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Statin Therapy Reduces Growth of Abdominal Aortic Aneurysms

Wassef Karrowni, M.D.[1], **Saadeddine Dughman, M.D.**[1], **Georges P Hajj, M.D.**[1], and **Francis J. Miller Jr., M.D.**[1,2]

[1] Department of Internal Medicine, The University of Iowa, Iowa City, IA 52242

[2] Department of Medicine, Veterans Affair Medical Center, Iowa City, IA 52242

Abstract

Background—The aim of this study was to evaluate the influence of statins on the growth of small abdominal aortic aneurysms (AAA).

Methods—We retrospectively examined AAA diameter in two hundred and eleven patients who had undergone serial imaging surveillance.

Results—Patients treated with and without statins were similar in regards to the age, initial aneurysm size, diabetes, hypertension, and smoking. Those patients receiving statins had a decreased aneurysm growth rate as compared to those patients not receiving statins (0.9 mm/year (IQR: -1.0 - +1.0) vs 3.2 mm/year (IQR 2.0-4.9, p<0.0001). This difference in the rate of growth was maintained after adjusting for potential confounding factors.

Conclusions—This is the one of the largest retrospective studies to date demonstrating an association between statin use and decreased growth rate of AAA.

Keywords

statins; atherosclerosis; aneurysm

Introduction

Abdominal aortic aneurysm (AAA) is common with a prevalence of 4% to 9% in men and 1% in women in population-based screening studies from various countries [1-4]. Patients with AAA have a high mortality, primarily due to rupture and AAA is among the top fifteen leading causes of death in the United States [5]. The U.S. Preventive Services Task Force recommends one-time screening for AAA by ultrasonography in men age 65 to 75 years who have ever smoked.

Surgical or endovascular repair is recommended for those AAAs ≥ 5.5 cm in diameter because of increased risk of catastrophic rupture. In contrast, small AAAs (<5.5 cm), have a

Corresponding author: Francis J. Miller, Jr Department of Internal Medicine 285 Newton Road, Room 2269 CBRB Iowa City, IA 52242 francis-miller@uiowa.edu Voice: 319-354-4524 Fax: 319-353-5552.

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low risk of rupture, and there is currently no validated treatment strategy to limit progression. During routine abdominal screening of asymptomatic patients, 90% of AAAs identified are <5.5 cm in diameter [6]. Two large randomized trials reported that survival was not improved by elective surgical repair of small AAAs [7]. Therefore, the development of non-invasive therapeutic approaches to slow the rate of AAA growth is of significant clinical relevance.

Statins, 3-hydrox-3-ymethylglutaryl-coenzyme A reductase inhibitors, are widely prescribed for their lipid-lowering effects. There are conflicting studies reporting an association between AAA risk and hypercholesterolemia, with most, but not all, indicating an association between AAA and increased serum level of cholesterol [8-12]. Reducing cholesterol concentrations in patients is therefore desirable, but there is no clear relationship between serum cholesterol level and AAA growth [13,14]. However, recent advances have led to a better understanding of the molecular mechanisms involved of AAA formation and many of the pleiotropic effects of statins, including anti-inflammatory, anti-oxidative, and the reduction of matrix metalloproteinases (MMP) secretion, may prevent the progression of AAA.

To date, there have been no randomized controlled studies in patients to assess the efficacy of statins in reducing the growth of AAA. Numerous studies have showed association of coronary heart disease and peripheral atherosclerosis with AAA [12,15]. It is unknown whether this association between AAA and atherosclerosis is causal or due to common risk factors [16]. However, it is currently advised by American Heart Association guidelines that AAA be considered an atherosclerotic equivalent [17]. This makes conducting a randomized controlled study with and without statin therapy unethical. Current human studies are limited to small observational studies and are inconclusive. Herein we report the results of one of the largest retrospective studies evaluating the effect of statins on abdominal aortic aneurysm growth.

Materials and Methods

We retrospectively identified patients under surveillance for AAA at University of Iowa Hospitals and Clinics between January 2001 and January 2005. The study was approved by the University of Iowa Institutional Review Board. Patient data was collected from electronic medical records and all patients with a diagnosis of AAA were screened for eligibility of enrollment. We included only those patients with an AAA of at least 3 cm and who had undergone repeat imaging follow-up of at least one year. Two hundred and eleven patients were included in this study and their clinical data are summarized in Table 1. Statin users were identified as patients who were on any statin therapy at the initial imaging study. Non-statin users were identified as patients not on any statin during the entire study period. A medication history was obtained at each visit associated with AAA imaging. Patients who were found at follow-up to have had a change in statin therapy (initiation or discontinuation) as compared to the initial imaging study of AAA were excluded from analysis. The imaging modalities used included ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). Ultrasound was the imaging modality of choice in 40% of the patients, CT in 37% and MRI in 23%. Ninety percent of patients had two imaging examinations completed, 7% had three examinations, and 3% had four examinations. The AAA diameter was defined by the maximum diameter.

Linear aneurysm growth rate (change in aneurysm size from initial imaging to follow-up/ years of follow-up) was initially compared between patients who were on statin therapy and patients who did not use statins using Wilcoxon rank-sum test. The demographic and clinical variables of these two groups of patients were also compared using Pearson chi-

square test for the categorical variables, and two-sample t-test or Wilcoxon rank-sum test for the continuous variables. Since there are other factors that may be associated with change in aneurysm size, the effect of statin use on change in aneurysm size was also tested adjusting for the effect of other covariates in a multi-variable linear regression model. In addition to statin use, the other independent variables included in this model were the demographic and clinical variables with p-value<0.10 from tests comparing between the statin and non-statin groups, and tests of association with change in aneurysm size.

For linear regression analysis, the dependent variable was assumed to have a normal distribution. However, test of normality of change in aneurysm size showed that the data distribution was not normally distributed. As an alternative, the change in the natural log (ln) of aneurysm size was used in the regression analysis. By using the difference in ln(aneurysm size), the analysis was based on the relative change in aneurysm size. The estimated mean change in ln(aneurysm size) from the fitted regression model, after back transformation, is expressed as the percentage change from initial aneurysm size. Also, to account for the possibility that follow-up differed among the subjects, ln(duration) was included as a covariate in the regression model.

Results

The study population included 136 patients in the statin and 75 patients in the non-statin group. The mean follow-up duration was 1 year for both groups. The prevalence of coronary artery disease, hypertension, diabetes, cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease (COPD) and tobacco use was similarly high in both groups. The diagnosis of hyperlipidemia (HLP) was 82% in the statin users and 71% in the non-statin users (p=0.052). The concomitant use of beta blockers, angiotensin converting enzyme inhibitors (ACEI), and aspirin was also higher in the statin group, whereas the use of calcium channel blockers (CCB) was greater in the non-statin patients (Table 2).

The size of the AAA on presentation was similar in both groups (4.1 cm, p=0.96). Patients treated with a statin had a decreased linear aneurysm growth rate with a median of 0.9 mm/year (interquartile range (IQR): -1.0 to +1.0 mm/year) as compared to 3.2 mm/year (IQR: 2.0 to 4.9 mm/year) for those not receiving statins (p<0.0001). After adjusting for observed differences in HLP, use of beta blockers, ACEI, CCB, and aspirin (Tables 1 and 2), the significant difference in the rate of aneurysm growth between statin and non-statin groups was maintained (p<0.0001). The estimated mean relative change in aneurysm size computed from the fitted regression model for the statin and non-statin groups and adjusted for the other covariates are shown in Table 3. Using the median initial aneurysm size of 4.1cm, this corresponds to a 1 year mean change in aneurysm size of -0.3mm (95% CI: -1.1 to 0.6 mm) for the statin group and 3.1 mm (95% CI: 2.2 to 3.9 mm) for the non-statin group. Subgroup analysis was performed for patients who had the same imaging modality throughout the study period (117 statin and 65 non-statin patients respectively). The median linear aneurysm growth rate was 0.9 mm/year (IQR: -1.0 to +1.0 mm/year) for the statin group compared to 2.9 mm/year (IQR: 1.9 to 4.4 mm/year) for those not receiving statins (p<0.0001).

Discussion

The pathogenesis of AAA formation is complex and not completely understood, partly explaining the absence of effective medical therapy. AAA formation is a product of the complex interaction between inflammation, vascular smooth muscle cell (VSMC) apoptosis, extracellular matrix (ECM) degradation, and remodeling [18]. Studies of human AAA tissue have shown extensive inflammatory infiltrates containing macrophages and lymphocytes in

both the media and adventitia [19]. Activated macrophages secrete various proteinases leading to imbalance between the synthesis and degradation of connective tissue proteins. Various extracellular proteinases participate in the process of the destruction of the human aortic wall, in particular, MMP-2 and MMP-9 have attracted interest in this process [20-23]. MMP activation directly contributes to AAA formation in murine models [24,25].

Reactive oxygen species (ROS) are increased in the aneurysm wall compared with the normal aorta and adjacent non-aneurysmal aortic wall [26]. The infiltrated inflammatory cells are the primary source of ROS production through the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase [26]. Excess ROS generation increases expression of MMPs and induces apoptosis of VSMC in the aneurysm wall [27-29]. Antioxidant therapy or the inhibition of NADPH oxidase activity reduced expression of MMPs and protected from AAA development in murine models [30-32].

Statins possess several pleiotropic effects that target the pathophysiologic mechanisms of AAA formation. They are expected to prevent AAA development through anti-inflammatory effects, anti-oxidative effects, inhibition of proteases, and upregulation of synthesis of extracellular matrix proteins [33]. Statins inhibit various inflammatory mediators and other key molecules, including MMPs produced by VSMCs and macrophages [34,35]. These effects are attributed in part to interference with protein isoprenylation, which plays a major role in inflammatory signaling pathways [36,37]. Simvastatin suppressed AAA progression in a mouse model, and was accompanied by a reduction of MMP-9 [38]. In an ex vivo human organ culture system, the application of cerivastatin reduced the tissue level of MMP-9 in a concentration-dependent manner, accompanied by the inhibition of the activation of infiltrated inflammatory cells [31]. Experimental studies have also shown that statins have multiple other beneficial effects including improvement of endothelial function through increase in endothelial nitric oxide synthase, suppression of medial VSMC apoptosis, and a reduction in recruitment of macrophages into the vascular wall [39,40].

The clinical evidence for the efficacy of statins for AAA is sparse. In a prospective study, 37 patients were randomized to a 3-week course of simvastatin versus placebo before open aneurysm repair [41]. The excised aneurysm tissue from the simvastatin group had decreased MMP-9 levels consistent with animal studies described above. A recent meta-analysis identified seven high quality clinical controlled studies that examined the effect of statin therapy on AAA expansion rate [42]. Of these, six were retrospective cohort and one was prospective cohort study, whereas only four contained more than 200 patients. There was significant reduction in AAA expansion in patients taking a statin in three of the studies [25,43,44]; however, no significant difference was found in AAA growth between patients taking statins and control patients in four of the studies [45-48]. Following meta-analysis of these seven studies (1006 patients taking statin; 3191 control patients) sensitivity analysis showed no difference in AAA expansion rate with statin therapy [17]. Because of the different methodologies employed in the estimation of AAA growth in the different studies, the validity of utilizing meta-analysis of these data is unclear and may introduce bias [49]. A separate recent meta-analysis reached the contrasting conclusion that statin therapy is associated with reduced AAA growth, but did not include some of the larger more recently published studies [50].

Our study shows an association between statin use and decreased growth rate of AAA. The mean growth rate for the non-statin group was 3.2 mm per year, which is consistent with the expected rate for small AAAs (2.6 to 3.2 mm per year) [51]. In contrast, the mean growth rate in the statin group was 0.9 mm per year. Known risk factors that affect the AAA growth rate, including age, gender, aneurysm diameter at first presentation, smoking, and diabetes, are similar in both groups. In addition, we did not find a relationship between

hyperlipidemia and the growth of AAA. The use of beta-blockers and ACEI were significantly higher in the statin group. There is evidence that the usage of these medications might slow the development of AAA [52-54]. In our study, neither of these classes of medication affected the growth rate of the AAA, however, this conclusion is limited by the possibility of a Type II error. On the other hand, our data does show an association of the use of CCB with a slower rate of aneurysm growth (Table 3). However, since the non-statin users had the greater use of CCB (Table 2) this variable did not contribute to our primary finding of the protective effect of statins on aneurysm growth. The potential protective effect of CCB is consistent with animal studies showing inhibition in progression of experimental AAA by CCB, in part through suppression of MMP activity [55,56], however, a protective of CCB has not been found in human AAA [57].

There are several methodological limitations of this study. The study was performed without a pre-study sample size calculation, and thus, may be underpowered. The compliance of patients with daily statin therapy throughout the study period is not known. It is important to note that the majority of the patients in our study had a single repeat imaging study approximately one year following the initial study, resulting in a mean follow up period of only a little over one year. This average follow up is short for a research study on aneurysm growth. The rate of AAA growth is likely to be more accurate in the 10% of patients havng more than two measurements of AAA size over a couple of years. In addition, the study includes patients who had different imaging modalities (ultrasound, CT, and MRI), which introduce potential errors by increasing the variability of the measurements. Inter- and intra-observer variability in the measurement of the AAA diameter is also a variable with the potential to influence the outcome. And finally, the growth of AAA within a patient does not occur at a linear rate. Instead, the change in aortic diameter is characterized by periods of rapid growth and quiescence. As a result, simple estimates of growth usually overestimate the rate of progression.

In conclusion, our study contributes to the limited human data available regarding the beneficial effects of statin therapy in asymptomatic AAA, and demonstrates an association between statin use and decreased growth rate of AAA.

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Table 1

Baseline clinical characteristics of patients with abdominal aortic aneurysm treated with and without statins.

Variable	Statins Users (n=136)	Non-users (n=75)	p-value
Male	91 (67%)	50 (67%)	0.971
Age (± SD)	70 (± 7.88)	69 (± 9.08)	0.450
Initial lesion size (cm)	4.1 (3.7-4.4)	4.1 (3.7-4.3)	0.957
Follow-up (yrs)	1.04 (1.01-1.10)	1.04 (1.02-1.12)	0.286
BMI	27.58 ± 4.88	26.92 ± 4.65	0.333
CAD	55 (41%)	31 (41%)	0.933
DM	32 (24%)	19 (25%)	0.792
PVD	29 (22%)	14 (19%)	0.628
CVA/TIA	33 (24%)	16 (21%)	0.609
CRI	40 (30%)	16 (21%)	0.193
HLP	111 (82%)	53 (71%)	0.052
COPD	87 (64%)	45 (60%)	0.523
HTN	122 (90%)	67 (89%)	0.810
Tobacco use	122 (90%)	65 (87%)	0.410

Abbreviations: BMI, body mass index; CAD, coronary artery disease; DM, diabetes mellitus; PVD, peripheral vascular disease; CVA/TIA, cerebral vascular attack or transient ischemic attack; CRI, chronic renal insufficiency; HLP, hyperlipidemia; COPD, chronic obstructive pulmonary disease; HTN, hypertension.

Table 2

Medication use in patients with abdominal aortic aneurysm treated with and without statins.

Variable	Statins Users (n=136)	Non-users (n=75)	p-value
BB	66 (49%)	24 (32%)	0.020
ACEI	59 (43%)	10 (13%)	<0.0001
ASA	109 (80%)	36 (48%)	<0.0001
CCB	4 (3%)	14 (19%)	<0.0001
Steroids	23 (17%)	10 (13%)	0.493
Vitamin E	11 (8%)	4 (5%)	0.456

Abbreviations: BB, beta-blocker; ACEI, angiotensin converting enzyme inhibitors; ASA, aspirin; CCB, calcium channel blocker.

Table 3

Test of significance of variables in the multi-variable linear regression model.

Variable	Level	Mean % change in lesion size(95% CI)	p-value
Statins	Y	-0.7% (-2.8%, 1.5%)	<0.0001
	N	7.5% (5.4%, 9.6%)	
CCB	Y	1.4% (-1.9%, 4.7%)	0.027
	N	5.3% (3.9%, 6.6%)	
ASA	Y	3.9% (2.0%, 5.8%)	0.289
	N	2.8% (0.5%, 5.1%)	
BB	Y	3.9% (1.8%, 5.9%)	0.270
	N	2.8% (0.6%, 5.0%)	
ACEI	Y	3.3% (0.9%, 5.8%)	0.984
	N	3.3% (1.6%, 5.1%)	
HLP	Y	3.4% (1.6%, 5.2%)	0.925
	N	3.3% (0.8%, 5.8%)	

Estimates of relative mean change were computed for 1 year duration.

Abbreviations: CCB, calcium channel blocker; ASA, aspirin; BB, beta-blocker; ACEI, angiotensin converting enzyme inhibitors; HLP, hyperlipidemia.