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## Abdominal Aortic Aneurysm Expansion Risk Factors and Time Intervals for Surveillance

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on behalf of the UK Small Aneurysm Trial Participants

**Background**—Intervention to reduce abdominal aortic aneurysm (AAA) expansion and optimization of screening intervals would improve current surveillance programs. The aim of this study was to characterize AAA growth in a national cohort of patients with AAA both overall and by cardiovascular risk factors.

**Methods and Results**—In this study, 1743 patients were monitored for changes in AAA diameter by ultrasonography over a mean follow-up of 1.9 years. Mean initial AAA diameter and growth rate were 43 mm (range 28 to 85 mm) and 2.6 mm/year (95% range, -1.0 to 6.1 mm/year), respectively. Baseline diameter was strongly associated with growth, suggesting that AAA growth accelerates as the aneurysm enlarges. AAA growth rate was lower in those with low ankle/brachial pressure index and diabetes but higher for current smokers (all  $P < 0.001$ ). No other factor (including lipids and blood pressure) was associated with AAA growth. Intervals of 36, 24, 12, and 3 months for aneurysms of 35, 40, 45, and 50 mm, respectively, would restrict the probability of breaching the 55-mm limit at rescreening to below 1%.

**Conclusions**—Annual, or less frequent, surveillance intervals are safe for all AAAs  $\leq 45$  mm in diameter. Smoking increases AAA growth, but atherosclerosis plays a minor role. (*Circulation*. 2004;110:16-21.)

**Key Words:** aneurysm ■ aorta ■ atherosclerosis ■ smoking

Abdominal aortic aneurysm (AAA), defined as an aortic diameter  $\geq 30$  mm, is a common condition in older men. Large screening studies have suggested a prevalence of around 5% in men over the age of 50.<sup>1,2</sup> Two randomized controlled trials, the UK Small Aneurysm Trial and the US-based Aneurysm Detection and Management Trial (ADAM), have shown that a policy of early elective surgery for small AAA (40 to 55 mm in diameter) does not save lives.<sup>3-5</sup> These trials and follow-up of patients with AAA detected in the UK Multicenter Aneurysm Screening Study (MASS)<sup>1</sup> also showed that a policy of surveillance until the AAA diameter exceeded 55 mm (approximately 3 times the normal aortic diameter) was safe and associated with a very low rate of AAA rupture, around 1% per annum.

One outstanding issue of management is how frequently surveillance should be offered to patients with AAA  $< 55$  mm in diameter. It is not clear what data, if any, current practice is based on. The MASS trial<sup>1</sup> scanned patients with diameter 45 to 50 mm at 3-month intervals, whereas the UK Small Aneurysm Trial<sup>3</sup> used 6-month intervals for these patients. ADAM<sup>4</sup> rescreened patients with AAA diameter 50 to 55 mm every 6 months, compared with every 3 months in the UK.<sup>1,3</sup> A previous study of AAA growth and rupture investigated

screening intervals. The data were derived from only two centers and these yielded different results; for instance, the predicted percentage of 40-mm aneurysms exceeding 60 mm within 3 years was 0.6% at one center and 5.8% at the other.<sup>6</sup> Recently, screening intervals for those with AAA  $< 40$  mm in diameter have been derived from a UK screening program.<sup>7</sup> A screening interval of 1 year for those with AAA 35 to 39 mm in diameter was recommended because, during this interval, only 2 of 166 patients had aneurysms of 55 mm or greater and no patient had required surgery or suffered AAA rupture.<sup>7</sup> Others have suggested a 2- or 3-year screening interval for AAA  $< 40$  mm.<sup>8,9</sup>

Studies of AAA expansion, and the factors associated with expansion, have been limited by small sample sizes and mostly analyzed by linear regression. The last measurement in a series of AAA measurements will tend to be biased toward larger diameter because measurement errors, which by chance overestimate AAA diameter, may lead to the measurement series being terminated (by elective surgery). Linear regression analysis is affected by this bias, overestimating the slope of aneurysm growth. We analyzed longitudinal AAA diameter measurements from a large national cohort using likelihood-based methods that are not subject to

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**TABLE 1. Summary of Longitudinal AAA Measurement Data Collected During UK Small Aneurysm Trial and Study (Patients With 2 or More Measurements Only)**

	Trial*		Study				Total
	Immediate Surgery	Surveillance	Unfit	Small Aneurysm	Awaiting Surgery	Refused Trial	
Patients, n	193	511	397	527	15	100	1743
AAA diameter at baseline, mm, mean (SD)	43 (5)	45 (5)	47 (8)	37 (4)	59 (6)	45 (4)	43 (7)
Duration of follow-up, years, mean (SD)	1.4 (1.3)	2.5 (1.6)	1.5 (0.9)	2.0 (1.0)	1.3 (0.9)	1.5 (1.0)	1.9 (1.3)
AAA measurements per patient, mean (SD)	4.1 (2.9)	7.3 (4.0)	4.2 (2.1)	4.6 (1.9)	3.9 (2.0)	4.4 (2.5)	5.2 (3.1)
Reason for termination of AAA measurement, n (%)							
Surgery	159 (82)	315 (62)	96 (24)	50 (10)	5 (33)	23 (23)	648 (37)
Death	13 (7)	70 (14)	111 (28)	71 (13)	5 (33)	13 (13)	283 (16)
End of follow-up	21 (11)	126 (25)	190 (48)	406 (77)	5 (33)	64 (64)	812 (47)

\*For 367 Trial patients, baseline preceded randomization (by a median of 7 months).

this bias.<sup>10</sup> The aim of the analysis was to characterize average and interpatient variability in AAA expansion to inform surveillance protocols, and to investigate a predefined set of cardiovascular characteristics and risk factors for association with aneurysm growth.

## Methods

Patients with AAA referred to vascular surgeons at 93 UK hospitals were entered into the UK Small Aneurysm Trial or Study.<sup>11</sup> Patients fit for surgery with AAA diameter 40 to 55 mm were invited to participate in the UK Small Aneurysm Trial, which compared the treatment options of immediate surgery and surveillance, the latter with aneurysm repair only when AAA diameter exceeded 55 mm, AAA expansion of 10 mm or more per year was observed, or patients experienced symptoms related to their AAA.<sup>3</sup> All patients were followed up every 3 months (in AAA  $\geq$ 50 mm) or 6 months (in AAA <50 mm) for aneurysm diameter measurement until surgery, death, or end of scheduled follow-up. The maximum anterior-posterior aneurysm diameter was measured by ultrasonography using an Aloka SSD500 with a 3.5-MHz transducer (Keymed). The repeatability of measurement of aneurysm diameter was  $\pm$ 2 mm. All studies had approval from local ethics committees.

A predefined statistical analysis plan was followed, in which each predictor of growth was considered adjusted for age and sex alone and adjusted for age, sex, and other predictors in its risk factor group (smoking, hypertension, atherosclerosis, and cardiovascular). Patients without follow-up AAA diameter measurements were omitted. Variables with very skewed distributions were log transformed to reduce the influence of outliers. The results were checked after the addition of potential confounding variables: diabetes, angina from Rose questionnaire, creatinine, plasma glucose concentration, FEV<sub>1</sub>, source of referral (family practitioner, other clinic, or other), region (based on centers in Edinburgh, Bath, London, Leicester, and Manchester), hospital type (teaching or district general hospital), patient group (trial, refused trial, study unfit, study small AAA, or study waiting for surgery; Table 1), and aspirin use. Due to resource constraints, HDL-cholesterol and cotinine (a stable metabolite of nicotine) were only measured in Trial patients.

## Model Fitting

Random effects linear and quadratic growth models were fitted using Markov Chain Monte Carlo methods in WinBUGS<sup>12</sup> and compared by the Deviance Information Criterion (DIC).<sup>13</sup> Intercept, slope, and curvature terms were assumed to follow a multivariate normal distribution except for the overall model without covariates when the normality assumption on the intercepts was relaxed. Noninformative priors were used. Exponential growth models<sup>6</sup> were not used as they did not fit the data as well. The average linear growth rate reported is the median of the posterior slope distribution. Patients contribute

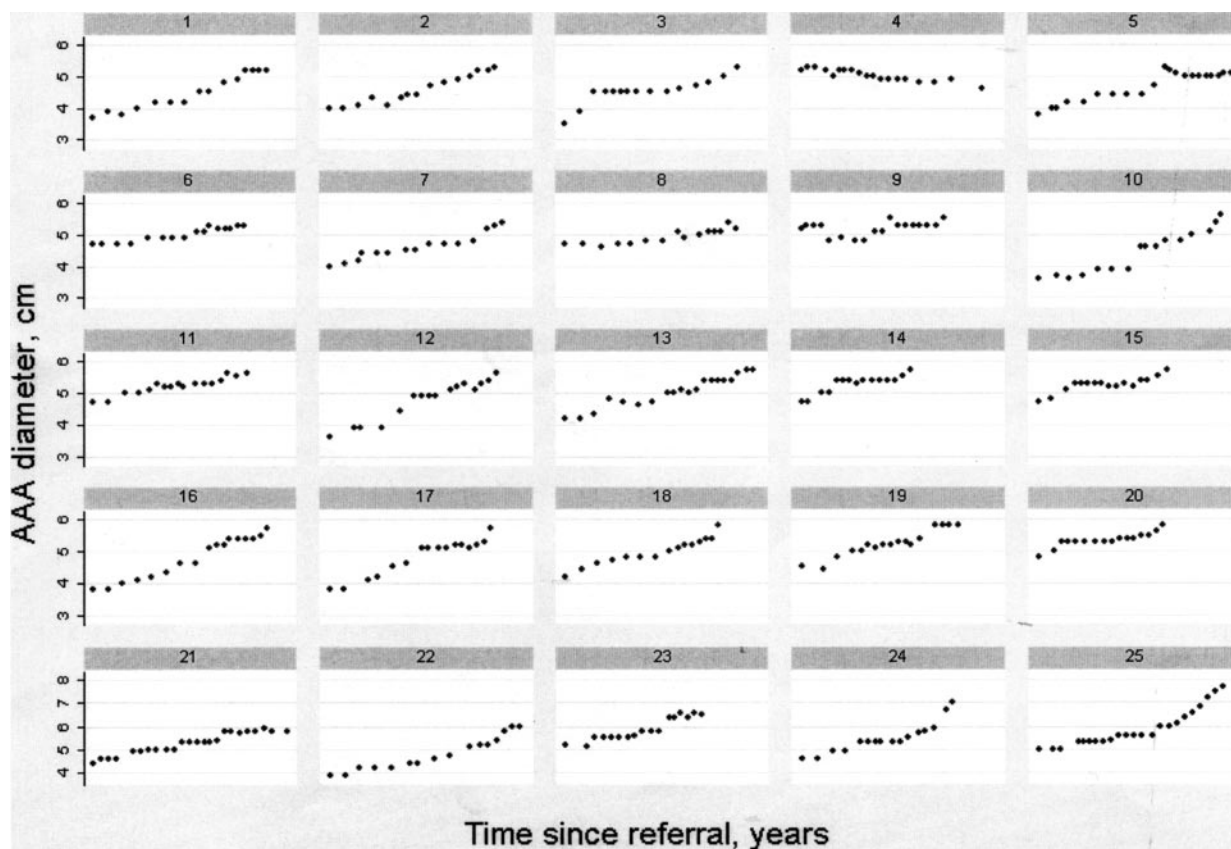
equally to the estimation of this distribution regardless of number of follow-up measurements. The within-subject errors about each individual's regression line were assumed to be drawn from a t-distribution with degrees of freedom estimated from the data. Patient characteristics and risk factors were entered into the model as fixed effects allowed to influence the linear component of growth. The relation between growth and initial diameter was estimated from the relevant covariance term in the model, and was thus not biased by regression to the mean. All parameter estimates reported are medians and 95% credible intervals (CI) of the relevant posterior distributions for a change in continuous variables of approximately one standard deviation. Further details on the statistical modeling are available from <http://www.mrc-bsu.cam.ac.uk/BSUsite/Publications/preslid.shtml>.

## Results

For this study, 2366 patients (1090 Trial and 1276 Study) were recruited. After exclusion of 623 patients with only one AAA measurement, a total of 9125 AAA diameter measurements were taken on 1743 patients between August 1991 and June 1998. The mean age of patients was 69.4 years (range 58 to 77), and 1356 (78%) were male. The mean AAA diameter at baseline, when patients were referred to a vascular surgeon, was 43 mm (standard deviation 7 mm; Table 1). Patients in the surveillance arm of the Trial and Study patients with small aneurysms contributed most measurements to the data set (29% and 30%, respectively; Table 1). Measurement of AAA diameter was terminated more often due to surgery in Trial patients and due to end of follow-up in Study patients (Table 1). The greatest risk of death was observed in unfit Study patients and in the small number awaiting surgery for large AAA (Table 1).

The growth profiles of the 25 patients with longest follow-up are shown in Figure 1. Many patients can be seen to have linear or accelerating expansion, although one patient (No. 4) experienced a steady reduction in AAA diameter. A noticeable feature of some patients is "growth spurts" followed by periods of stasis (patients 3, 10, 12, 15, 17, and 25, for example).

For patients in the surveillance arm of the trial or initially considered unfit for surgery, where diameter measurement series were truncated by surgery (n=411), the mean growth rate calculated by linear regression analysis was 5.6 mm/year, compared with an average linear expansion rate of 4.0 mm/year using the likelihood-based method. The average linear



**Figure 1.** AAA diameter measurements for 25 patients with longest follow-up (the bottom row has a different vertical scale).

expansion rate across all patients was 2.6 mm/year (95% CI 2.5 to 2.6 mm/year), although there was a wide variation between individuals (95% reference range,  $-1.0$  to  $6.1$  mm/year). Negative growth was observed in 6.4% of patients in this cohort. A quadratic model fitted the data substantially better than the linear model (reduction in DIC<sup>13</sup> of 1177), and there was evidence of acceleration in the mean profile of AAA expansion (coefficient on mean quadratic term for time  $0.11$  mm/year,<sup>2</sup> 95% CI 0.07 to 0.16).

AAA expansion was not associated with age or sex but was strongly associated with diameter at baseline (Table 2), reflecting the tendency of AAA expansion to accelerate with time. Self-reported current smokers had significantly faster AAA expansion (by approximately 0.4 mm/year; Table 2), but growth was not significantly associated with lifetime measures of smoking exposure at baseline (pack-years). The association between AAA expansion and current smoking persisted after adjustment for potential confounding factors. In the 689 patients with plasma cotinine measurements, there was no clear evidence for a dose-dependent relationship with AAA expansion.

None of the measures of hypertension considered were significantly associated with AAA expansion (Table 2). Lower ankle/brachial pressure index (ABPI), indicating more severe peripheral arterial disease, was associated with slower AAA growth (Table 2), although the effect was attenuated after adjustment for diabetes and other potential confounding factors ( $0.10$  mm/year per  $0.2$  U, 95% CI  $-0.03$  to  $0.25$ ).

Only 45 (2.6%) patients at baseline and 32 of 871 (3.7%) at 2 years were being prescribed lipid-lowering medication. However, neither total nor HDL plasma cholesterol concentration was associated with AAA growth. Patients with the lowest body mass index tended to have the fastest AAA growth, but none of the atherosclerotic or cardiovascular risk factors except ABPI showed a significant association with AAA growth. Among the potential confounding factors there was slower growth in 75 patients with diabetes (less by  $0.79$  mm/year, 95% CI  $0.27$  to  $1.33$ ).

The probability that the AAA diameter would exceed 55 mm was estimated from the quadratic model without covariates according to baseline AAA diameter and time to rescreening, with lines for 1%, 5%, and 10% of patients exceeding 55 mm shown in Figure 2. 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. Because smoking was strongly associated with AAA expansion, the probability that mean AAA diameter would exceed 55 mm was estimated separately for current smokers and nonsmokers (Figure 3). The probabilities were similar for smokers and nonsmokers, except at the smallest AAA diameters.

## Discussion

The evidence from clinical trials indicates that surveillance is a safe, cost-effective management of small AAAs.<sup>1,3-5,14</sup> A strategy to reduce cardiovascular risk factors of those en-

**TABLE 2. Estimated AAA Growth by Patient Characteristics and Risk Factors**

Factor	No. Patients	Linear Growth Rate, mm/year		
		Average	Difference* (95% CI)	Adjusted Difference† (95% CI)
Age at baseline, years (tertiles)				
58–67	581	2.63	–0.003 per 5 years (–0.14–0.14)	...
68–71	581	2.57		
72–77	581	2.68		
Sex				
Male	1356	2.66	0.03 (–0.36 to 0.26)	...
Female	387	2.53	Reference	
AAA diameter at baseline, mm (tertiles)				
28–39	653	1.85	1.29 per 10 mm (1.05–1.53)	...
40–45	518	2.69		
46–85	572	3.50		
Group: Smoking				
Smoking status				
Never	105	2.53	0.004 (–0.49–0.43)	–0.04 (–0.56–0.48)
Ex	971	2.51	Reference	Reference
Current	614	2.83	0.42 (0.17–0.68)	0.38 (0.10–0.65)
Pack-years (tertiles)				
0–25	553	2.65	0.05 per 30 pack-years (–0.07–0.17)	0.004 per 30 pack-years (–0.14–0.13)
26–48	548	2.57		
49–210	529	2.67		
Plasma cotinine concentration‡, ng/mL				
<10	388	2.99	0.13 per 3.6 log units (–0.05–0.31)§	
10–500	83	3.54		
>500	218	3.04		
Group: Hypertension				
History of hypertension				
No	723	2.58	Reference	Reference
Yes	959	2.70	0.08 (–0.16–0.33)	0.26 (–0.03–0.55)
Systolic blood pressure at baseline (tertiles), mm Hg				
70–142	573	2.53	–0.06 per 30 mm Hg (–0.18–0.08)	–0.07 per 30 mm Hg (–0.22–0.09)
143–170	638	2.82		
171–250	465	2.55		
Antihypertensive medication				
No	765	2.65	Reference	Reference
Yes	932	2.61	–0.11 (–0.33–0.12)	–0.23 (–0.50–0.07)
Group: Atherosclerosis risk factors and measures of disease				
ABPI (tertiles)				
0–0.85	553	2.35	0.20 per 0.2 units (0.07–0.33)	0.22 per 0.2 units (0.10–0.34)
0.86–1.02	555	2.68		
1.03–1.81	550	2.74		
IHD from ECG				
Unlikely	878	2.54	Reference	Reference
Possible	469	2.76	0.17 (–0.15–0.50)	0.19 (–0.10–0.49)
Probable	265	2.46	–0.12 (–0.52–0.29)	–0.06 (–0.48–0.33)
BMI, kg/m <sup>2</sup> (tertiles)				
15.0–23.2	552	2.70	–0.08 per 3.8 kg/m <sup>2</sup> (–0.21–0.06)	–0.09 per 3.8 kg/m <sup>2</sup> (–0.23–0.05)
23.3–26.4	552	2.57		
26.5–42.1	551	2.62		
Total cholesterol, mmol/L (tertiles)				
1.6–5.6	519	2.64	0.02 per 1.2 mmol/L (–0.11–0.16)	0.07 per 1.2 mmol/L (–0.07–0.21)
5.7–6.6	527	2.55		
6.7–16.9	510	2.59		
WCC, 10 <sup>9</sup> /L (tertiles)				
1.2–6.7	563	2.54	0.07 per 0.3 log units (–0.07–0.23)	0.11 per 0.3 log units (–0.04–0.25)
6.8–8.5	575	2.71		
8.6–74	531	2.51		

(continued)

TABLE 2. (Continued)

Factor	No. Patients	Linear Growth Rate, mm/year		
		Average	Difference* (95% CI)	Adjusted Difference† (95% CI)
Triglycerides, mmol/L (tertiles)				
0.5–1.4	473	2.56	–0.03 per 0.5 log units (–0.16–0.11)	–0.04 per 0.5 log units (–0.18–0.11)
1.5–2.3	464	2.66		
2.4–12.9	435	2.54		
HDL cholesterol,‡ mmol/L (tertiles)				
0.44–0.94	230	3.06	0.14 per 0.4 mmol/L (–0.05–0.34)	0.11 per 0.4 mmol/L (–0.11–0.32)
0.95–1.23	232	3.02		
1.24–4.55	227	3.04		

CI indicates credible interval; IHD, ischemic heart disease; ECG, electrocardiogram; BMI, body mass index; WCC, white cell count; and HDL, high-density lipoprotein.

\*Adjusted for age, sex, baseline diameter, and curvature in growth pattern.

†Adjusted for age, sex, baseline diameter, curvature in growth pattern, and other variables in group except those available on Trial patients only.

‡Available on Trial patients only.

§No adjusted figure presented, because smoking habit was an adjustment variable.

rolled in surveillance programs is likely to improve patient survival, but we show that, with the exception of smoking cessation, such a strategy is unlikely to slow AAA growth. We also provide a rational basis for determining appropriate rescreening intervals for those enrolled in surveillance programs.

The average rate of AAA expansion, 2.6 mm/year, is lower than that reported in studies using linear regression modeling.<sup>3,15,16</sup> The upward bias imposed by using linear regression modeling to calculate AAA growth on a series of AAA diameter measurements truncated by surgery above the 55-mm threshold was demonstrated clearly. Our model suggested that AAAs of 50 mm in diameter grow around 70% faster than those of 40 mm, a less dramatic difference than the more than doubling of growth rates over the same range reported by a previous study that used similar methods to ours.<sup>6</sup>

Previous studies have identified that AAAs appear to expand faster in current smokers, but most of these studies have been too small to quantify the effect reliably.<sup>15–17</sup> We show that smoking increases AAA growth rates by 15% to 20%. Although highly significant, this is a small effect and insufficient to warrant the recommendation of different screening intervals for smokers (Figure 3). There was little

evidence, from cotinine analyses, of a dose-response effect, but the more limited cohort (about 40% of the total) may have been too small to investigate this reliably.

Diabetes, the only other cardiovascular risk factor to demonstrate a significant association with AAA growth, had a negative effect: Patients with diabetes had a crude reduction of over 30%. ABPI is a measure of atherosclerotic burden,<sup>18,19</sup> and this also was inversely associated with AAA growth, with growth rates reducing by 0.2 mm/year for each fall of 0.2 in ABPI. Patients with most atherosclerotic burden had the slowest AAA growth. There was no evidence that blood pressure or lipids were associated with AAA growth. These data suggest that atherosclerosis has a minimal role in the continuing expansion that characterizes the natural history of AAA. This accords with recent findings for thoracic aortic dilatation, where atherosclerosis also appeared to play but a minor role.<sup>20</sup>

Our findings may have biological implications. Proteolysis, with destruction of structural connective tissue, and inflammation are the pathological hallmarks of AAA.<sup>19</sup> Diabetes is associated with modification and glycation of collagens, resistance to metalloproteinase digestion, and decreased synthesis and activity of metalloproteinases.<sup>21</sup> The observa-

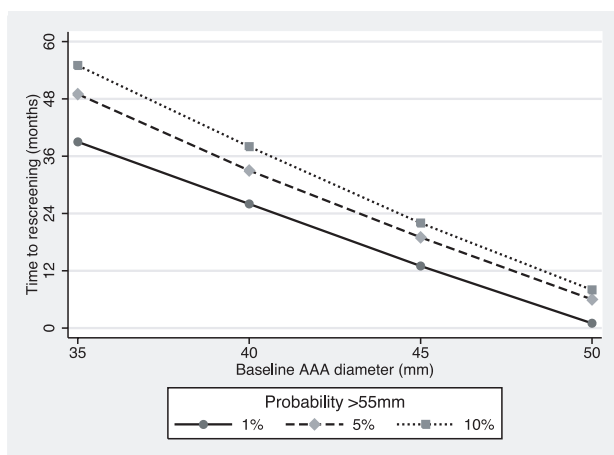


Figure 2. Probability of an individual's AAA diameter exceeding 55 mm at rescreening by time since referral to vascular surgeon.

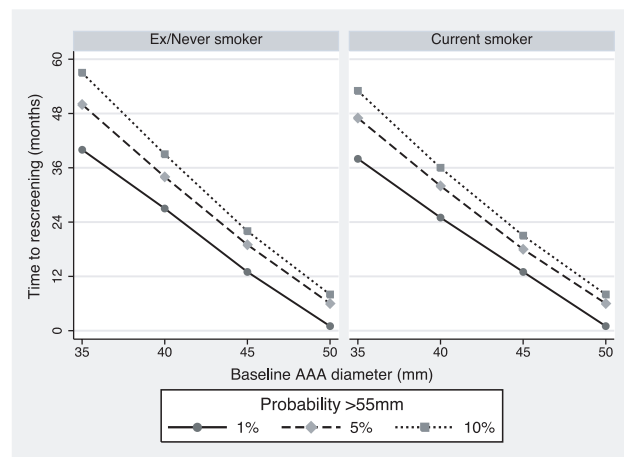


Figure 3. Probability of an individual's AAA diameter exceeding 55 mm at rescreening by time since referral to vascular surgeon according to baseline self-reported smoking status.

tion that AAA expansion is slower in patients with diabetes would support the hypothesis that smoking accelerates AAA expansion by increasing the degradation of aortic connective tissue rather than by promoting atherosclerosis.

The long-term outcome of aneurysm exclusion, either by endovascular repair or open, is likely to be affected by changes in aortic dimensions after grafting. An endovascular device or Dacron bypass are fitted exactly to the aortic size, but if aortic size changes with time, particularly at the anastomosis sites, then late leaks and rupture can occur.<sup>5,22</sup> It is important to apply the findings of this study not only to the surveillance of small aneurysms, but also postoperative follow-up, particularly after endovascular repair. Patients need to appreciate that the durability of AAA repair could be threatened if they continue to smoke and the dilatation process continues.

Screening for AAA and continued surveillance incur costs to health providers and some anxiety for patients.<sup>14</sup> Both can be minimized by using the maximum interval between surveillance visits that does not compromise patient safety. Above the 55-mm threshold, the risk of rupture increases substantially and intervention to exclude the aneurysm must be considered.<sup>23,24</sup> Therefore, we chose the criterion that less than 1% of patients would have an aneurysm that exceeded the 55-mm threshold at the subsequent visit, which provides a high safety margin, particularly because the pilot data for the MASS trial indicated that surveillance is safe using a higher 60-mm threshold in men.<sup>6</sup> This criterion allows time for attendance reminder in cases of noncompliance. Using this criterion, patients with AAA of  $\leq 40$ -mm diameter would not need rescreening for a further 24 months. Patients with AAA 41 to 45 mm in diameter could be safely returned for surveillance at 12-month intervals. Further, screening in a specific month of the year may enhance compliance. Although surveillance at 6-month intervals for those with AAA  $\geq 46$  mm in diameter has proved safe in practice,<sup>4</sup> when the diameter exceeds 50 mm, surveillance at 3-month intervals would have a higher safety margin (Figure 2). The different studies<sup>6,7,9,25</sup> evaluating time to reach a threshold diameter have used different populations, thresholds, and methodologies, providing variable results: Pooling data in a metaanalysis could resolve these differences and improve the evidence base for screening interval guidelines.

Although this study has been able to offer a scientific basis for screening intervals in surveillance programs, it has been less successful in identifying strategies to reduce AAA expansion rates. Smoking cessation must be encouraged, because smoking was the only modifiable factor associated with AAA expansion.

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