 to April 2004. The data from ≤6 years of follow-up for the WALCS cohort and ≤2 years of follow-up for the WALCS II cohort were used in the present report. The institutional review boards of Northwestern University Feinberg School of Medicine and Catholic Health Partners Hospitals (Chicago, Illinois) approved the protocol. All participants gave written informed consent.

In WALCS and WALCS II, the participants with PAD were identified consecutively from among patients diagnosed with PAD in 3 Chicago-area noninvasive vascular laboratories. A small number of participants were identified from among consecutive patients in a large general internal medicine practice who were screened using the ankle brachial index (ABI) and found to have an ABI <0.90. The participants were age ≥55 years at baseline.

We defined PAD as an ABI of <0.90.[5] Exclusion criteria have been reported and are summarized here.[3,4] Patients with dementia were excluded because of their inability to answer questions accurately. Nursing home residents, wheel-chair-bound patients, patients with foot or leg amputations, and patients with recent major surgery were excluded, because they have uniquely impaired functioning, and because WALCS and WALCS II were designed to study the natural history of lower extremity functioning over time. Non-English–speaking patients were excluded, because investigators were not fluent in non-English languages.

After the participants had rested supine for 5 minutes, we used a hand-held Doppler probe (Nicolet Vascular Pocket Dop II, Golden, Colorado) to measure the systolic pressures in the right brachial, dorsalis pedis, and posterior tibial arteries and left dorsalis pedis, posterior tibial, and brachial arteries. Each pressure was measured twice.[3] We calculated the ABI in each leg by dividing the average pressures in each leg by the average of the 4 brachial pressures.[6] We used the average brachial pressures in the arm with the greatest pressure when one brachial pressure was greater than the opposite brachial pressure in both measurement sets, and the 2 brachial pressures differed by ≥ 10 mm Hg in at least one measurement set.[7] In these cases, subclavian stenosis was possible.[8] The lowest leg ABI was used in analyses.

We used algorithms developed for the Women's Health and Aging Study to document baseline co-morbidities.[9] These algorithms combine data from patient report, physical examination, medical record review, medications, relevant laboratory values, and a primary care physician questionnaire. Baseline co-morbidities were stroke, myocardial infarction,

angina, heart failure, diabetes, history of hypertension, pulmonary disease, and cancer. The history of hypertension was derived from self-report and physician questionnaires.

The principal study investigator (MMM) reviewed the lists of medication for each study visit, unaware of all other patient data and identified the presence versus absence of statin use for each participant.

The blood was collected into ethylenediamine-tetra-acetic acid and sodium citrate vacutainer tubes and immediately iced. The tubes were spun at 3,000 revolutions per minute for 20 minutes at 4°C in a refrigerated centrifuge. The blood was stored at −70°C until analyses were completed ≤3 years after blood collection.

We measured the CRP using an immunotechnique on the Behring, BN II analyzer (Dade Behring, Wilmington, Delaware. This method can detect CRP concentrations as low as 0.15 mg/L.[10] The coefficient of variability was 4.26% for CRP. We used an Asserachrom D-Di kit (Diagnostica Stago, Asnières-sur-Seine, France) to measure D-dimer using an enzyme-linked immunosorbent assay procedure. The coefficient of variability was 9.4%.

The total cholesterol was measured using enzymatic reaction with peroxidase/phenol-4-aminoiphenazone indicator reaction.[11] High-density lipoprotein cholesterol was measured with direct enzymatic colorimetric assay.[12]

We determined cigarette smoking history by patient report using a structured interview. The pack-years of smoking were calculated according to the number of years smoked and the average number of packs daily. The physical activity was measured using patient-reported number of blocks walked during the past week. Height and weight were measured at the baseline study visit. Body mass index was calculated as kilograms per meter squared.

The deaths were ascertained from the Social Security Death index. The survival status for all participants was available. The death certificates were obtained from the state of Illinois or medical records. The cause of death was determined by a certified nosologist. Cardiovascular deaths were those with International Classification of Disease, version 10, codes ranging from I01.0 to I99.9, including deaths from coronary heart disease, stroke, peripheral vascular disease, and other CVD. Decedents without certificates were excluded from the CVD mortality analyses but not the all-cause mortality analyses.

We compared the baseline characteristics between the statin users and nonusers with PAD using general linear models for continuous variables and chi-square tests for categorical variables. The time-dependent Cox regression analyses were used to evaluate the associations of statin use and mortality. The time-dependent analyses allowed us to incorporate the onset of statin therapy during follow-up in our analyses. To determine whether baseline CRP value or D-dimer modified associations of statin use and mortality, analyses were repeated separately in participants with baseline CRP or D-dimer values greater than versus less than the median. We tested for the presence of an interaction between high versus low CRP levels and statin use in the association of statin use and mortality. Similar analyses were performed for high versus low D-dimer levels. The analyses were adjusted for age, gender, race, ABI, BMI, pack-years of smoking, stroke,

myocardial infarction, angina, heart failure, diabetes, hypertension, pulmonary disease, cancer, total cholesterol, high-density lipoprotein, blocks walked in the past week, and WALCS I versus WALCS II cohort. We analyzed data, and the funding agency played no role in analyses.

Results

Of the 679 participants with PAD from WALCS and WALCS II, 579 (85%) had blood drawn at baseline and were included in these analyses. The mean age was 73 ± 8.5 years, the mean ABI was 0.65 ± 0.15, and 58% were men. Four participants had blood analyzed only for D-dimer, and 10 had blood analyzed only for CRP. The median baseline CRP and D-dimer values were 2.6 mg/L and 0.65 μg/ml, respectively. Of the 287 participants with a baseline CRP value greater than the median (ie, CRP >2.6 mg/L), 155 (54%) also had an elevated D-dimer level greater than the median (ie, D-dimer >0.65 μg/ml). During a mean follow-up of 3.7 years, 129 participants (22%) died; 43 deaths (33%) were from CVD. Death certificates were located for 77% of the decedents.

Of the 679 participants with PAD, 242 (42%) included in the present analyses were taking a statin at baseline. Table 1 lists the baseline characteristics of statin users versus nonusers. Statin users included a greater prevalence of whites and a greater prevalence of cardiac or cerebrovascular disease compared to nonusers. Statin users had greater BMI values, lower total cholesterol, and lower CRP levels.

Compared to statin nonusers, statin users had lower all-cause mortality (hazard ratio 0.51, 95% confidence 0.30 to 0.86, p = 0.012) and CVD mortality (hazard ratio 0.36, 95% confidence interval 0.14 to 0.89, p = 0.027), adjusting for age, gender, race, ABI, BMI, cigarette smoking, stroke, myocardial infarction, angina, heart failure, diabetes, hypertension, pulmonary disease, cancer, total cholesterol, high-density lipoprotein, physical activity, and WALCS I versus WALCS II cohort.

Table 2 lists the associations of statin use with all-cause and CVD mortality, according to the baseline CRP levels. In participants with baseline CRP levels greater than the median (CRP >2.6 mg/L), statin use was associated with a significantly lower risk of all-cause mortality and CVD mortality compared to statin nonuse, adjusting for known and potential confounders (Table 2). For participants with low baseline CRP levels, no significant associations were found of statin use with lower all-cause or CVD mortality (Table 2). No significant interactions were found between the high versus low CRP level and statin use in the association of statin use with all-cause mortality (p for interaction term = 0.67) or CVD mortality (p for interaction term = 0.39).

In participants with baseline D-dimer greater than the median, the statin use was associated with significantly lower all-cause mortality and CVD mortality compared to statin nonuse, adjusting for known and potential confounders (Table 3). For participants with low baseline D-dimer levels, the hazard ratios for the association of statin use with all-cause mortality and CVD mortality were similar to participants with high baseline D-dimer levels, but statin use was not associated with a statistically significant survival benefit compared to statin nonuse

(Table 3). No significant interactions were found between D-dimer levels and statin use in the association of statin use with all-cause mortality (p for interaction term = 0.60) or CVD mortality (p for interaction term = 0.61).

Discussion

Of the 579 participants with PAD, the data we have reported have shown that statin users had significantly lower all-cause and CVD mortality compared to statin nonusers during a mean follow-up of 3.7 years. In analyses stratifying participants according to the median baseline levels of CRP and D-dimer, respectively, statistically significant protective associations of statin use with all-cause and CVD mortality were observed among participants with CRP and D-dimer levels greater than the baseline median values. No significant associations were found for statin use with all-cause or CVD mortality among participants with CRP and D-dimer levels less than the baseline median values. However, no statistically significant interaction was found between the high versus low CRP or D-dimer levels and statin use in the analyses of statin use with mortality. These latter findings have demonstrated that among the 579 participants with PAD, participants with baseline CRP or D-dimer values greater than the median did not have significantly greater benefit from statin use than those with baseline CRP or D-dimer values less than the median. These findings are consistent with results of the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, in which rosuvastatin therapy significantly reduced cardiovascular events among men and women with relatively low cholesterol who had elevated CRP levels.[13] However, the present study is an observational study of participants with PAD, and JUPITER was a randomized controlled clinical trial studying participants who did not have PAD.

It is important to note that baseline CRP levels were likely influenced by statin therapy at baseline. Many participants with high CRP and D-dimer levels at baseline were taking statin therapy. These participants had high biomarker levels despite statin therapy. However, as a group these participants had lower all-cause and CVD mortality than those with high CRP or D-dimer levels who were not taking statin therapy.

To our knowledge, no previous reports have described the associations of statin use with mortality among participants with PAD with high versus low levels of D-dimer. A previous study has demonstrated that elevated D-dimer levels are associated with greater all-cause and CVD mortality among participants with PAD.[14] D-dimer is the primary degradation product of cross-linked fibrin and indicates ongoing fibrinolysis associated with thrombosis.[15,16] Greater D-dimer levels might reflect greater atherosclerotic plaque remodeling or atherosclerotic disease burden. Statins improve atherosclerotic plaque stability and restore endothelial function.[17–19] Thus, statins could potentially be more beneficial in patients with PAD with elevated D-dimer levels, if greater levels of D-dimer denote greater atherosclerotic disease activity that is inhibited by statin therapy. Our results demonstrating no significant interaction of D-dimer level and statin use in the association of statin use with mortality among participants with PAD might reflect that even PAD participants with lower D-dimer levels had a large atherosclerotic disease burden.

Inflammation is an integral component of atherosclerosis and influences atherosclerotic disease progression at both early and late stages.[20] Conceivably, statins could have a more favorable association with mortality among participants with PAD and elevated CRP levels, if statins reduce mortality rates by reducing systemic inflammation, because in this case, participants with PAD with greater levels of inflammation might derive greater benefit from statin therapy. Consistent with this hypothesis, our findings suggested that the relative statin benefit was somewhat greater in persons with CRP levels greater than the median compared to those with CRP levels less than the median at baseline. However, the difference in the relative benefit of statin therapy for participants with PAD with high versus low CRP values was not statistically significant. Again, a lack of sufficient statistical power might have influenced our findings.

In contrast to our findings, Schillinger et al[21] demonstrated a significant interaction between high versus low CRP levels in the association of statin use with mortality among 515 participants with PAD. There are several potential explanations for differences in our findings from those of Schillinger et al.[21] First, the characteristics of the PAD population studied by Schillinger et al[21] differed from those in the WALCS II cohort. Schillinger et al[22] studied patients (median age 70 years, 57% men) with more severe PAD (median ABI 0.51) who had undergone lower extremity revascularization procedures. Previous studies have shown that the levels of CRP increase significantly after lower extremity revascularization procedures.[22] Thus, patients with PAD undergoing lower extremity revascularization might derive greater benefit from statin therapy because of the increases in CRP levels associated with lower extremity revascularization. The median CRP level in the PAD population studied by Schillinger et al[22] was 4.2 mg/L, which is greater than the median CRP level in the present study.

Our study had limitations. First, the study was observational. Unmeasured differences in the characteristics between the statin users and statin nonusers might have accounted for differences in mortality between them. Second, the changes in the biomarker levels over time were not incorporated into the analyses. Third, we did not have data on the statin dose or duration of therapy. Fourth, the sample size limited our statistical power to identify significant interactions. Our results differed from other studies of PAD in that CVD accounted for <50% of the deaths. It is possible that improved treatment of atherosclerotic risk factors in patients with PAD reduced the incidence of cardiovascular death. Additional study is needed to further evaluate the associations we have reported.

Acknowledgments

This study was supported by grants R01-HL58099, R01-HL64739, R01-HL071223, and R01-HL076298 from the National Heart and Lung and Blood Institute (Bethesda, Maryland) and by grant RR-00048 from the National Center for Research Resources, National Institutes of Health (Bethesda, Maryland). This study was also supported in part by the Intramural Research Program, National Institute on Aging, National Institutes of Health (Bethesda, Maryland).

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Table 1
Participant characteristics stratified by statin use at baseline

Variable	Statin Use		p Value*
	No (n = 337)	Yes (n = 242)	
Age (years)	73.0 ± 8.9	72.1 ± 7.9	0.21
Men	56.3%	59.5%	0.44
Black race	18.1%	12.0%	0.045
Ankle brachial index	0.64 ± 0.15	0.65 ± 0.15	0.91
Body mass index (kg/m^2)	27.2 ± 5.3	28.2 ± 4.8	0.02
Cigarette smoking (pack years)	37.0 ± 36.7	37.6 ± 34.5	0.86
Total cholesterol (mg/dl)	185.3 ± 40.4	169.8 ± 35.7	<0.001
High-density lipoprotein cholesterol (mg/dl)	45.3 ± 19.1	43.6 ± 15.4	0.27
Blocks walked during past week	36.9 ± 69.1	29.9 ± 52.7	0.18
Diabetes mellitus	34.1%	31.4%	0.49
Pulmonary disease	38.0%	34.7%	0.42
Cancer	17.8%	18.6%	0.81
Hypertension (by history)	88.0%	91.2%	0.23
Cardiac or cerebrovascular disease†	47.8%	64.0%	<0.001
Baseline C-reactive protein level (mg/L)	6.1 ± 10.5	3.8 ± 4.0	0.002
Baseline D-dimer level‡ (μg/ml)	1.1 ± 1.4	0.97 ± 1.4	0.50

Data are presented as mean ± SD or %, unless otherwise noted.

*Derived from comparisons between statin users and statin nonusers.

†Cardiac or cerebrovascular disease was defined as ≥ 1 of the following: history of myocardial infarction, heart failure, angina, and stroke.

‡Data are presented as mean ± SD.

Table 2

Adjusted associations between time-dependent statin use and mortality stratified by baseline C-reactive protein (CRP) level*

CRP (mg/L)	All-Cause Mortality				Cardiovascular Mortality			
	Participants	Death	HR (95% CI)	p Value	Participants	Death	HR (95% CI)	p Value
<2.6								
Statin nonuser	160	32	1.0 (Referent)	NA	160	8	1.0 (Referent)	NA
Statin user	128	21	0.73 (0.31–1.75)	0.48	128	4	0.59 (0.093–3.79)	0.58
>2.6								
Statin nonuser	175	50	1.0 (Referent)	NA	175	21	1.0 (Referent)	NA
Statin user	112	26	0.44 (0.23–0.88)	0.019	112	10	0.20 (0.063–0.65)	0.0075

*Adjusted for age, gender, race, ankle brachial index, body mass index, pack-years of cigarette smoking, stroke, myocardial infarction, angina, heart failure, diabetes mellitus, history of hypertension, pulmonary disease, cancer, total cholesterol, high-density lipoprotein cholesterol, blocks walked in past week, and WALCS I versus WALCS II cohort.

Table 3

Adjusted associations between time-dependent statin use and mortality stratified by baseline D-dimer level*

D-Dimer (μg/ml)	All-Cause Mortality				Cardiovascular Mortality			
	Participants	Deaths	HR (95% CI)	p Value	Participants	Deaths	HR (95% CI)	p Value
<0.65								
Statin nonuser	163	33	1.0 (referent)	NA	163	9	1.0 (referent)	NA
Statin user	119	21	0.45 (0.17–1.18)	0.10	119	5	0.26 (0.04–1.64)	0.15
>0.65								
Statin nonuser	167	48	1.0 (referent)	NA	167	19	1.0 (referent)	NA
Statin user	120	25	0.49 (0.25–0.95)	0.034	120	9	0.26 (0.09–0.79)	0.018

*Adjusted for age, gender, race, ankle brachial index, body mass index, pack-years of cigarette smoking, stroke, myocardial infarction, angina, heart failure, diabetes mellitus, history of hypertension, pulmonary disease, cancer, total cholesterol, high-density lipoprotein cholesterol, blocks walked in past week, and WALCS I versus WALCS II cohort.