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Low-Dose Aspirin May Prevent Growth and Later Surgical Repair of Medium-Sized Abdominal Aortic Aneurysms

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Experimental data suggest that aspirin-induced platelet inhibition may retard growth of abdominal aortic aneurysms. In this article, whether low-dose aspirin use is associated with reduced aneurysm progression and subsequent need for surgery is examined. In this observational cohort study within a screening trial, 148 patients with small aneurysms (maximum diameter 30-48 mm) annually are followed. Patients were referred for surgery when the aneurysmal diameter exceeded 50 mm. Median follow-up time was 6.6 years. Among patients whose abdominal aortic aneurysms were initially 40 to 49 mm in size, the abdominal aortic aneurysm expansion rate for low-dose aspirin users compared with nonusers was 2.92 mm/y versus 5.18 mm/y (difference 2.27 mm/y, 95% CI, 0.42-4.11). No difference in expansion rates and risk ratios for operative repair was found for patients with abdominal aortic aneurysms <40 mm. For medium-sized abdominal aortic aneurysms, low-dose aspirin may prevent abdominal aortic aneurysm growth and need for subsequent repair, but residual confounding cannot be excluded.

Keywords: aneurysms; aspirin; follow-up studies; prevention; surgery

Human abdominal aortic aneurysm (AAA) is a common vascular disease whose risk factors include age, male sex, hypertension, and smoking.[1] The efficacy of population screening for AAAs has recently been shown in the United Kingdom[2] and Denmark.[2] However, surgery for asymptomatic AAA is expensive and incurs substantial postoperative mortality.[1,3] Thus, chemoprevention of the development and the progression of AAAs has substantial public health benefits.

Abdominal aortic aneurysm is characterized by progressive proteolytic injury of the arterial wall, which in the absence of intervention, inexorably leads to rupture.[4] Enlargement of an AAA is usually associated with the development of a mural thrombus.[5] Progression of aneurysms and rupture has been related to thrombus size,[6] circulating surrogate markers of fibrinogenesis,[7] and fibrinolysis.[8] A crescent sign of acute fibrinolysis within the thrombus is considered to be a warning of the imminent rupture of large AAAs.[9] Evidence is increasing that the mural thrombus is a source of proteases in AAA. The interface between the luminal side of the thrombus and the flowing blood is a site of constant thrombus renewal, which is linked to platelet aggregation-induced fibrin generation and neutrophil accumulation. Exposure to abciximab (a potent platelet inhibitor) in rats with experimental AAA was associated with lower AAA expansion

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rates compared with controls.[10-14] This suggests that use of platelet aggregation inhibitors may limit AAA progression. Therefore, we examined the effect of self-reported low-dose aspirin therapy on the progression of small-to-medium-sized AAAs and the need for later surgery, using cohort data available from a randomized controlled trial (RCT) on the efficacy of screening for AAA.

Materials and Methods

Patients

From 1994 to 1998, we randomly assigned all men born between 1921 and 1933 and living in Viborg County, Denmark, either to a group that offered ultrasonographic screening for AAA (n = 6333) or to a control group (n = 6306).[2] Overall, 76.6% of the men underwent screening. We considered an AAA to be present if the maximal infrarenal aortic diameter was 30 mm or greater.[2] Participants with aneurysms equal to or greater than 50 mm in size were referred to a vascular surgeon. Remaining participants with aneurysms were offered annual scans.[2]

Procedures

At the time of initial diagnosis, participants were interviewed to obtain data on previous cardiovascular events, present symptoms (including hypertension), smoking habits, and use of medications, including low-dose aspirin (75 or 150 mg acetylsalicylic acid daily). Among the 191 patients with AAA identified, 24 men had an initial diameter of more than 50 mm and were referred for surgery; the remaining 167 men (87%) were offered annual control scans and referral for surgery if the maximum AAA diameter progressed to more than 50 mm. Two observers and 1 ultrasound scanner were involved in determination of size. Interobserver variability was 1.48 mm for anterior-posterior (AP) measurements.[15] Expansion rate was computed using AP measurements in a linear mixed-effect model (see statistical methods).

Data on surgical repairs of AAAs among study participants performed between April 1994 and March 2005 were obtained from the Danish National Vascular Registry, which covers all vascular surgical procedures in Denmark (http://www.karbase.dk).

Data on deaths that occurred between April 1994 and March 2005 were obtained from the Danish Civil Registration System.

The Charlson comorbidity index was used to quantify patients' burden of concomitant illness. It was originally based on 17 clinical diagnoses, with each diagnosis given a score between 1 and 6, according to severity. The sum of the scores constituted an indicator of the total level of comorbidity.[16] For patients and controls in our study, the index was computed based on *International Classification of Diseases* (ICD) codes for all discharge diagnoses in the Danish National Health Registry since 1977. Weights were assigned to defined categories of comorbid diseases, and the index was the sum of these weights.

Information on socioeconomic conditions, such as educational level, occupation, and income, were obtained from social registries maintained by Statistics Denmark (http://www.statbank.dk).[17]

The study was approved by the regional scientific ethics committee for North Jutland and Viborg Counties (Record No. 92/138), and the Danish Registry Board and registered at current controlled trials (ISRCTN65822028).

Statistical Analysis

We measured the annual AAA expansion rate as the slope of the linear regression line of AAA-diameter versus time. A linear mixed-effect model was fitted to account for differing numbers of observations per patient. The regression coefficients of the linear regression constituted the random effects, so each patient had his own intercept and annual growth rate. The fixed effects were the annual expansion rate of the independent variables. As the hypothesis of the involvement of the mural thrombus in AAA progression is new, the presence of the mural thrombus was not specifically assessed in 1994 to 1998 when the cohort was formed. However, the presence of a thrombus correlates positively with the dilatation size.[6,7] Thus, all the analyses were stratified by the initial AAA diameter, as follows: 40 to 49 mm and below 40 mm, in AP diameter.

The risk ratio (RR) of operative repair was assessed by means of the hazard rate computed in Cox proportional-hazard regression.

For both the linear mixed-effect model and the Cox proportional-hazard regression, Wald tests were performed, using a significance level of 5%.

We controlled for the same variables in the mixed-effect model and the Cox proportional-hazard regression model. In the analysis, the main predictor and the confounder variables were aspirin use (use of low-dose aspirin or no use of low-dose aspirin), smoking (smoking or no smoking), education level

Table 1. Baseline Characteristics According to Low-Dose Aspirin Intake and Initial Maximum Abdominal Aortic Aneurysm Diameter

	<40 mm		40-49 mm		Total	
Low-Dose Aspirin	No	Yes	No	Yes	No	Yes
Numbers	69	48	17	14	86	62
Observation time, y						
Median	7.3	7.6	2.2	5.1	6.6	6.5
Lower; upper quartile	4.7; 9.0	4.3; 9.9	1.3; 3.2	2.3; 5.6	3.2; 8.8	4.1; 9.6
Age, y						
Median	67.2	67.0	67.5	68.4	67.2	67.4
Lower; upper quartile	65.2; 70.9	65.2; 70.1	65.5; 69.1	65.3; 69.6	65.2; 70.7	65.3; 70.1
Initial AP-AAA diameter, mm						
Median	32	32	42	42	34	33
Lower; upper quartile	30; 35	30; 34	41; 43	40; 44	31; 38	31; 38
Charlson comorbidity index						
Median	0.0	1.0	0.0	0.0	0.0	1.0
Lower; upper quartile	0.0; 1.0	0.0; 1.0	0.0; 0.0	0.0; 1.0	0.0; 1.0	0.0; 1.0
Current smoking, n (%)						
No	22 (32%)	23 (48%)	6 (35%)	6 (43%)	28 (33%)	29 (47%)
Yes	47 (68%)	25 (52%)	11 (65%)	8 (57%)	58 (67%)	33 (53%)
Educational level						
No higher education	44 (64%)	32 (67%)	7 (41%)	2 (14%)	51 (59%)	34 (55%)
Higher education	25 (36%)	16 (33%)	10 (59%)	12 (86%)	35 (41%)	28 (45%)
Operations						
No	55 (80%)	39 (81%)	4 (24%)	7 (50%)	59 (69%)	46 (74%)
Yes	14 (20%)	9 (19%)	13 (76%)	7 (50%)	27 (31%)	16 (26%)

NOTES: AP = anterior-posterior; AAA = abdominal aortic aneurysms.

(only secondary school or further education), and comorbidity (Charlson comorbidity index as a continuous variable).

All statistical analyses were performed using SAS version 9.1.3 for SunOS.

Results

Descriptive Data

Complete data were available for 148 of 167 patients with AAA who had been offered annual control scans. In all, 19 patients with incomplete data were excluded from the analysis. Reasons for missing data included loss of follow-up during the first year, mainly due to death or severe illness (n = 14). As well, some data was lacking on smoking habits. During 931.5 years of follow-up, 43 men were referred for elective surgery due to AAA expansion (0.046 operations/y). The median observation time from baseline to planned surgery or death was 6.6 years (lower quartile, 3.3; upper quartile, 8.8).

Table 1 shows the baseline characteristics, grouped according to low-dose aspirin use and initial AAA diameter. The baseline characteristics of excluded patients were similar to those included.

Expansion Rate

We observed no difference in the crude expansion rate between low-dose aspirin users and nonusers among patients with AAAs smaller than 40 mm at diagnosis (2.52 vs 2.23 mm/y, difference = –0.30 mm/y, 95% confidence interval [CI], –0.91-0.31, P = .34; Table 2). The estimate remained unchanged when men with missing data on smoking were included in the crude analyses.

Data were complete for all patients whose AAA initially measured 40 to 49 mm. Among these men, we observed a clear difference in crude expansion rates among low-dose aspirin users compared with nonusers 2.92 versus 5.18 mm/y (difference = 2.27 mm/y, 95% CI, 0.42-4.11, P = .017; Table 2).

Table 2. Linear Regression Analysis of Annual Expansion Rate and Use of Low-Dose Aspirin in Patients With Abdominal Aortic Aneurysm, Stratified by Abdominal Aortic Aneurysm Size (Initial Measurement <40 mm or 40-49 mm in diameter). Controlled for Smoking, Charlson Comorbidity Index, and Educational Level

	<40 mm		40-49 mm	
Parameter	Estimate (95% CI)	*P* Value	Estimate (95% CI)	*P* Value
Crude				
Low-dose aspirin	2.23 (1.82; 2.64)	<.0001	5.18 (3.92; 6.45)	<.0001
No aspirin	2.52 (2.04; 3.01)	<.0001	2.92 (1.56; 4.27)	<.0001
Difference	–0.30 (–0.91; 0.32)	.3447	2.27 (0.42; 4.11)	.0173
Adjusted				
Aspirin, low/no	–0.44 (–1.06; 0.17)	.1563	2.13 (0.58; 3.68)	.0082
Smoke, no/yes	–0.85 (–1.47; –0.24)	.0066	–3.52 (–5.23; –1.80)	.0002
Charlson comorbidity index	–0.17 (–0.53; 0.19)	.3513	1.13 (0.01; 2.25)	.0475
Education, low/high	0.07 (–0.55; 0.69)	.8256	1.27 (–0.42; 2.95)	.1363

NOTE: CI = confidence interval.

Table 3. Risk Ratios (95% CI) for Surgery to Repair Aneurysmal Expansion, Stratified by Abdominal Aortic Aneurysm Size (Initial Measurement <40 mm or 40-49 mm in Diameter) and by Use of Low-Dose Aspirin

	<40 mm	40-49 mm
Parameter	RR (95% CI)	RR (95% CI)
Crude		
No/low dose	1.02 (0.44; 2.35)	2.74 (1.06; 7.07)
Adjusted		
Aspirin, no/low	0.91 (0.38; 2.13)	2.75 (0.86; 8.77)
Smoke, no/yes	0.89 (0.37; 2.14)	0.24 (0.08; 0.76)
Charlson comorbidity index	0.51 (0.24; 1.09)	0.97 (0.46; 2.03)
Education, low/high	0.98 (0.41; 2.31)	1.97 (0.73; 5.37)

NOTES: RR = risk ratio; CI = confidence interval.

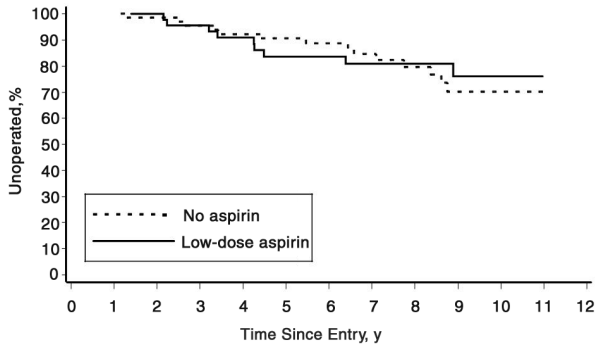

Figure 1. Kaplan-Meier curves for risk of undergoing surgery versus time since study entry for patients with an aneurysm initially measuring less than 40 mm in diameter.

This difference decreased slightly after controlling for smoking, educational level, and comorbidity (difference = 2.13 mm/y, 95% CI, 0.58-3.68, *P* = .008; Table 2).

Risk for Surgery

The RR for having an elective operation during the follow-up period among nonusers compared with low-dose aspirin users was 1.02 (95% CI, 0.44-2.35) if their AAAs were initially smaller than 40 mm (Figure 1; Table 3).

The corresponding crude relative risk for those whose initial AAA measured 40 to 49 mm was 2.74 (95% CI, 1.06-7.07). This increased risk persisted after adjusting for smoking, educational level, and comorbidity (RR = 2.75 [95% CI, 0.86-8.77], Table 3; Figure 2), but failed to reach statistical significance.

All estimates remained almost unchanged when excluded men in the 2 subgroups were included in the crude and the adjusted analyses.

Discussion

In this analysis of an observational cohort study within a population-based RCT, we found that use of low-dose aspirin was associated with a reduction in AAA growth and aneurysmal repair surgery, in patients with medium-sized AAAs.

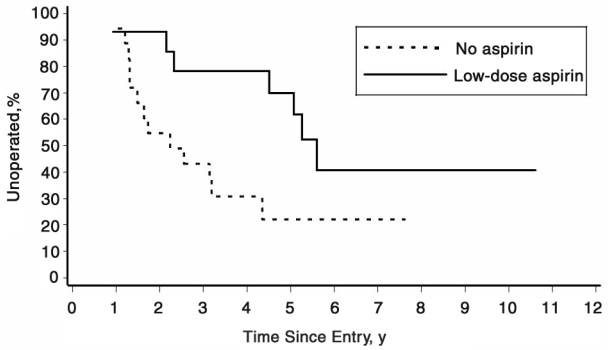

Figure 2. Kaplan-Meier curves for risk of undergoing surgery versus time since study entry for patients with an aneurysm initially measuring 40 to 49 mm in diameter.

The validity of our data depends ultimately on the quality of self-reported low-dose aspirin use, on our ability to control for confounding, and on measurement of outcomes. We consider the sensitivity of the information on low-dose aspirin intake to be relatively high, since it was collected by personal interview at baseline. However, because low-dose aspirin can be obtained without prescription and subsequent registration, validation of the interview is difficult. As use of low-dose aspirin was documented at study entry, nonusers may have commenced its use later on, and users without a medical indication may have stopped their intake. In addition, information on use of high-dose aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) was not taken into account, though both sources of bias would tend to mask a preventive effect.

Statins have been reported to reduce the growth rate of AAAs,[18] probably due to their anti-inflammatory properties, and angiotensin-converting enzyme (ACE) inhibitors have shown potential to lower the risk of rupture, purportedly through matrix-remodeling properties.[19] Although use of low-dose aspirin is likely to be associated with use of statins or ACE inhibitors, no study participants received statins and only 4 received ACE-inhibitors at baseline, making this cause of confounding unlikely.

Men with a history of cardiovascular symptoms may be more likely than healthy men to use low-dose aspirin, and to be former smokers and smoking is a risk factor for aneurysmal progression.[20] Low-dose aspirin users may also be more likely to adopt general cardiovascular preventive measures, such as lifestyle changes, proper antihypertensive treatment, and other actions, which could influence the expansion of AAAs. Such preventive behavior is known to be associated with educational level. However, for medium-sized AAAs, the association of low-dose aspirin use with lower expansion rates remained robust after adjustment for smoking, comorbidity, and educational level. Although the risk of later surgery was lower among aspirin users than among nonusers, the RR failed to reach statistical significance in the adjusted analysis.

When men who had been excluded in the crude analyses were added back into the analysis, the estimates did not change markedly, suggesting a lack of major selection bias in this respect.

The low interobserver variation[15] and use of a validated nationwide database to identify AAA surgeries[21] makes it likely that the outcome measures are of high quality.

The observation that low-dose aspirin was protective for medium-sized AAA, but not small AAA, supports the hypothesized involvement of the mural thrombus in AAA progression because the mural thrombus is closely associated to AAA size. This opens the question whether platelet-inhibitors more efficient would be better agents than low-dose aspirin for repairing aneurysmal progression.

Conclusion

In this prospective secondary analysis, men with an AAA initially measuring 40 mm to 49 mm who used low-dose aspirin had a lower mean annual aneurysmal expansion rate and a lower risk of later AAA surgical repair than nonusers. This finding was not affected by adjustment for smoking, comorbidity, and educational level. However, because our data were observational, residual confounding cannot be excluded.

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