CLINICAL RESEARCH STUDIES

From the Peripheral Vascular Surgical Society

Growth predictors and prognosis of small abdominal aortic aneurysms

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Objective: **Evidence regarding the influence of cardiovascular risk factors, comorbidities, and patient characteristics on the growth of small abdominal aortic aneurysms (AAA) is limited. We assessed, in an observational cohort study, rupture rates, risks of mortality, and the effects of cardiovascular risk factors and patient demographics on growth rates of small AAAs.**

Methods: **Between September 1996 and January 2005, 5057 patients with manifest arterial vascular disease or cardiovascular risk factors were included in the Second Manifestation of ARTerial disease (SMART) study. Measurements of the abdominal aortic diameter were performed in all patients. All patients with an initial AAA diameter between 30 and 55 mm were selected for this study. All AAA measurements during follow-up until August 2007 were collected. Multivariate regression analysis was performed to calculate the effects of demographic patient characteristics, initial AAA diameter, and cardiovascular risk factors on AAA growth.**

Results: **Included were 230 patients, with a mean age of 66 years and 90% were male. Seven AAA ruptures (six fatal) occurred in 755 patient years of follow-up (rupture rate 0.9% per patient-year). In 147 patients, AAA measurements were performed for a period of more than 6 months. The median follow-up time was 3.3 years (mean 4.0, range 0.5 to 11.1 years, standard deviation (SD) 2.5). Mean AAA diameter was 38.8 mm (SD 6.8) and mean expansion rate 2.5 mm/y. Patients using lipid-lowering drugs had a 1.2 mm/y (95% confidence interval [CI] −2.34 to −0.060 mm/y) lower AAA growth rate compared to nonusers of these drugs. Initial AAA diameter was associated with a 0.09 mm/y (95% CI 0.01 to 0.18 mm/y) higher growth rate per millimetre increase of the diameter. No other factors, including blood lipid values, were independently associated with AAA growth.**

Conclusions: **Lipid-lowering drug treatment and initial AAA diameter appear to be independently associated with lower AAA growth rates. The risk of rupture of these small abdominal aortic aneurysms was low, which pleads for watchful waiting. (J Vasc Surg 2008;47:1127-33.)**

Abdominal aortic aneurysms (AAA) are generally diagnosed when the maximal aortic diameter reaches 30 mm or more. Evidence on factors that determine an AAA expansion rate is limited. Recently, results of animal studies suggested an association between statin use and suppression of the development of aortic aneurysms.[1] Few authors have reported the effect of statins on human aortic aneurysms in vivo. Sukhija showed in a nonrandomized observational cohort study that statins were significantly associated with attenuation of AAA growth.[2] Schouten et al[3] showed a similar effect of statins on AAA growth and adjusted the effect for several other factors. Until present and as far as we know, no more data are available on the impact of statins on human abdominal aneurysm expansion rates.

Good evidence exists for the association between the initial AAA diameter and AAA growth rates.[3-11] However, data on the predictive value of smoking,[4,9,12-15] hypertension,[4,12,16-18] age,[3-4,9,15,17,19] gender,[3-5,19] B-blockers usage,[8,10,20-22] and diabetes mellitus[3-4,12,15] are inconsistent. Factors that are consistently *not* associated with AAA growth rates include chronic obstructive pulmonary disease,[3,12,23] lipids,[4,12,18] and body weight.[4,8,13,17] Other factors and their association with AAA growth rates are reported to a lesser extent and include alcohol abuse, genetics, *Chlamydia pneumonia*, usage of NSAIDs,

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Competition of interest: none.

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doxycycline, roxithromycine, steroids, chemotherapeutic drugs, past medical history of peripheral vascular disease, cardiac disease and other cardiovascular diseases, organ transplantation, body length, several laboratory values, and the extend of thrombus in the aneurysm sac. Better insight into predictors of AAA expansion may lead to future improvements in the efficiency of follow-up, future therapies to slow AAA growth, and a better selection of patients for surgery to prevent AAA rupture.

The aim of this study is to estimate overall rupture rates of small AAAs and to investigate a predefined set of demographic characteristics and cardiovascular risk factors for association with abdominal aortic aneurysm growth.

METHODS

Study population. The Second Manifestations of ARTerial disease (SMART) study is a prospective cohort study among patients aged 18 to 79 years, referred to the University Medical Center Utrecht, The Netherlands, with clinically manifest (symptomatic) atherosclerotic disease or risk factors for atherosclerosis. Clinically manifest atherosclerotic diseases included internal carotid artery stenosis, transient ischemic attack, peripheral arterial disease, minor stroke, angina pectoris, myocardial infarction, renal artery stenosis, and abdominal aortic aneurysm. Risk factors for atherosclerosis included hyperlipidemia, diabetes mellitus, hypertension, and renal insufficiency. The detailed study design has been described previously.[24] The main objectives of the SMART study are to determine the prevalence of concomitant arterial disease, and risk factors in patients and to investigate the incidence of future cardiovascular events and its predictors in these patients. The study was approved by the ethics committee. Written informed consent was obtained from all patients. For the current study, we included the first consecutive 5057 participants who were recruited in SMART between September 1996 and January 2005.

Measurements. All patients underwent a standardized vascular screening including a health questionnaire, laboratory assessment, and ultrasonography. Ultrasound scanning of the abdomen was performed to measure the anteroposterior juxtarenal diameter and the distal anteroposterior diameter of the aorta and the length and volume of the kidneys. All ultrasonographic measurements were taken in the University Medical Center Utrecht by well-trained registered vascular technologists in a certified vascular laboratory. Ultrasonography of the abdomen was performed with an ATL 3000 HDI (Advanced Technology Laboratories, Bethel, Wash) equipped with a 4-MHz curved-array transducer. No bowel preparation was performed before the ultrasound measurement. If an AAA was detected during the SMART study, this finding was reported to the treating specialist and general practitioner with a treatment suggestion. The following treatment policy was recommended to the patient's general practitioner if an AAA was detected: indication for surgical repair if the diameter of the AAA was 55 mm or larger; smaller aneurysms required follow-up ultrasound examinations to determine the growth rate, every 12 months was recommended for AAAs with a diameter between 30 and 39 mm; and every 6 months for AAAs with a diameter of 40 to 55 mm. The treatment policy was recommended. A final decision about treatment was subsequently made by the treating specialists and patients.

The following definitions were used in this study: cerebral vascular disease: a history of a stroke, transient ischemic attack, or carotid artery surgery; diabetes: fasting plasma glucose $\geq$126 mg/dl, nonfasting serum glucose $\geq$200 mg/dl, or use of oral antidiabetic drugs or insulin; hyperlipidemia: a total cholesterol $\geq$250 mg/dl, triglycerides $\geq$210 mg/dl or high-density lipoprotein (HDL)-cholesterol $\leq$40 mg/dl; renal failure was defined by plasma creatinine $>$1.35 mg/dl or microproteinuria $>$30 mg per 1 g of creatinine; homocysteinemia: homocysteine in males $\geq$2.5 mg/l and in females $\geq$2.2 mg/l. Assessment of creatinine clearance (Cockcroft) resulted in classification into "normal ($\geq$80.0 ml/min)" and "moderate or severe insufficiency ($<$80.0 ml/min)." Hypertension was analyzed for two definitions: (1) hypertension $\geq$160/95 mm Hg: systolic blood pressure $\geq$160 mm Hg, diastolic blood pressure $\geq$95 mm Hg or use of antihypertensive drugs; and (2) hypertension $\geq$140/80 mm Hg: systolic blood pressure $\geq$140 mmHg, diastolic blood pressure $\geq$80 mm Hg or use of antihypertensive drugs. Smoking was classified into "no smoking history or past smoking" and "recently quitted or current smoking." Questionnaires were sent to the included patients every 6 months, or information about their health status was obtained from their general practitioners. All patients that were examined for their AAA size more than 12 months ago were invited for new ultrasound measurement of the actual AAA diameter to minimize the number of patients lost to follow-up. Outcome events that were recorded included death, cause of death, AAA ruptures, AAA surgery, and other vascular diseases. Calculation of the rupture rate was performed by dividing the total number of ruptures by the total follow-up time of patients at risk for AAA rupture. The follow-up time of patients at risk for AAA rupture was defined by the total follow-up time of all patients between the initial AAA diameter measurements and subsequent surgical AAA repair, rupture, death, or end of follow-up of the study.

All patients with AAAs with a maximal diameter between 30 and 55 mm who were examined by at least two AAA diameter measurements and with at least 6 months of follow-up were selected. The follow-up period for this study ended in August 2007.

Data analysis. The change in maximum AAA diameter was calculated with linear regression analysis. The regression coefficient, using time as the independent variable and diameter of AAA as the dependent variable, was used as an estimation of the AAA expansion rate for each patient.[3] Associations between demographic patient characteristics, AAA diameters and cardiovascular risk factors, and AAA growth rate were calculated with univariate linear regression analysis. Age, sex, initial AAA diameter, and variables

Table I. Clinical baseline characteristics at first screening visit

	Total (N = 230)	*Selection for study of AAA expansion rates[a] (N = 147)*
Males, (%)	207 (90)	131 (89)
Age in y (SD)	66 (7.6)	65 (7.7)
AAA diameter in mm (SD)	41 (8.0)	39 (6.8)
Medical history		
Myocardial infarction (%)	61 (27)	38 (26)
Stroke (%)	29 (13)	20 (14)
Cardiac surgery (%)	50 (22)	29 (20)
Cardiac vascular disease (%)	97 (42)	57 (39)
Peripheral vascular disease (%)	34 (15)	23 (16)
Hypertension ≥ 160/95 mm Hg (%)	132 (57)	90 (61)
Hypertension ≥ 140/80 mm Hg (%)	189 (82)	128 (87)
Diabetes mellitus (%)	47 (20)	35 (24)
Weight in kg (SD)	82 (14)	83 (14)
Body length in cm (SD)	176 (7.8)	176 (7.9)
BMI in kg/m^2 (SD)	26 (3.6)	27 (3.7)
Obesities, BMI > 30 (%)	33 (14)	23 (16)
Ankle brachial index ≤ 0.9 (%)	68 (30)	43 (29)
Carotid artery stenosis > 50% (%)	56 (24)	36 (24)
Carotid artery stenosis > 70% (%)	46 (20)	28 (19)
Hyperlipidemia (%)	159 (69)	102 (69)
Lipid-lowering drug treatment (%)	86 (37)	63 (43)
Renal failure (%)	58 (25)	37 (25)
Hyperhomocysteinemia (%)	53 (23)	36 (24)
Smoking (%)	91 (40)	59 (40)

BMI, Body mass index; *SD,* standard deviation.
[a]Patients with ≥2 documented AAA diameter measurements and ≥6 months of follow-up.

with a P value < .2, with a maximum of one variable per disease-specific category, were entered in a multivariate regression model to calculate independent effects on AAA growth rate. Cox regression analysis was used to model age-adjusted survival time.

RESULTS

Patient characteristics. The total study population consisted of 230 patients (90% men). Four patients were lost to follow-up (1.7%). All other patients were followed until death, AAA surgery, or till the most recent AAA examination within 1 year before the end of follow-up of this study.

From the total population, 79 AAAs (34%) were not detected before the patient participated in the vascular screening program. The baseline patient characteristics are given in Table I. The mean age at first presentation was 66 years (range 45-79 years), and 90% were male. Considerable cardiovascular comorbidity was present, and 37% used lipid-lowering drugs. Medical history investigation revealed that 98% of the patients with lipid-lowering drug treatment were using statins. The mean maximum diameter at first presentation of the AAA was 41 ± 8.0 mm. The mean maximum initial AAA diameter was not significantly different between men and women (41.5 mm vs 39.0 mm, respectively).

Ruptures. In 47% of the 230 patients, elective AAA surgery was performed: in 62 (57%) conventional and in 46 (43%) endovascular repair. The AAA diameters of patients who underwent elective AAA repair are shown in Fig 1. The mean AAA diameter was 54.4 ± 5.7 mm before surgery. In total, seven AAA ruptures occurred in 755.3 patient years of follow-up time of patients at risk (before surgery) for AAA rupture. This corresponds with a rupture rate of 0.9% per patient-year. Table II shows characteristics of the seven patients with AAA ruptures. The two smallest aneurysms where 43 mm at the last measurement: one had an expansion rate of only 1.9 mm/y, whereas the other was a female patient with a growth rate of 5.2 mm/y. In three patients, emergency repair was performed and one of those survived.

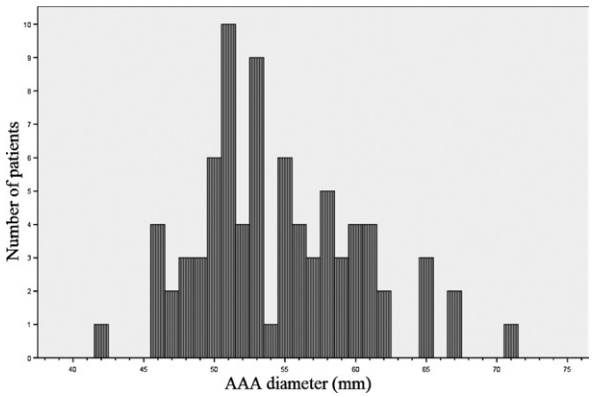

Fig 1. Abdominal aortic aneurysms (AAA) sizes of patients who underwent elective AAA surgery. The AAA diameters are shown of patients who underwent elective AAA repair and the AAA diameters were measured recently before surgery (≤6 months).

Table II. Characteristics of the seven patients with AAA ruptures

	Age[b] *(y)*	*Sex*	*AAA diameter*[a] *(mm)*	*AAA expansion rate (mm/y)*
1	78	Male	52	NA
2	71	Male	43	1.9
3	80	Female	43	5.2
4	74	Male	50	1.7
5	73	Male	50	5.3
6	72	Male	55[c]	3.4
7	70	Male	59	3.5

AAA, Abdominal aortic aneurysms; *NA*, Not available, only one ultrasound measurement of the AAA diameter available.
[a]AAA diameter measured at last AAA examination before AAA rupture occurred.
[b]Age at moment of AAA rupture.
[c]Dilatation of the iliac arteries present too.

The other six ruptured AAAs were all fatal. Aneurysmal dilatation of the iliac arteries was documented in one patient. No association between AAA expansion rate and AAA rupture could be established (Cox regression analysis, *P* .22).

Expansion rate. All patients who had been examined by at least two AAA diameter measurements and with at least 6 months of follow-up were selected for analysis of the AAA expansion rates. Total follow-up time of the AAA expansion rates was 599 patient-years. Patients who were excluded (n = 83) had not been examined by at least two AAA diameter measurements or did not have 6 months of follow-up. Efforts were made during the last year to obtain recent AAA measurements of all patients. Four patients were lost to follow-up. The AAAs of the other patients could not be measured anymore because they already had a history of AAA surgery (n = 52), AAA rupture (n = 1), or death (n = 26). The median period of AAA surveillance was 3.3 years (range 0.5 to 11.1 years).

The mean aneurysm expansion rate during follow-up was 2.5 mm per year (SD 3.2). A wide variation was found between individuals (SD 3.2, range −7.8 to 19 mm per year). Univariate analysis revealed that lipid-lowering drug use was associated with significant lower aneurysm growth rates. The difference between nonusers and users was 1.21 mm per year (95% CI 0.19 to 2.24 mm per year, $P = .02$). Low-density lipoprotein (LDL), HDL cholesterol, and triglycerides did not significantly influence the AAA growth rate. Other possible risk factors, such as smoking, hypertension, and hyperhomocysteinemia were also not significantly associated with differences in AAA expansion rates. The results of the univariate regression analysis are presented in Table III.

Table IV shows the results of the multivariate linear regression analysis. Lipid-lowering drug use and lower initial AAA diameter were independently associated with lower AAA growth rates. Lipid-lowering drug users had a 1.20 mm per year attenuation in AAA growth compared with nonusers (95% CI .060 to 2.34 mm per year).

Growth rates increased with 0.094 mm per year (95% CI .009 to .178) with every mm increase in initial AAA diameter. We did not find significant influences of other factors on aneurysm growth rate.

Mortality. Cox regression was used for modeling survival time. Total follow-up time for mortality was 1147 patient-years. Fig 2 shows the overall survival plot of the patients in our study (n = 230). After adjustments for age were made, no significant association between lipid-lowering drug use and survival time was found (*P* value .30). The causes of death of the patients are presented in Table V.

DISCUSSION

Higher initial AAA diameter appears to be associated with higher AAA expansion rates and lipid-lowering drug use with lower expansion rates. The rupture rate of these small abdominal aortic aneurysms was low: 0.9% per patient per year.

Lipid-lowering treatment consisted of statins in virtually all patients (98%) in this cohort. The pathophysiology of aortic aneurysm growth and rupture, and the mechanisms of effects of statins on this are still not fully understood. The association between LDL cholesterol and AAA formation has been shown by Hobbs et al.[25] They compared males with AAAs with age-matched controls and concluded that LDL cholesterol was significantly associated with the formation of small AAAs. In our study, we found no significant effects of LDL and HDL cholesterol on the growth rate of AAAs, which may plead for so called pleiotropic effects of statins as an underlying mechanism of decreasing AAA growth. Several experimental studies in mice and rats have reported the effect of statins on AAA growth rates. A Taiwanese study by Liu et al concluded that pravastatin significantly reduced the area of aortic atherosclerotic lesions in ApoE-deficient mice.[26] Steinmetz et al demonstrated that simvastatin reduced AAA growth in mice. This was associated with preservation of medial elastin and vascular smooth muscle cells, a relative reduction in aortic wall expression of matrix metalloproteinase (MMP)-9, and a relative increase in expression of tissue inhibitor of metalloproteinases (TIMP)-1.[1] Another study showed that simvastatin significantly suppressed experimental aneurysm expansion and reduces protein levels of MMP-9 and nuclear factor-κβ in rats, and that several mediators of inflammation, matrix remodeling, and oxidative stress were downregulated by simvastatin treatment.[27] A recent randomized placebo-controlled trial in only 21 patients elective for open AAA repair demonstrated that simvastatin reduced levels of MMP-9 in the AAA wall by 40%.[28] MMPs play probably a pivotal role in the development and progression of AAAs, and the reduction of levels and activity of these enzymes may explain the mechanism behind the observed association of statins and reduced growth of AAA.

Our results are in line with the first two studies that showed a slowing influence of statins on AAA expansion rates. Schouten et al showed, comparable to our result, a

Table III. Estimated differences in mean annual AAA growth

	Adj. estimated difference (mm/y)	*95% confidence interval*		P *value*
		Lower bound	*Upper bound*	
Age (per y increase)	.07	−.00	.13	.056
Female gender	1.1	−.58	2.8	.199
AAA diameter at first screening (per mm increase)	.07	−.01	.15	.073
Cerebral vascular disease	−1.2	−2.4	.06	.062
Myocardial infarction	−.50	−1.7	.69	.410
Peripheral vascular disease	−.65	−.78	2.1	.373
Mean systolic blood pressure (per mm Hg increase)	.01	−.03	.05	.616
Mean diastolic blood pressure (per mm Hg increase)	.04	−.03	.12	.237
Antihypertensive treatment	.60	−.46	1.7	.263
Hypertension ≥ 160/95 mm Hg	.89	−.18	2.0	.104
Hypertension ≥ 140/80 mm Hg	.23	−1.3	1.7	.770
Diabetes mellitus	−1.2	−2.4	.04	.057
Weight (per kg increase)	−.03	−.07	.01	.131
Length (per dm increase)	−.55	−1.2	.10	.099
Body mass index (per kg/m^2 increase)	−.06	−.20	.09	.432
Waist to hip ratio (per unit increase)	−2.2	−12	7.3	.649
Mean abdominal fat (per cm increase)	−.06	−.25	−.36	.708
Lower resting ankle brachial index (≤ 0.90)	−.06	−1.2	1.1	.912
Mean intima media thickness (per mm)	−.25	−1.4	.91	.670
Carotid stenosis ≥ 70% (duplex)	−.51	−1.8	.81	.445
Hyperlipidemia	−.33	−1.5	.81	.573
Lipid-lowering drug use	−1.2	−2.2	−.19	.021
Triglycerides (mg/dl)	.00	−.01	.01	.706
HDL cholesterol (mg/dl)	−.01	−.06	.03	.565
LDL cholesterol (mg/dl)	.00	−.02	.02	.983
Blood creatinine (mg/dl)	.06	−.39	.51	.792
Renal failure	.23	−1.0	1.5	.710
Assessment of creatinine clearance (Cockcroft)	−.73	−1.6	.10	.083
Hyperhomocysteinemia	.04	−1.3	1.4	.947
Smoking	−.30	−.34	.95	.351

HDL, High-density lipoprotein; *LDL*, low-density lipoprotein.

Table IV. Adjusted estimated difference in mean annual AAA growth

	Adjusted estimated difference (mm/y)	*95% confidence interval*		P *value*
		Lower bound	*Upper bound*	
Age (per y)	.02	−.07	.11	.700
Female gender	.45	−1.5	2.4	.655
AAA diameter at first screening (per mm)	.09	.01	.18	.029*
Length (per dm)	−.51	−1.5	.50	.318
Weight (per kg)	.02	−.04	.07	.519
Diabetes mellitus	−.91	−2.2	.36	.158
Cerebral vascular disease	−.70	−2.1	.68	.315
Hypertension	.88	−.25	2.0	.124
Assessment of creatinine clearance (Cockcroft)	−.22	−1.3	.82	.677
Hyperlipidemia	−.78	−2.0	.45	.210
Lipid-lowering drug use	−1.2	−2.3	−.06	.039[a]

AAA, Abdominal aortic aneurysms.
[a]*P* value < .05

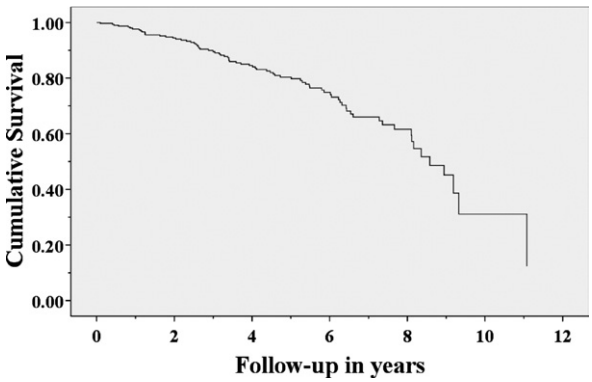

Fig 2. Cumulative long-term survival plot.

1.16 mm per year (95% CI 0.33-1.99) lower AAA growth rate in users of statins compared with nonusers.[3] Sukhija et al[2] reported that the sizes of AAAs of patients not treated with statins significantly increased after 2 years of follow-up, but the sizes of AAAs did not significantly change in patients treated with statins for the same period of follow-up.

From the total study population, 79 AAAs (34%) were not detected before the patient participated in the vascular screening program. Implementation of a screening program like the SMART study can considerably increase the number of early detected AAAs. We found a low rupture risk of 0.9% per patient-year for AAAs between 30 and 55 mm. Both the UK Small Aneurysm Trial and the Aneurysm

Table V. Causes of death of the patients in this cohort

	All patients (n = 230)		*Patients selected for AAA growth rate analysis (n = 147)*	
	n	*%*	*n*	*%*
Fatal myocardial infarction	3	3.9	1	2.9
Fatal cerebral infarction	4	5.2	1	2.9
Fatal cerebral hemorrhage	1	1.3	0	0.0
Definite sudden death	3	3.9	2	5.9
Probable sudden death	12	16	5	14.7
Congestive heart failure	4	5.2	1	2.9
Fatal AAA rupture	6	7.8	5	14.7
Other vascular death	22	29	10	29.4
Fatal infection	2	2.6	1	2.9
Fatal malignancy	16	21	7	20.6
Unnatural death	1	1.3	0	0.0
Other nonvascular death	3	3.9	1	2.9
Total	77	100	34	100

AAA, Abdominal aortic aneurysms.

Detection and Management Veterans Affairs Cooperative Study Group have shown that early elective surgery for small AAA (40 to 55mm) does not improve survival compared with ultrasound surveillance, despite low operative mortality.[29-30] Lederle et al found a risk of 0.6% per year for patients with AAAs between 40 and 55 mm.[30] This low rupture risk, added to the trial data, pleads for watchful waiting rather than surgical exclusion of small AAA. Brady et al suggested that screening intervals of 36, 24, 12, and 3 months for patients with AAA diameter 35, 40, 45, and 50 mm, respectively, yield less than a 1% chance of exceeding 55 mm at the subsequent screening.[31]

This study has some limitations. Interobserver variation in ultrasound measurements has been described to be ± 2 mm in 95% of the cases.[32-33] The calculated expansion rates of patients in this study might therefore not correspond with the real expansion rate in all patients. However, by including all recorded AAA measurements in the linear regression analysis (instead of only the first and last examinations), the effect of variability in diameter measurements have been reduced. Statin use was slightly less common in the first 20% of included patients (statin use 25% to 30%), but thereafter a constant proportion of 45% to 50% used statins. We believe that this did not affect our results importantly; however, we may underestimate the effect of statins slightly compared with the current population with more frequent use of statins and with longer duration. Finally, patients enrolled in this study were not randomized for lipid-lowering drug treatment. Comparison of baseline characteristics between patients with and without lipid-lowering drugs revealed that five variables significantly differed between users and nonusers: age, initial AAA diameter, history of cardiac disease, hyperlipidemia, and intima media thickness (IMT). AAA expansion rates were already adjusted for age, initial AAA diameter, and hyperlipidemia in the multivariate linear regression model. The two other significantly different factors ("IMT" and "history of cardiac disease") were apparently not associated with AAA expansion rates and therefore not incorporated in the multivariate model. Other variables did not significantly differ between users and nonusers of lipid-lowering drugs. Although we adjusted for several possibly confounding factors in the multivariate linear regression analysis, we could not adjust for possible other, unknown confounders.

Given the inherent limitations of observational cohort studies, the apparent slowing effect of statins on AAA growth rate needs ideally confirmation by a randomized placebo-controlled trial. However, as the majority of the patients with an AAA are nowadays treated with statins, this would hardly be possible in a placebo-controlled design.

CONCLUSIONS

Statins appear to be associated with lower AAA growth rates. Higher initial diameters are associated with higher growth rates. Other potential factors were not associated with a significant difference in aneurysm growth rate. The rupture risk of small abdominal aortic aneurysms is very small, which pleads for watchful waiting.

AUTHOR CONTRIBUTIONS

Conception and design: FS, MT, HV, YG, FM.
Analysis and interpretation: FS, MT, GH, BM, YG.
Data collection: FS, MT, FM.
Writing the article: FS, MT, GH
Critical revision of the article: FS, MT, HV, GH, BM, YG, FM.
Final approval of the article: FS, MT, HV, GH, BM, YG, FM.
Statistical analysis: FS, MT, GH, YG.
Obtained funding: Not applicable
Overall responsibility: FS

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