Aortic Aneurysm Diameter and Risk of Cardiovascular Mortality

Anthony R. Brady, F. Gerald R. Fowkes, Simon G. Thompson, Janet T. Powell

Abstract—After successful surgical repair of an abdominal aortic aneurysm, patients have for many years an increased risk of death from cardiovascular causes. We have tested the hypothesis that for patients with abdominal aortic aneurysms, the risk of nonaneurysm cardiovascular mortality before and after surgery increased with aneurysm diameter. Records of aneurysm repair or rupture and mortality were available from 2305 patients entered into the UK Small Aneurysm Trial and Study. Two hundred fifty-nine deaths occurred before aneurysm repair or rupture (mean follow-up 1.7 years), and 325 occurred after surgical repair (mean follow-up 3.6 years). The risk of nonaneurysm-related mortality and cardiovascular death before and after surgery increased with aneurysm diameter at baseline, even after adjustment for other known risk factors. The adjusted hazard ratios for cardiovascular mortality, per standard deviation (0.8-cm) increase in aneurysm diameter, were 1.34 (95% CI 1.01 to 1.79) and 1.31 (95% CI 1.06 to 1.63) in the periods before aneurysm repair or rupture and after aneurysm repair, respectively. The significant association between aortic diameter and cardiovascular mortality, excluding aneurysm-related deaths, suggests that aneurysm diameter is an independent marker of cardiovascular disease risk. (Arterioscler Thromb Vasc Biol. 2001;21:1203-1207.)

Key Words: aneurysm ■ aorta ■ survival

The presence of an abdominal aortic aneurysm (AAA) is a common finding in men aged >65 years. Surgical repair is recommended for large asymptomatic AAAs (>5.5 cm in diameter) but not for smaller aneurysms.1 The case fatality associated with elective surgical repair is considerable, ≈5% in prospective studies.1,2 There are numerous reports of mortality related to elective surgery, with a recent overview identifying 72 publications representing 37 654 patients from 1985 to 1996.2 In comparison, far fewer studies have investigated late survival after AAA repair.

Studies of late survival are often complicated by the unavailability of comprehensive follow-up data. Nevertheless, several recent studies have indicated that even after patients experience a full recovery from surgical repair, their survival appears to be worse than that in an age- and sex-matched population.3–6 The population-based study from the Mayo clinic reported a 5-year survival of only 60% after repair of AAAs >5 cm in diameter compared with the expected survival of 77% of other age- and sex-matched community residents (P<0.01).3 The majority of late deaths were from cardiovascular causes. The difference between the survival of patients undergoing surgery for small aneurysms (<5 cm in diameter) and other community residents was less marked and only of borderline significance (P=0.05).3 In a recent French study, the 5-year survival after aortic repair was reported as 72% compared with 90% in the age- and sex-matched population.5 Similarly, a study in Berkshire, England, showed that the 5-year survival of patients undergoing surveillance with AAAs <4 cm and 4 to 5.5 cm in diameter was 62% and 45%, respectively, compared with 80% in an age- and sex-matched population.7 Again, the majority of late deaths were from cardiovascular causes.7 Only an earlier American study, with a policy of selective coronary artery revascularization, and a recent Australian study have shown 5-year survival for AAA patients to be equivalent to age- and sex-matched populations.8,9 In the Australian study, however, women with AAAs still experienced worse 5-year survival rates than did the age-matched controls.9 These studies suggest that the presence of small AAAs may be a marker for risk of death from cardiovascular diseases in general rather than specifically from aneurysm rupture. We can investigate this hypothesis further by looking for a dose-response relationship in patients with AAAs according to aneurysm diameter. We have used the prospective data from the UK Small Aneurysm Trial and Study to test the hypothesis that for AAA patients, the risk of nonaneurysm cardiovascular mortality increased with aneurysm diameter before rupture and repair and after surgery.

Methods

In the UK Small Aneurysm Trial and Study,10 2305 patients with abdominal aortic aneurysm were recruited and followed up. These patients, aged 58 to 78 years, had been referred to participating surgeons at 93 UK hospitals between 1991 and 1995. From the UK Small Aneurysm Trial, there were 1090 individuals (referred to in the present study as trial patients) with asymptomatic AAA who

Received January 17, 2001; revision accepted January 17, 2001.
From MRC Clinical Trials Unit (A.R.B.), London, UK; the Department of Public Health Sciences (F.G.R.F.), University of Edinburgh, UK; MRC Biostatistics Unit (S.G.T.), Cambridge, UK; and the University Hospitals of Coventry and Warwickshire (J.T.P.), Coventry, UK.
Correspondence to Mr A.R. Brady, MRC Clinical Trials Unit, 222 Euston Rd, London NW1 2DA, UK. E-mail abrady@ctu.mrc.ac.uk
© 2001 American Heart Association, Inc.
Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org

1203
are available for the present investigation. In addition, study patients (n=1215) were those excluded from the randomized trial for the following reasons: unfit (n=443), AAA diameter outside 4.0- to 5.5-cm range (n=631), AAA tender (n=11), or refusal (n=130). Copies of death certificates were obtained from the Office of National Statistics, where all patients in the trial and study were registered. The underlying cause of death was determined by 2 separate assessors working with an agreed protocol. Five trained trial coordinators performed the baseline assessment, including demographic details, previous medical history, smoking history, clinical examination (including blood pressure, height, weight, and lung function), blood tests, ECG at rest, and aneurysm diameter. Patients with aneurysms <5 cm in diameter were invited to attend follow-up appointments every 6 months; those with larger aneurysms were invited to attend every 3 months. The maximum anterior-posterior aneurysm diameter was measured by ultrasonography with use of an Aloka SSD500 with 3.5-MHz transducer (Keymed). The interobserver repeatability of measurement of aneurysm diameter was ±0.2 cm. Approval for the trial and the study was obtained from local research ethics committees.

The relationship between aneurysm diameter and survival was considered in 2 time periods: (1) the surveillance period before surgical intervention or aneurysm rupture and (2) the long-term postoperative period after AAA surgery. For the purposes of analysis, the surveillance period extended from initial assessment until aneurysm repair/rupture or end of active follow-up. The postoperative period extended from surgery until notification of deaths from the Office of National Statistics was discontinued (end of November 1998 for study patients and end of June 1999 for trial patients).

Univariate estimates of survival were calculated by using the Kaplan-Meier method according to tertiles of AAA diameter. Cox proportional hazards models were used to estimate adjusted hazard ratios (HRs) for the effect of baseline aneurysm diameter on survival. All Cox models included adjustments for “design” effects: source of referral (eg, general practitioner, hospital clinic, or other), region (Scotland, London, Leicester, Manchester, or Bath), hospital type (teaching or district general), and study group (trial group, unfit group, small aneurysm group, group scheduled for surgery, and group who refused trial). Further adjustments were made for the following baseline measurements: age, sex, ankle/brachial pressure index, angina (from Rose questionnaire), ischemic heart disease on baseline ECG, smoking status, total serum cholesterol, diabetes, systolic and diastolic blood pressure, body mass index, white cell count, blood creatinine, and forced expiratory volume in 1 second. Aneurysm diameter, white cell count, and creatinine were logarithmically transformed because of right skew in their original distributions. Nonlinearity in the association between aneurysm diameter and survival was investigated by comparing a first-degree fractional polynomial with a linear model. Nonproportional hazards for aneurysm diameter were investigated by a test for nonzero slope in a regression of the scaled Schoenfeld residuals on time. For analysis of cardiovascular mortality, patients were censored at their times of death from noncardiovascular causes.

### Results

#### Demographic Details

The characteristics of the trial and study patients are shown in Table 1. Study patients, particularly the unfit or those who refused the trial, were older, on average, than the trial patients. Women were underrepresented in the trial, mainly because they were more likely to have smaller aneurysms (<4.0 cm in diameter). Some trial patients (n=141) had baseline aneurysm diameter measurements of <4.0 cm, although they were later randomized when their aneurysms grew into the 4.0- to 5.5-cm range. The death rate of unfit study patients was noticeably higher than that of other patients before and after surgery. The majority of the postoperative follow-up was observed in the trial patients, reflecting the much larger proportion of these patients that underwent AAA repair.

#### Surveillance Period Before Surgery or Rupture

Patients (n=2305) were followed up for a mean of 1.7 years in the surveillance period before aneurysm repair or rupture. There were 259 deaths; 175 (68%) were from cardiovascular causes (Table 2). The 40 deaths from aneurysm rupture were excluded from subsequent analyses. Median aneurysm diameter at baseline was 4.4 cm (range 3.0 to 9.7 cm). There was

<table>
<thead>
<tr>
<th>TABLE 1. Demographic Details at Baseline and Mortality of UK Small Aneurysm Trial and Study Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, N</td>
</tr>
<tr>
<td>Median age, y (range)</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
</tr>
<tr>
<td>Median AAA diameter, cm (range)</td>
</tr>
<tr>
<td>Died in surveillance period/person-years of observation, n (rate per 100 person-years)</td>
</tr>
<tr>
<td>AAA repair, n (%)</td>
</tr>
<tr>
<td>Died in postoperative period/person-years of observation, n (rate per 100 person-years)</td>
</tr>
</tbody>
</table>

#### TABLE 2. Number of Deaths by Cause

<table>
<thead>
<tr>
<th>Cause</th>
<th>Surveillance Period</th>
<th>Postoperative Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>48</td>
<td>62</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>175</td>
<td>221</td>
</tr>
<tr>
<td>Acute MI</td>
<td>51</td>
<td>60</td>
</tr>
<tr>
<td>AAA</td>
<td>40*</td>
<td>84†</td>
</tr>
<tr>
<td>Chronic IHD</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>Stroke</td>
<td>23</td>
<td>7</td>
</tr>
<tr>
<td>Other cardiovascular</td>
<td>35</td>
<td>39</td>
</tr>
<tr>
<td>Other</td>
<td>34</td>
<td>40</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total‡</td>
<td>259</td>
<td>325</td>
</tr>
</tbody>
</table>

*MI indicates myocardial infarction; IHD, ischemic heart disease.
†Deaths within 30 days of AAA repair.
‡Total = cancer + cardiovascular + other + unknown.
a clear association between aneurysm diameter and survival (Figure 1). For all-cause mortality, the HR for a 1-SD increase in logarithmic aneurysm diameter (corresponding to 18% of original diameter, or ≈0.8 cm) was 1.32 (Table 3). The HR was higher for patients enrolled in the trial (HR 2.25, 95% CI 1.57 to 3.23) than for those in the study (HR 1.12, 95% CI 0.92 to 1.37; \(P<0.001\) by test of interaction). This interaction appeared to be caused by unfit study patients, for whom little evidence of an association between aneurysm diameter and survival could be found (HR 0.96, 95% CI 0.75 to 1.23). The HR in the remaining study patients was 1.70 (95% CI 1.12 to 2.57). There was little evidence of nonlinearity in the relationship between logarithmic aneurysm diameter and survival (\(P=0.12\)) or nonproportional hazards over time (\(P=0.18\)).

Aneurysm diameter was weakly associated with sex (median was 4.4 cm in men compared with 4.2 cm in women) but was not correlated with other baseline measurements. Consequently, adjustment for baseline measures in the Cox model made little difference to the estimated effect for aneurysm diameter (HR 1.31, Table 3).

The relative hazard of cardiovascular death per SD increase in logarithmic aneurysm diameter was 1.35 when unadjusted and 1.34 when adjusted for all baseline measures (Table 3).

### Postoperative Period

Aneurysm repair was performed in 1139 patients. Mean follow-up time for mortality after repair was 3.6 years. There were 325 deaths; 221 (68%) were from cardiovascular causes (Table 2). Median aneurysm diameter immediately before surgery was 5.1 cm (range 3.2 to 9.2 cm). Five-year survival was 69% (95% CI 66% to 72%). The association between aneurysm diameter and survival (Figure 2) corresponds to a marginally significant HR of 1.12 for a 1 SD increase in logarithmic aneurysm diameter (Table 3). This was similar in trial and study patients (\(P=0.58\) by test of interaction). There was no evidence of nonlinearity in the relationship between logarithmic aneurysm diameter and survival (\(P=1.00\)) or nonproportional hazards over time (\(P=0.61\)).

Aneurysm diameter at surgery was weakly associated with sex (median 5.1 cm in men and 4.9 cm in women) and was correlated with age at surgery (by Spearman rank correlation, \(r=0.11\)) and body mass index (\(r=0.13\)). Adjustment for baseline measures in the Cox model increased the estimated effect for aneurysm diameter (HR 1.26, Table 3). After exclusion of 84 patients who died within 30 days of AAA repair, the adjusted HR was 1.20 (95% CI 0.99 to 1.46).

Therefore, the effect of aneurysm diameter on mortality in the postoperative period was not merely a result of early surgical deaths.

### TABLE 3. Survival by Aneurysm Diameter in Surveillance and Postoperative Periods

<table>
<thead>
<tr>
<th>Period Tertiles of AAA Diameter, cm</th>
<th>Patients, n (Patient-Years of Follow-Up)</th>
<th>Total deaths,* n (Estimated 3-y Survival)</th>
<th>All Cause</th>
<th>Cardiovascular</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>HR† (95% CI)</td>
<td>Adjusted HR‡ (95% CI)</td>
</tr>
<tr>
<td>Surveillance</td>
<td></td>
<td></td>
<td>1.32 (1.12 to 1.55)</td>
<td>1.31 (1.05 to 1.63)</td>
</tr>
<tr>
<td>3.0–4.1</td>
<td>851 (1994)</td>
<td>83 (89%)</td>
<td>1.35 (1.10 to 1.66)</td>
<td>1.34 (1.01 to 1.79)</td>
</tr>
<tr>
<td>4.2–4.7</td>
<td>779 (1328)</td>
<td>83 (83%)</td>
<td>1.10 (0.99 to 1.25)</td>
<td>1.26 (1.06 to 1.48)</td>
</tr>
<tr>
<td>4.8–9.7</td>
<td>675 (664)</td>
<td>53 (76%)</td>
<td>1.13 (0.99 to 1.30)</td>
<td>1.31 (1.06 to 1.63)</td>
</tr>
<tr>
<td>Postoperative</td>
<td></td>
<td></td>
<td>1.12 (0.99 to 1.25)</td>
<td>1.26 (1.06 to 1.48)</td>
</tr>
<tr>
<td>3.2–4.7</td>
<td>417 (1678)</td>
<td>119 (82%)</td>
<td>1.13 (0.99 to 1.30)</td>
<td>1.31 (1.06 to 1.63)</td>
</tr>
<tr>
<td>4.8–5.4</td>
<td>382 (1394)</td>
<td>109 (78%)</td>
<td>1.13 (0.99 to 1.30)</td>
<td>1.31 (1.06 to 1.63)</td>
</tr>
<tr>
<td>5.5–9.2</td>
<td>340 (1012)</td>
<td>97 (75%)</td>
<td>1.13 (0.99 to 1.30)</td>
<td>1.31 (1.06 to 1.63)</td>
</tr>
</tbody>
</table>

*Excluding ruptures in surveillance period.
†Per SD increase in logarithmic aneurysm diameter, adjusted for source of referral, region, hospital type, and study group.
‡Adjusted in addition for age, sex, ankle/brachial pressure index, angina, evidence of ischemic heart disease from ECG, smoking status, plasma cholesterol, diabetes, systolic and diastolic blood pressure, body mass index, white cell count, blood creatinine, and forced expiratory volume in 1 second.
The association between aneurysm diameter and cardiovascular mortality was similar to that for all-cause mortality. The relative hazard of cardiovascular death per SD increase in logarithmic aneurysm diameter was 1.13 when unadjusted and 1.31 when adjusted for all baseline measures (Table 3).

Discussion
This is the first large prospective study to report that AAA diameter is an independent and important predictor of nonaneurysm cardiovascular and all-cause mortality before aneurysm surgery or rupture and after successful surgical repair of the aneurysm. This suggests that AAA diameter is a marker of progressive cardiovascular disease. The findings were robust, even after adjustment for known cardiovascular risk factors (including smoking, the presence of ischemic changes on resting ECG, ankle/brachial pressure index, blood pressure, and plasma cholesterol concentration) and exclusion of the surgical deaths. The finding that AAA diameter is an important predictor of mortality before aneurysm rupture or repair is supported by the previous small prospective study from Berkshire.7 An association between AAA diameter and mortality after aneurysm repair was also identified in the French multicenter study (Association for Academic Research in Vascular Surgery [AURC]).6

There is considerable literature on predictors of survival for patients with AAA. Several previous studies have identified renal function as having prognostic significance in these patients.6,8,14,15 There has been much discussion about whether myocardial revascularization should precede AAA repair and whether coronary artery disease predicts early and late survival in AAA patients,6,8,14,16,17 and the data are not consistent. Very recently, we have reported that the ankle/brachial pressure index is a powerful predictor of survival for AAA patients.18 The ankle/brachial pressure index has been shown to indicate the extent of generalized atherosclerosis in population studies.19 Patients presenting with AAA and having an ankle/brachial pressure index of <0.9 should be targeted for modification of cardiovascular risk factors, including lifestyle changes and cholesterol reduction.

Certainly, the proposition that aneurysms are caused by atherosclerosis20 might explain the high proportion (68%) of deaths from cardiovascular causes. If aneurysms are caused by atherosclerosis, one might anticipate that increasing aneurysm diameter would be an index of atherosclerotic burden. However, if anything, adjustment for atherosclerotic risk factors (smoking, cholesterol, diabetes, and blood pressure) and other known cardiovascular indices, including ECG findings and ankle/brachial pressure index, strengthens the association between aneurysm diameter and cardiovascular mortality. This suggests that other, nonatherosclerotic mechanisms may underlie the association between aneurysm diameter and survival. For instance, circulating interleukin-6 (IL-6) has recently been confirmed as a cardiovascular risk factor.21 Aortic aneurysms are an important source of this cytokine, and the secretion of IL-6 increases with aortic diameter.22 The aneurysm wall could be a source of IL-6 and other circulating factors that influence myocardial function, inflammation, or thrombosis.

The principal limitation of the present study is the ascertainment of cause of death, because a postmortem examination was performed for only 30% of the deaths. Therefore, the deaths due to AAA rupture may have been underestimated: the risk of rupture increases with AAA diameter.23 However, the association between AAA diameter and cardiovascular mortality before surgery was strongest for trial patients, in whom the risk of cardiovascular death increased >2-fold for each 0.8-cm increase in aneurysm diameter. These patients were followed very closely, making unreported ruptures unlikely. Therefore, we do not think that unreported ruptures explain the association between AAA diameter and mortality. The strengths of the present study include its size and high quality of prospective data, obtained by dedicated trial coordinators. The present study also benefited from the British system of tracing and reporting deaths, which avoids patients being lost to follow-up.

The association between AAA diameter and survival, which we report, may have more importance for elucidation of the mechanism underlying the association than for patient management, particularly because the HRs in the surveillance and postoperative period were very similar. Current evidence-based guidelines suggest that aneurysms >5.5 cm in diameter should be repaired, to minimize the risk of aneurysm rupture. Because of the clear association between smoking and aneurysm rupture,23 all patients should be counseled to stop smoking. Many of the patients in the present study were continuing smokers. In vascular surgical clinics, measurement of ankle/brachial pressure index may provide a more useful guide to management of cardiovascular risk factors than aortic diameter, at least until we understand the mechanisms underlying the association between aneurysm diameter and survival.

Acknowledgments
This study was supported by the BUPA Foundation. The UK Small Aneurysm Trial and Study were supported by the Medical Research Council and the British Heart Foundation.

References


Aortic Aneurysm Diameter and Risk of Cardiovascular Mortality
Anthony R. Brady, F. Gerald R. Fowkes, Simon G. Thompson and Janet T. Powell

doi: 10.1161/hq0701.091999
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/21/7/1203

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/