International Journal of Cardiology 191 (2015) 52–55

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Effects of statin therapy on ascending aorta aneurysms growth: A propensity-matched analysis ☆

Emiliano Angeloni [a,b,*], Angelo Vitaterna [b], Michele Pirelli [b], Simone Refice [a,b]

[a] Sapienza, University of Rome, Department of Cardiovascular Pathophysiology and Imaging, Italy
[b] Eurytmia Medical Center, Anagni, Italy

ARTICLE INFO

Article history:
Received 2 February 2015
Received in revised form 24 April 2015
Accepted 2 May 2015
Available online 5 May 2015

Keywords:
Ascending aorta
Aortic aneurysms
Statins

ABSTRACT

Background: Pleiotropic effects of statins have been advocated for remodeling of the vascular wall. The aim of the present study was to investigate whether statin therapy influences the growth rate of ascending aorta (AA) diameter.
Methods: A total of 1348 patients was referred to our outpatient clinic for initial AA ectasia from September 2005 to December 2011. A propensity score was built to perfectly match (1:1) patients administered (Group A) or not (Group B) with statin therapy. Clinical and echocardiographic follow-up was 100% completed at 3 years after the first visit. Treatment groups were investigated for differences in AA maximum diameter, furthermore rates of survival free from death and/or complications were assessed by Kaplan–Meier analysis.
Results: Finally, two fairly-comparable groups of 329 patients each were obtained (Propensity model c-statistic 0.86, $p < 0.0001$). At baseline, mean AA diameters were 38.88 ± 2.48 mm and 39.09 ± 2.60 mm in Groups A and B, respectively. At 3-years, similar rates of hypertension control (86 ± 12% vs. 85 ± 14%) were found, whilst growth rate of AA diameter was +2.84 ± 1.33 mm (or +0.95 mm/year) in Group A and +3.80 ± 1.69 mm (or +1.27 mm/year) in Group B ($p < 0.0001$). Three-year survival free from the composite outcome (death, dissection/rupture, need for operative repair) was found to be significantly improved in Group A (85.4 ± 2.0%) rather than in Group B (79.7 ± 2.2%), with a log-rank $p = 0.05$ (HR 0.69, 95% CI 0.47 to 1.01).
Conclusions: In this study, statin treatment is associated with reduced growth rate of ascending aorta aneurysms. The latter resulted in improved survival free from complications for patients receiving statins.

1. Introduction

The primary effect of statins is the inhibition of 3-hydroxy-3methylglutaryl coenzyme A reductase, which reduces mevalonic acid levels and induces upregulation of low-density lipoprotein (LDL) receptors determining lower levels of LDL in the blood. Aside from this, it has been shown that statins exert many pleiotropic effects, resulting in net clinical benefit among a wide range of cardiovascular disorders, including heart failure, arrhythmias, valvular and vascular diseases. These include modulation of the inflammatory response, improvement of blood flow and endothelial function [1–3].

Indeed, endothelial dysfunction has been recognized as an independent predictor of cardiovascular disease, and statins significantly ameliorate endothelial dysfunction [4,5].

Aortic aneurysm represents a common vascular pathology belonging to the spectrum of atherosclerotic diseases. Etiology is multifaceted, involving systemic hypertension, connective tissue disorders, pro-inflammatory mediators such as macrophages, T-cells, B-cells and neutrophils, as well as multiple pro-inflammatory transcription factors [6]. Previous studies have shown that statin therapy is likely effective in prevention of the growth of small abdominal aorta aneurysms [7,8]. To date, only one study investigated the effect of statin therapy on thoracic aorta aneurysm growth [9], and found a significant correlation between statin therapy and a decreased progression to dissection, rupture, or death; although no significant difference was found with regard to the aortic root, and the investigation included the whole thoracic aorta.

The aim of the present investigation was to focus on the ascending aorta and assess whether statin therapy influences the growth rate of such aneurysms, comparing fairly-matched population.

2. Methods

This study was reviewed and approved by the Institutional Review Board of Eurytmia Medical Center, and a waiver of consent was granted. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration

☆ All the author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Sapienza, Università di Roma, Via di Grottarossa 1035, 00189 Rome, Italy.
E-mail addresses: emiliano.angeloni@uniroma1.it, emilianoangeloni@gmail.com (E. Angeloni).

http://dx.doi.org/10.1016/j.ijcard.2015.05.001
0167-5273/

of Helsinki as reflected in a priori approval by the institution's human research committee.

2.1. Patients and variables

We retrospectively reviewed a series of patients referred to our outpatient clinic for initial AA ectasia from September 2005 to December 2011. The presence of connective tissue disorders, concomitant severe heart valve disease, and coronary artery disease was considered as exclusion criteria.

Statins received by patients were atorvastatin, simvastatin, rosuvastatin and lovastatin in order to keep low-density lipoprotein cholesterol levels <100 mg/dl, in compliance with current guidelines [10]. If needed, statins' dosage was increased to reach the previously cited therapeutic goal. To avoid cross-over bias, patients who suspended or started statin therapy during follow-up were excluded from the analysis.

Among patients not receiving statins there were some administered with other lipid lowering therapies, including fenofibrate, gemfibrozil, ezetimibe and cholestyramine. Even among the latter group, cross-over patients were excluded from the analysis.

A propensity score [11] was built to perfectly match (1:1) patients administered (Group A) or not (Group B) with statin therapy. Clinical and echocardiographic follow-up was completed at 3 years after the first visit.

Treatment groups were investigated for differences in AA maximum diameter, and rates of survival free from death and/or complications, such as dissection, rupture or needing for surgical repair.

Maximum diameter of the ascending aorta was estimated by means of complete M-mode, and bi-dimensional trans-thoracic echocardiographic assessments performed with a MyLab 30 Gold Cardiovascular system (Esaote SPA, Genoa, Italy). All echocardiographic studies were reviewed in core laboratory and independently reviewed by two echocardiologists. In the case of aortic diameters greater than 45 mm, and in cases of difficult interpretation an angio-CT scan was performed and the resulting diameter was used.

2.2. Statistical analysis

Continuous data are expressed as the mean and standard deviation; categorical data are expressed as count and percentage; comparisons were made using the 2-sample t and the χ^2 or the Fischer exact tests, respectively.

Because patients receiving statin tend to have more comorbidities we used a propensity score analysis [11] to control for selection bias. Categorical and continuous variables were used in order to obtain a semi-saturated model, including: age, gender, history of hypertension, diabetes mellitus, previous cerebrovascular accident, peripheral vascular disease, smoking history, body mass index >35 kg/m^2, left ventricular ejection fraction, creatinine clearance, total cholesterol level, LDL-cholesterol level, usage of angiotensin converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium-channel blockers, and diuretics. Two propensity-matched (1:1) cohorts were identified: patients receiving statin treatment (Group "A") and patients not receiving statin therapy (Group "B"). Cumulative incidence of the composite outcome was then compared. Actuarial estimates of survival and freedom from morbid events were made using the Kaplan–Meier method. The survival time of a patient started at index visit and ended at event or at last follow-up (censoring).

Statistical analysis was performed using Statistical Package for the Social Sciences, version 11 (SPSS, Chicago, IL).

2.3. Limitations

The main limitation of the present study is its retrospective nature. Indeed, despite the use of propensity scoring, the lack of randomization makes possible that unidentified confounders may affect results.

3. Results

Among the whole study population (n = 1348), 775/1348 (57.5%) patients were receiving statins, whilst 573/1348 (42.5%) were not. Baseline characteristics (Table 1) showed several significant differences between patients administered or not with statin therapy. Indeed, patients assuming statins were likely to be older (p = 0.002), and with increased prevalence of comorbidities such as hypertension (p = 0.0001), diabetes (p = 0.06), and hypercholesterolemia (p < 0.0001).

After propensity-matching (model c-statistic 0.86, p < 0.0001), two fairly-comparable groups of 329 patients each were obtained. No significant differences were noted in baseline characteristics between matched populations, as shown in Table 2. In particular, mean AA diameters at baseline were 38.88 ± 2.48 mm in Group A, and 39.09 ± 2.60 mm B; respectively (p = 0.27).

Aortic diameters at different time-points are depicted in Fig. 1. As depicted, aortic diameters started diverging at 1 year after the index visit (39.81 ± 3.32 mm vs. 40.39 ± 3.35 mm for Groups A and B, respectively; p = 0.02), and the latter difference became even more statistically significant at 3-year follow-up (41.72 ± 3.46 mm vs. 42.89 ± 3.67 mm for Groups A and B, respectively; p < 0.0001).

At 3-year FU (mean 34.58 ± 6.6 months) similar rates of hypertension control (86 ± 12% vs. 85 ± 14%; p = 0.79) were found, whilst growth rate of AA diameter was significantly different: +2.84 ± 1.33 mm (or +0.95 mm/year) in Group A and +3.80 ± 1.69 mm (or +1.27 mm/year) in Group B (p < 0.0001). In addition, growth rates did not significantly differ between smaller (<40 mm; +1.10 ± 0.17 mm/y) and larger (≥40 mm; +1.11 ± 0.18 mm/y) aneurysms (p = 0.53).

Kaplan–Meier analysis showed that 3-year survival free from the occurrence of the composite outcome (death, dissection/rupture, need for operative repair) was significantly improved in Group A (85.4 ± 2.0%) rather than in Group B (79.7 ± 2.2%), with a log-rank p = 0.05 (HR 0.69, 95% CI 0.47 to 1.01; Fig. 2).

4. Discussion

Main finding of the present study was the reduced growth rate of aortic aneurysms among patients administered with statin therapy. The latter resulted in better survival free from complications such as dissection, rupture or need for repair for those patients receiving statin therapy.

Table 1
Baseline characteristics of the study population before propensity-matching.

	Statin usage (n = 775)	No statins (n = 573)	p value
Age, years	68.1 ± 14.2	63.5 ± 9.6	0.002
Sex female	294 (37.9)	220 (38.4)	0.12
Hypertension	591 (76.3)	418 (72.9)	0.0001
Diabetes mellitus	144 (18.6)	96 (16.8)	0.06
Creatinine clearance, ml/min	66.3 ± 12.1	65.4 ± 13.5	0.27
Total cholesterol, mg/dl	196 ± 29.2	169 ± 39.5	<0.0001
LDL-cholesterol, mg/dl	97 ± 6.6	80 ± 10.2	<0.0001
Cerebrovascular accident	65 (8.4)	41 (7.2)	0.09
Peripheral vascular disease	38 (4.9)	26 (4.5)	0.19
Smoking history	426 (54.9)	356 (62.1)	0.04
Body mass index, kg/m^2	29.9 ± 6.3	27.4 ± 5.1	0.07
LV ejection fraction, %	58.1 ± 12.6	57.8 ± 16.3	0.26
Basal aortic diameter, mm	38.8 ± 2.53	38.8 ± 2.64	0.98
Medications			
ACE-inhibitors	513 (66.2)	268 (46.8)	<0.0001
Angiotensin receptor blockers	249 (32.1)	137 (23.9)	0.003
Beta-blockers	457 (58.9)	274 (47.8)	0.002
Calcium-channel blockers	251 (32.3)	182 (31.8)	0.14
Diuretics	286 (36.9)	183 (31.9)	0.04