

Institutional report - Aortic and aneurysmal

The use of statins and fate of small abdominal aortic aneurysms

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Abstract

The aim of this study was to evaluate the value of statins in reducing abdominal aortic aneurysm (AAA) growth rate and improving freedom from aneurysm repair or rupture. One hundred and twenty-one patients with AAA undergoing ultrasonographic surveillance for at least one year were included in this retrospective study. Patients treated with statins had a decreased linear aneurysm growth rate than those not receiving statins (1.9 ± 1.8 mm/year vs. 2.6 ± 2.4 mm/year, $P=0.27$), but this difference did not reach statistical significance. Statin users had a better survival freedom from aneurysm repair or rupture (at 5 years: 72.3% vs. 52.5%, $P=0.048$). The impact of treatment with statins was even more evident in patients with a baseline aneurysm diameter <40 mm (at 5 years: 84.0% vs. 58.8%, $P=0.022$). When adjusted for age, coronary artery disease and baseline aneurysm diameter, treatment with statins had significantly better survival freedom from aneurysm repair or rupture ($P=0.012$, RR 0.34, 95% CI 0.14–0.78). The use of statins seems to slightly decrease the AAA growth rate and to significantly improve freedom from aneurysm repair and rupture.

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Keywords: Abdominal aortic aneurysm; Growth rate; Rupture; Repair; Statin

1. Introduction

The fate of abdominal aortic aneurysms (AAAs) is ultimately to enlarge in size and to rupture. The risk of rupture is related to the aneurysm size, but also the outcome of very small AAAs is not benign [1]. A strategy of screening, surveillance and repair when indicated may dramatically decrease the risk of aneurysm rupture. Beside this, any medical intervention able to decrease the aneurysm growth may have a dramatic, positive impact on the outcome of these patients. Recent observations from experimental studies have suggested that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) may prevent aneurysmal degeneration of the abdominal aorta [2–5]. Furthermore, two clinical studies have provided evidence on the impact of statins on the AAA growth rate [6, 7]. Herein we report the results of a retrospective study evaluating the potential value of statins in reducing AAA growth rate and improving freedom from aneurysm repair or rupture.

2. Patients and methods

In the present study we have retrospectively collected the data regarding patients who underwent evaluation and surveillance for AAA at the Division of Cardio-thoracic and

Vascular Surgery, Department of Surgery, Oulu University Hospital, Oulu, Finland, from April 1993 and March 2005. We included only those patients having had an AAA of at least 30 mm, who have undergone ultrasound follow-up of at least one year and in whom serum levels of intact N-terminal propeptide of type III procollagen (PIIINP, UniQ PIIINP RIA, Orion Diagnostica, Espoo, Finland) have been measured at each control. One hundred and twenty-one patients were included in this study and their clinical data are summarized in Table 1. These patients underwent serial ultrasonographic examinations at 3- to 12-month intervals according to AAA diameter and patients' conditions. The decision whether to repair the aneurysm was based on the aneurysm diameter, growth rate, patients' operative risk, symptoms and willingness of the patient to be operated on.

Statistical analysis was performed using SPSS statistical software (SPSS v. 10.0.5, SPSS Inc., Chicago, IL, USA). The linear expansion rate was calculated as the difference between the final and baseline aneurysm diameter divided by the period of surveillance. Continuous variables are reported as the mean \pm S.D. The χ^2 -test and the Fisher's exact test were used for univariate analysis of categorical data. The Mann–Whitney test was used to assess the distribution of continuous variables in different subgroups. The Spearman test was used to evaluate correlation between continuous variables. The Kaplan–Meier test was used to assess freedom from aneurysm repair or rupture in patient subgroups. Linear regression and Cox-regression

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Table 1
Preoperative clinical details

Risk factors	Overall (n=121)	Statin users (n=34)	Non-users (n=87)	P-value
Patients' age (years)	70±7.9	70.5±7.7	69.8±8.0	0.73
Females	13 (10.7%)	4 (11.8%)	9 (10.3%)	0.76
Chronic obstructive pulmonary disease	39 (32.2%)	7 (20.6%)	32 (36.8%)	0.13
Diabetes	14 (11.6%)	5 (14.7%)	9 (10.3%)	0.53
Hypertension	53 (43.8%)	15 (44.1%)	38 (43.7%)	1.00
Lower limb ischemia	10 (8.3%)	3 (8.8%)	7 (8.0%)	1.00
Transient ischemic attack or stroke	18 (14.9%)	7 (20.6%)	11 (12.6%)	0.27
Previous vascular/endovascular procedures	21 (17.4%)	11 (32.4%)	10 (11.5%)	0.014
Coronary artery disease	70 (57.9%)	26 (76.5%)	44 (50.6%)	0.013
Current smokers	38 (31.4%)	8 (23.5%)	30 (34.5%)	0.28
Ever smoked	59 (48.8%)	13 (38.2%)	46 (52.9%)	0.16
Treatment with				
Statins	34 (28.1%)	–	–	–
Beta-blockers	67 (55.4%)	24 (70.6%)	43 (49.4%)	0.43
Angiotensin-convertin enzyme blockers	14 (11.6%)	5 (14.3%)	9 (10.3%)	0.53
Angiotensin II receptor blockers	9 (7.4%)	3 (8.8%)	6 (6.9%)	0.71
Baseline diameter of the aneurysm (mm)	39.2±6.4	38.7±7.0	39.3±6.3	0.94
Baseline PIIINP (µg/l)	3.5±1.3	3.7±1.2	3.5±1.3	0.51

Continuous variables are reported as mean±S.D.

tests, with the help of backward selection, were used for multivariable analysis. A $P < 0.05$ was considered statistically significant.

3. Results

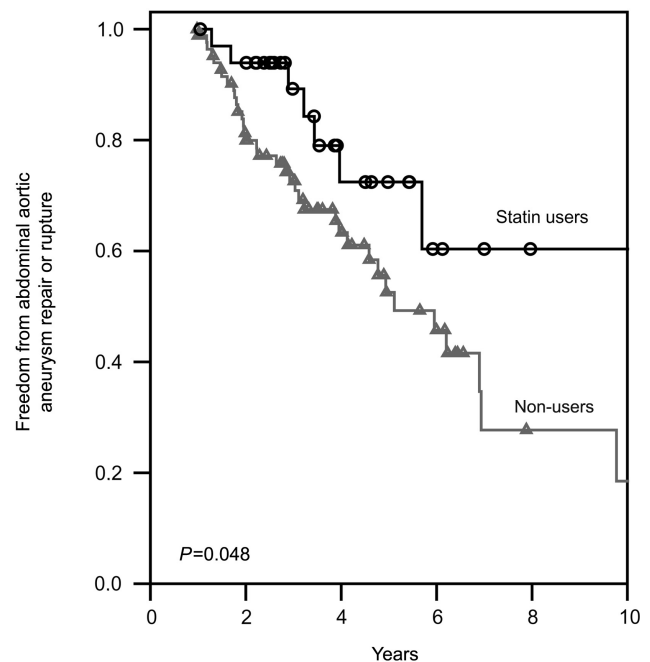
After a mean clinical follow-up of 3.6 ± 2.2 years, 31 patients had elective open repair of AAA, eight patients underwent endovascular repair, one had emergency repair for symptomatic, unruptured AAA, one had emergency repair for ruptured AAA, and two died of ruptured AAA. The mean linear AAA growth rate was 2.4 ± 2.3 mm/year.

Baseline levels of PIIINP significantly correlated with baseline aneurysm diameter ($P = 0.017$, rho: 0.217), but final levels of PIIINP did not correlate with the final aneurysm diameter ($P = 0.958$, rho: -0.005). Baseline PIIINP levels did not correlate with the linear aneurysm growth rate and were not predictive of survival freedom from aneurysm repair or rupture.

Patients treated with statins had a decreased linear aneurysm growth rate than those not receiving statins (1.9 ± 1.8 mm/year vs. 2.6 ± 2.4 mm/year, $P = 0.27$), but this difference did not reach statistical significance. Among patients with baseline aneurysm diameter < 40 mm, the aneurysm growth rate was 1.6 ± 1.5 mm/year in statin users and 2.3 ± 2.2 mm/year in non-users ($P = 0.31$). Previous vascular and endovascular procedures ($P = 0.047$) and history of transient ischemic attack/stroke ($P = 0.026$) were the only risk factors associated with significantly lower linear aneurysm growth rates.

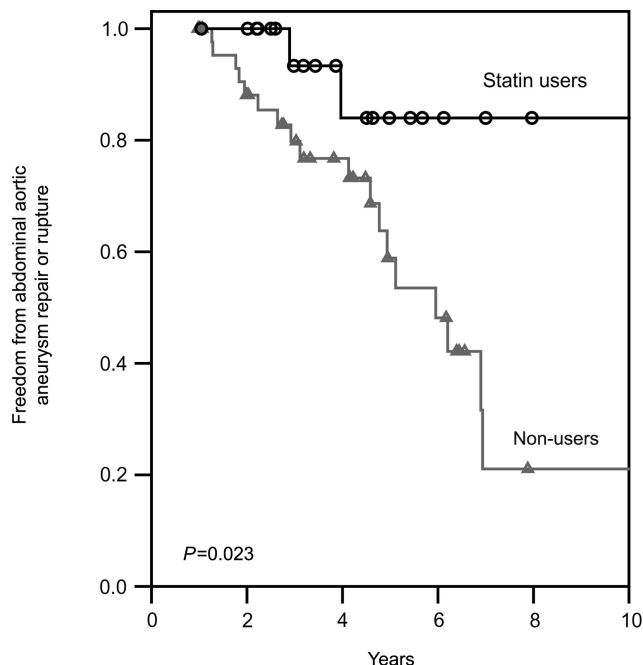
Statin users had a better survival freedom from aneurysm repair or rupture ($P = 0.048$, S.E. < 0.14 , Fig. 1). At five years, statin users had a freedom rate from aneurysm repair or rupture of 72.3% whereas it was 52.5% among non-users. The impact of treatment with statins was even more evident in patients with a baseline aneurysm diameter < 40 mm ($P = 0.022$, at five years 84.0% vs. 58.8%, respectively, Fig. 2). Previous vascular and endovascular procedures ($P = 0.036$), coronary artery disease ($P = 0.028$), age ($P = 0.003$) and baseline aneurysm diameter ($P = 0.013$)

were the other risk factors associated at univariate analysis with better survival freedom from aneurysm repair or rupture. Even when adjusted for age, coronary artery disease and baseline aneurysm diameter, treatment with statins was still associated with better survival freedom from aneurysm repair or rupture ($P = 0.012$, RR 0.34, 95% CI 0.14–0.78).



Patients at risk	0	2	4	6	8	10
Statin users	34	31	11	4	1	1
Statin non-users	87	58	28	11	2	1

Fig. 1. Survival freedom from any abdominal aortic aneurysm repair or rupture in statin users and non-users (S.E. < 0.14).



Patients at risk

Statin users	21	21	9	4	1	1
Statin non-users	48	36	22	9	1	1

Fig. 2. Survival freedom from any abdominal aortic aneurysm repair or rupture among patients with a baseline aneurysm diameter <40 mm according to statin treatment (statin users: 21 patients, non-users: 48 patients) (S.E. <0.11).

4. Discussion

There is a burden of evidence showing that the development and fate of abdominal aortic aneurysm are related to derangements in the metabolism of collagen and elastin of the aortic wall [8, 9]. In particular, matrix metalloproteinases play a major role in this scenario [9, 10]. Since several pathogenetic mechanisms involved in aneurysmal degeneration are analogous to those resulting in atherosclerosis and its related complications [4], pharmacologic intervention to modulate collagen and elastin metabolism seems to be a logical and potentially valuable approach in the treatment of abdominal aortic aneurysms.

Statins are increasingly used in the management of atherosclerosis and it has been shown that their pleiotropic effects have a significant impact on collagen metabolism. Their main effect is likely related to their ability to suppress the activity of matrix metalloproteinases, which in turn reduces collagen degradation. A reduction in the activity of metalloproteinases 3 and 9 has been demonstrated in the aortic aneurysm wall of patients on statin treatment [5]. Interestingly, a recent study has shown that simvastatin preserves elastic lamellae within the aortic media of mice whose aorta was transiently perfused with elastase [4]. This effect was likely mediated by inhibition of the expression of matrix metalloproteinase 9 [4].

The results of the present study confirm the reported preliminary data of two clinical studies which demonstrated the benefit of using statins in patients with abdominal aortic aneurysm [6, 7]. However, the decrease of aneurysm

growth rate did not reach statistical significance and it was not of the same extent as reported in the study by Schouten et al. [6]. However, the mean linear aneurysm growth rate was slower in this study as compared to that reported by Schouten et al. (2.4 ± 2.3 vs. 2.9 ± 2.8 mm/year) [6]. This slightly decreased aneurysm growth rate resulted anyway in a significantly better survival freedom from aneurysm repair or rupture among statin users. Interestingly, this effect was even more evident among patients with very small AAA (diameter <40 mm), likely because pharmacologic intervention is more effective during the initial stages of aneurysmal degeneration.

Contrary to the findings reported by Lindholt et al. [11], the present study provided evidence that PIIINP is not associated with AAA growth rate and fate. However, this observation is not conclusive as the lack of ultrasonographic controls and PIIINP measurements at fixed time intervals prevent any evaluation of possible changes in serum concentrations of these markers and their relationship with changes in aneurysm size.

The retrospective nature is a major limitation of this study. This may greatly affect the results as we do not have data about when the statin treatment was started on and whether the patient was not taking the drug despite it being on the patient's drug list. Furthermore, we do not have the possibility to verify whether the type and dosages of statin have been changed and whether these factors may affect the AAA growth rate and the need for repair or the occurrence of aneurysm rupture. With such limitations in mind, we believe that the present study provides further evidence on the potential benefits of statin treatment in patients with AAA. A prospective, randomized study would be justified on the basis of these preliminary findings, but hardly would it be feasible because the use of statins is currently indicated in a growing number of patients with AAA for the management of hypercholesterolemia as well as of coronary and peripheral vascular disease.

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eComment: Approaching the beneficial impact of statins in patients with abdominal aortic aneurysms

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Undoubtedly, your study has a great interest as it reflects the beneficial effect of statins concerning their anti-inflammatory action. It is notable the fact that patients treated with statins had a better survival freedom from aneurysm repair or rupture especially in the long-term (72.3% at five years) [1]. However, the beneficial impact of statins was even more significant in patients with very small abdominal aortic aneurysms (AAA) (baseline aneurysm diameter <40 mm), a fact that possibly confirms the more effective action of statins during the initial stage of aneurysmal degeneration. Probably, statins affect the aneurysm expansion through reduced proteolytic activity and more specifically elastolytic activity within the aortic wall. In fact, Abisi et al. demonstrated that the aortic wall of patients receiving statin treatment had a significantly lower level of active MMP-9 ($P < 0.001$) than in those not on statin treatment, a lower but non-significantly level of active MMP-3 and finally a significantly lower activity of cathepsins H and L [2]. Evans et al. randomized patients undergoing elective open repair of an AAA to a preoperative course of either simvastatin or placebo. It was observed, except for a lower activity of MMP-9, an additional 40% reduction in total MMP-9 concentration in the aortic wall of the simvastatin group [3]. So, your study offers us additional significant clinical evidence concerning the benefit of using statins in patients with abdominal aortic aneurysms, but in our opinion there is a great need for a prospective controlled randomized trial. In addition, trials concerning small aneurysms require long follow-up and accurate aortic imaging in order to assess medication value. In this regard, entry and exit CT with aortic volume and maximum orthogonal aortic diameter would be valuable [4]. Finally, the growth is neither regular nor linear and as a consequence, complex statistical modelling is needed in order to provide unbiased estimates of AAA growth.

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eComment: Statins and ACE-inhibitors

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In the present study the authors demonstrated the benefit of using statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) in patients with abdominal aortic aneurysm (AAA) with few limitations (lack of dosages, types of statin, start point of statin treatment etc.) [1].

Lately, a trend towards fewer interventions for small abdominal aortic aneurysms (AAA) has been noticeable in our hospital. If risk factor reduction and in particular statin therapy is in fact having an effect on the rates of AAA, this may influence interpretation of trials that do not include contemporary controls with optimum medication. For that reason we have looked at the trends in AAA and prescribing of the statin lipid lowering class of medication in our country over the past 10 years to further evaluate the situation. Data on statin usage were obtained from the Croatian Ministry of Health and Welfare between 1994 and 2004. These data included all prescriptions subsidized through Pharmaceutical Benefits Scheme (PBS) and the Repatriation Pharmaceutical Benefits Scheme (RPBS). Data provided came in the form of total numbers of prescriptions dispensed according to PBS or RPBS for each item number corresponding to atorvastatin, fluvastatin, pravastatin and simvastatin. Total numbers of statin prescriptions dispensed were obtained for each calendar year, and subsequently divided by 12 to obtain a monthly estimate. As each statin prescription dispensed in our country contains a 14-day supply of medication, this calculation was assumed to approximate the number of persons taking statin drugs in any given year. Our results show that the exponential-like rise in the prescribing of statin medications over the last decade is remarkable. According to our field evaluation results, the main reason for such a rise is the fact that the doctors accept that the primary mechanism of action of the statin group drugs is a lowering of serum cholesterol through the inhibition of the hepatic enzyme HMG-CoA reductase. Another concern is that experimental studies have shown that cholesterol lowering with statin therapy may slow the progression [2], and induce regression of atherosclerotic plaques involving peripheral arteries [3].

Our investigation shows another important factor. Another class of cardiovascular drugs, the angiotensin converting enzyme (ACE) inhibitors has also been shown to reduce proliferation of vascular smooth muscle and to decrease angiotensin-II mediated atherosclerosis, plaque rupture and vascular occlusion [4], independent of their blood pressure lowering effects. The ACE inhibitors are also subsidized under the PBS and RPBS and have experienced significant growth in prescribing rates in recent years. It is possible that the widespread use of this class of medications may also have contributed to the postulated effect of statin medications on the incidence of increasing the AAA. The impact of risk factor lowering medication, such as the statins, on asymptomatic AAA patients may alter the need for open surgical repair (OSR) or endovascular aortic repair (EVAR) for AAA.

Although no definitive conclusions can be drawn yet, I am hoping that our data could have some benefit for future studies. Future studies clearly require contemporary controls 'best medical management' takes into account the prescribing of statins as well as other risks lowering medications in AAA patients.

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