LONG-TERM OUTCOMES OF IMMEDIATE REPAIR COMPARED WITH SURVEILLANCE OF SMALL ABDOMINAL AORTIC ANEURYSMS

THE UNITED KINGDOM SMALL ANEURYSM TRIAL PARTICIPANTS*

ABSTRACT

Background Two clinical trials, one British and one American, have shown that early, prophylactic elective surgery does not improve five-year survival among patients with small abdominal aortic aneurysms. We report long-term outcomes in the United Kingdom Small Aneurysm Trial.

Methods We randomly assigned 1090 patients, 60 to 75 years of age, with small abdominal aortic aneurysms (diameter, 4.0 to 5.5 cm) to one of two groups: 563 were assigned to undergo early elective surgery, and 527 were assigned to undergo surveillance by ultrasonography. Patients were followed in the trial until June 1998 and thereafter until August 2001; the mean duration of follow-up was 8 years (range, 6 to 10).

Results The mean duration of survival was 6.5 years among patients in the surveillance group, as compared with 6.7 years among patients in the early-surgery group (P = 0.29). The adjusted hazard ratio for death from any cause in the early-surgery group as compared with the surveillance group was 0.83 (95 percent confidence interval, 0.69 to 1.00; P = 0.05). The 30-day operative mortality in the early-surgery group (5.5 percent) led to an early disadvantage in terms of survival. The survival curves crossed at three years, and at eight years, mortality in the early-surgery group was 7.2 percentage points lower than that in the surveillance group (P = 0.03). There was no evidence that age, sex, or the initial size of the aneurysm modified the hazard ratio or that delayed surgery in the surveillance group increased 30-day postoperative mortality. Death was attributable to a ruptured aneurysm in 19 of the 411 men who died (5 percent) and in 12 of the 85 women who died (14 percent) (P = 0.001). The rate of early cessation of smoking was higher in the early-surgery group than in the surveillance group.

Conclusions Among patients with a small abdominal aortic aneurysm, we found no long-term difference in mean survival between the early-surgery and surveillance groups, although after eight years, total mortality was lower in the early-surgery group. This difference may be attributed in part to beneficial changes in lifestyle adopted by members of the early-surgery group. (N Engl J Med 2002;346:1445-52.)

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Rupture of an abdominal aortic aneurysm is associated with a high fatality rate and is an important cause of sudden death. Low rates of rupture of small abdominal aortic aneurysm were observed among patients enrolled in the United Kingdom Small Aneurysm Trial and the Aneurysm Detection and Management Trial in the United States — 1.0 percent and 0.6 percent per year, respectively.1,2 These low rates of rupture may explain in part why these trials did not demonstrate a five-year survival benefit for patients who were randomly assigned to undergo early elective surgery. Operative mortality rates of 5.8 percent in the British trial and 2.7 percent in the U.S. trial also contributed to the finding of a lack of benefit from early surgery. Moreover, the British trial demonstrated that a policy of early surgery was more costly than a policy of ultrasonographic surveillance.3

When active follow-up in the United Kingdom Small Aneurysm Trial was closed in June 1998, only 305 of the 1090 patients had died (28 percent). Therefore, in 1998, we decided to undertake a further analysis when 100 surviving patients would have reached nine years of follow-up and approximately half the original cohort would have died. Such an analysis could also illuminate some of the late complications of aneurysmal disease.4,5 Here we report the results of this long-term survival analysis.

METHODS

Study Patients

The study patients and methods have been described previously.6 Briefly, between September 1991 and October 1995, 1276 patients 60 to 76 years of age from 93 hospitals in the United Kingdom were identified as having an asymptomatic infrarenal abdominal aortic aneurysm of 4.0 to 5.5 cm in diameter. Written informed consent for random assignment to either early elective surgery or a period of ultrasonographic surveillance was obtained for 1090 of these patients.

Surgery and Follow-up

Patients in the surveillance group were offered surgery when the diameter of the aneurysm exceeded 5.5 cm, when the aneurysm expanded by more than 1 cm per year, when the aneurysm became

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*The participants in the United Kingdom Small Aneurysm Trial are listed in the Appendix.
tender or symptomatic, or when repair of a proximal or iliac aneurysm was scheduled. The patients' records at the Office of National Statistics remained flagged to enable continued reporting of the date, place, and cause of death. Patients were followed individually to ascertain whether they had undergone an emergency or elective repair of an abdominal aortic aneurysm (by open, endovascular, or laparoscopic surgery) between July 1998 and August 2001.

**Statistical Analysis**

Analyses were performed as previously described, except that the presence or absence of nonproportional hazards was assessed by a test for a nonzero regression slope of scaled Schoenfeld residuals plotted against the logarithm of the time. We used a log-rank test to compare the Kaplan-Meier curves for the duration of survival from randomization. We used Cox proportional-hazards regression to estimate hazard ratios and to adjust for sex, smoking status, initial diameter of the aneurysm, mean of left and right ankle-brachial pressure indexes, forced expiratory volume in one second (FEV₁), use or nonuse of aspirin, source of referral, regional center, and type of hospital (teaching or district). Tests of interaction in the Cox regression analyses were used to assess whether age, sex, or initial diameter of the aneurysm affected the overall hazard ratio. Rupture rates were calculated on the basis of the time at risk until the repair of the aneurysm or death.

We also analyzed, in a subgroup enrolled during the first 18 months of the trial, whether smoking status had changed during the first 12 months after randomization; this analysis involved the comparison of the plasma cotinine concentration measured after 1 year of follow-up (available only for patients enrolled early in the trial) with that measured at the time of randomization. Patients were classified as smokers if the cotinine concentration was higher than 0 nmol per liter and as nonsmokers otherwise, with no intermediate category for passive smoking. Logistic regression was used to determine the relation between smoking status at one year and repair of an abdominal aortic aneurysm, with adjustment for smoking status at base line as well as for the variables listed above. All P values are two-tailed.

**RESULTS**

**Study Patients**

Of the 1090 patients (902 men and 188 women) who consented to undergo randomization, 563 (52 percent) were assigned to undergo early elective surgery and 527 (48 percent) to undergo ultrasonographic surveillance. The mean (±SD) age of the patients assigned to early elective surgery (468 men and 95 women) was 69.3±4.4 years; the mean initial diameter of the aneurysm was 4.63±0.40 cm. The mean age of the patients assigned to ultrasonographic surveillance (434 men and 93 women) was 69.2±4.4 years; the mean initial diameter of the aneurysm was 4.61±0.37 cm.

**Aneurysm Repair**

By the end of the trial (June 30, 1998), 520 of the patients in the early-surgery group (92 percent) and 327 of those in the surveillance group (62 percent) had undergone surgical repair of an abdominal aortic aneurysm (Fig. 1). A total of 289 patients in the surveillance group (55 percent) had undergone surgery according to protocol; in the other 38 patients, the repair represented a protocol violation.

By the end of August 2001, an additional 6 patients in the early-surgery group (1 percent) and 62 in the surveillance group (12 percent) had undergone repair of an aneurysm, including one ruptured abdominal aortic aneurysm (Fig. 1). Only 4 of 140 patients who were alive with unrepaired aneurysms as of June 1998 (3 percent) were lost to follow-up. Treatment between the end of the trial and August 2001 did not necessarily adhere to the initial trial protocol, and an increasing proportion of the patients underwent endovascular repair of an aneurysm (13 of the 68 patients who underwent repair between July 1998 and August 2001 [19 percent], as compared with 14 of the 847 patients who underwent repair between randomization and July 1998 [2 percent]), but only 1 patient underwent repair for an asymptomatic abdominal aortic aneurysm of less than 5.5 cm in diameter. About one fifth of the patients in the surveillance group (105 of 527) died without having undergone repair of the aneurysm. The cumulative proportion of patients who underwent repair of an aneurysm is shown in Figure 2. Since only 39 patients who have not undergone repair of the abdominal aortic aneurysm remain alive, future changes to this curve will be minor.

**Mortality**

The 30-day mortality associated with elective procedures was 5.4 percent (49 of 905 patients). An additional 10 patients (7 in the surveillance group and 3 in the early-surgery group) underwent emergency surgery for a ruptured aneurysm. Only 2 of these patients (both in the surveillance group) survived, bringing the total 30-day mortality, including deaths due to rupture, to 6.2 percent: 5.5 percent in the early-surgery group (29 of 526 patients) and 7.2 percent in the surveillance group (28 of 389 patients) (P=0.30).

After a mean follow-up of 8 years (range, 6 to 10), there had been 254 deaths in the surveillance group and 242 in the early-surgery group. As of August 2001, the unadjusted hazard ratio for death in the early-surgery group as compared with the surveillance group was 0.84 (95 percent confidence interval, 0.70 to 1.00; P=0.05 by the log-rank test) (Fig. 3); after adjustment for two sets of base-line covariates, the hazard ratios were similar, at 0.81 and 0.83 (Table 1).

Survival was initially worse in the early-surgery group and was subsequently worse in the surveillance group; the survival curves crossed at about three years (Fig. 3). There was evidence of nonproportional hazards between the two groups over time (P=0.002). During the first six months after randomization, the rate of death in the early-surgery group was about two and a half times that in the surveillance group; thereafter, among those who survived at least six months, the rate of death in the early-surgery group was about three quarters of that in the surveillance group (Ta-
LONG-TERM OUTCOMES OF SMALL ABDOMINAL AORTIC ANEURYSMS

1276 Patients eligible
→ 186 Declined randomization

527 Assigned to ultrasonographic surveillance
→ 200 Did not undergo surgery by June 1998
→ 327 Underwent surgery by June 1998
  289 According to protocol
  38 In violation of protocol
→ 80 Died by June 1998
→ 120 Surviving as of June 1998
→ 33 Surviving without surgery as of August 2001
  48 Open
  13 Endovascular
  1 Laparoscopic
→ 6 Surviving without surgery as of August 2001
→ 6 Underwent surgery by August 2001
  5 Open
  1 Laparoscopic
→ 23 Died by June 1998
→ 20 Surviving as of June 1998
→ 520 Underwent surgery by August 2001

563 Assigned to early elective surgery

Figure 1. Patients, Randomization, and Outcomes.

Table 1: At two years, the estimated risk of death was
1.9 percentage points higher in the early-surgery group
than in the surveillance group (P = 0.33 by the z-test);
at four years, the risk was 1.4 percentage points lower
in the early-surgery group than in the surveillance
group (P = 0.58); at six years, it was 4.2 percentage
points lower (P = 0.15); and at eight years, it was 7.2
percentage points lower (P = 0.03). The adjusted haz-
ard ratios tended toward a greater benefit of surgery
among younger patients, men, and those with larger
aneurysms, but these trends were not significant ac-
cording to tests of interaction (Table 1). The restricted
mean duration of survival (the area under the sur-
vival curve) at 9 years was 6.5 years among patients
in the surveillance group, as compared with 6.7 years
among patients in the early-surgery group (P = 0.29).

The numbers of deaths from various causes are
shown in Table 2. More deaths from ruptured aneu-
rysms were reported among patients in the surveillance
group than among those in the early-surgery group.
More deaths from cancer were reported in the early-
surgery group than in the surveillance group (23 per-
cent vs. 17 percent). Other causes of death were dis-
tributed evenly between the two groups.

Smoking

Older age, larger diameter of the aneurysm, lower
ankle–brachial pressure index, and worse lung func-
tion (lower FEV₁) were all independently related to
an increased risk of death (Table 3). Patients who re-
ported current smoking had a higher risk of death
than did former smokers (Table 3). Data on cotinine
concentrations at randomization and one year after
randomization were available for 130 patients in the
early-surgery group and 97 patients in the surveillance
group. A total of 124 of these 227 patients (55 per-

percent) were classified as current smokers on the basis of the plasma cotinine concentration at the time of randomization; 71 of the patients in the early-surgery group were smokers (55 percent), as were 53 patients in the surveillance group (55 percent). One year after randomization, 37 of the patients in the early-surgery group (28 percent) and 47 of the patients in the surveillance group (48 percent) were still smokers ($P=0.002$ by the chi-square test). The only factor that was independently associated with smoking cessation was repair of an abdominal aortic aneurysm (odds ratio for smoking cessation, 12.8; 95 percent confidence interval, 4.2 to 38.9; $P<0.001$). Age, sex, size of the aneurysm, ankle-brachial pressure index, FEV$_1$, and the use or nonuse of aspirin therapy were not related to the likelihood of cessation. The death rate among those who continued to smoke was 12.0 per 100 patient-years; the death rate among those who stopped smoking was 3.8 per 100 patient-years (adjusted hazard ratio for death, 3.23; 95 percent confidence interval, 1.73 to 6.03).

**Operative Mortality**

To address the hypothesis that the risk of death increased in the surveillance group with the delay before elective repair of an abdominal aortic aneurysm, we compared the 30-day postoperative mortality rate during the period between randomization and June 30, 1998 (the end of the trial), with the rate between that date and August 31, 2001. A total of 389 patients in the surveillance group had undergone repair of an aneurysm by August 31, 2001; 355 of these repairs (91 percent) were recorded as elective open operations. The 30-day mortality associated with elective open surgery during the period before June 30, 1998, was 6.2 percent (19 of 308 patients), and the 30-day postoperative mortality between July 1998 and August 2001 was 4.3 percent (2 of 47 patients) ($P=1.0$ by Fisher's exact test). Logistic-regression analysis of 30-day outcomes according to the time to repair of an abdominal aortic aneurysm also failed to demonstrate that delaying surgery altered the 30-day postoperative mortality (odds ratio for postoperative death, 1.12).
**Table 1. Deaths from Any Cause in the Two Treatment Groups.**

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>SURVEILLANCE GROUP (N=527)</th>
<th>EARLY-SURGERY GROUP (N=563)</th>
<th>ADJUSTED HAZARD RATIO (95% CI)</th>
<th>P VALUE (TEST FOR INTERACTION)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no./no. of patients (no./100 patient-yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>254/527 (8.3)</td>
<td>242/563 (7.1)</td>
<td>0.88 (0.69–1.00)‡</td>
<td></td>
</tr>
<tr>
<td>Months after randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–6</td>
<td>12/527 (4.6)</td>
<td>31/563 (11.4)</td>
<td>2.52 (1.20–5.33)</td>
<td></td>
</tr>
<tr>
<td>&gt;6</td>
<td>242/515 (8.7)</td>
<td>211/532 (6.7)</td>
<td>0.77 (0.63–0.93)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–66 yr</td>
<td>66/181 (6.1)</td>
<td>56/182 (4.7)</td>
<td>0.72</td>
<td>0.18</td>
</tr>
<tr>
<td>67–71 yr</td>
<td>94/180 (9.3)</td>
<td>76/183 (6.7)</td>
<td>0.74</td>
<td></td>
</tr>
<tr>
<td>72–76 yr</td>
<td>92/166 (9.8)</td>
<td>110/197 (10.0)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>210/434 (3.3)</td>
<td>201/468 (7.1)</td>
<td>0.80</td>
<td>0.40</td>
</tr>
<tr>
<td>Female</td>
<td>44/93 (4.4)</td>
<td>41/95 (7.3)</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Diameter of aneurysm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.0–4.4 cm</td>
<td>93/213 (7.4)</td>
<td>91/214 (7.1)</td>
<td>0.95</td>
<td>0.28</td>
</tr>
<tr>
<td>4.5–4.8 cm</td>
<td>78/169 (7.9)</td>
<td>73/175 (6.7)</td>
<td>0.84</td>
<td></td>
</tr>
<tr>
<td>4.9–5.5 cm</td>
<td>83/145 (10.4)</td>
<td>73/174 (7.3)</td>
<td>0.70</td>
<td></td>
</tr>
</tbody>
</table>

*There were 3048 patient-years of follow-up in the surveillance group, and 3410 in the early-surgery group. For age and diameter of aneurysm, the patients were divided into three groups of approximately equal size.

‡Hazard ratios are for the early-surgery group relative to the surveillance group and were adjusted for the following baseline variables: age, sex, smoking status, initial aneurysm diameter, average of left and right ankle-brachial pressure index, forced expiratory volume in one second (FEV1), and use or nonuse of aspirin, as well as for the source of referral (general practice, other clinic, or other), regional center, and type of hospital (teaching or district general). CI denotes confidence interval.

When the data for patients who underwent an endovascular or laparoscopic repair were censored at the time of repair, the shapes of the survival curves and the significance of the difference between them were unchanged (P=0.05 by the log-rank test).

Rupture and Aneurysm-Related Deaths

We assessed the total rupture rate (including ruptures of aneurysms larger than 5.5 cm in diameter) for two periods. The total rupture rate (including nonfatal ruptures) was 1.6 percent per year before June 1998 and 3.2 percent per year between July 1998 and August 2001 (P=0.08). Fatal ruptures were more common among women than among men, causing 12 of the 85 deaths in women (14 percent) and 19 of the 411 deaths in men (5 percent, P=0.001). The risk of rupture of an abdominal aortic aneurysm was four times as high among women as among men (hazard ratio, 4.0; 95 percent confidence interval, 2.0 to 7.9; P<0.001).

In addition to 3 deaths from the rupture of an abdominal aortic aneurysm after open surgery for repair per 1-year delay; 95 percent confidence interval, 0.87 to 1.44; P=0.40). Adjustment for the age of the patient at the time of repair did not alter the results. Inclusion of the additional patients who underwent elective open surgery after June 1998 weakened the previously reported relation between the age at the time of repair and the 30-day outcome (adjusted odds ratio for postoperative death, 1.61 per 10-year increment in age; 95 percent confidence interval, 0.77 to 3.39; P=0.21).

Endovascular and Laparoscopic Repair

It is possible that the results were affected by the fact that, in the period after June 1998, some patients in the surveillance group underwent endovascular repair of an aneurysm at a time when clinicians had relatively little experience with this technique. Among the study patients, 27 endovascular repairs of abdominal aortic aneurysms were reported by August 2001, and one patient died within 30 days after such a repair. Two additional patients underwent laparoscopic repair, and one died within 30 days after the repair.
We tested the hypothesis that early elective surgery for small abdominal aortic aneurysms would confer a survival benefit at five years, resulting in 71 percent survival with early surgery and 62 percent survival with surveillance. Only much later in the follow-up period was there weak evidence to suggest a benefit of early elective surgery: nine-year survival was 53 percent in the early-surgery group and 45 percent in the surveillance group. There was no evidence that the number of life-years gained (mean duration of survival) was improved significantly by a policy of early surgery.

We considered the possibility that the small late survival advantage (at nine years) in the early-surgery group could have resulted from the larger size of the aneurysms and the older age of the patients who underwent delayed surgery, which might have led to an increased risk of postoperative death. There was no evidence to support this hypothesis. We also considered the possibility that after the trial had formally ended (in June 1998) and there was no longer the same rigorous surveillance by the trial coordinators, increased rates of aneurysm rupture and of surgery that did not adhere to the trial protocol could have accounted for the survival disadvantage in the surveillance group. Again, there was no strong evidence for these hypotheses. Only eight ruptures occurred between July 1998 and August 2001, mostly in men with aneurysms more than 5.5 cm in diameter or in women; the risk of rupture was four times as high among women as among men. The small increase in the rate of rupture was not significant, and the proportion of all deaths that were caused by the rupture of an unrepaired abdominal aortic aneurysm was very low (6 percent). Although there was increasing use of endovascular or laparoscopic surgery between July 1998 and August 2001, censoring the data of patients at the time of these procedures did not alter the long-term survival advantage of the early-surgery group. Therefore, there must be other explanations for the small late survival advantage in the early-surgery group.

Early surgery could have beneficial biologic or lifestyle-related effects. In the early-surgery group, patients’ perceptions of their health were improved 12 months after randomization. There was evidence of a higher rate of smoking cessation among patients who underwent early surgery, according to an analysis of a subgroup of patients who were recruited early in the trial. In this subgroup, patients who were motivated to stop smoking had much better survival than those who continued smoking. Major surgery is recognized as an important stimulus to smoking cessation, the survival benefits of which do not become apparent for five or more years. Smoking cessation results in a particular reduction in mortality from cardiovascular causes, and such an effect is consistent with

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Surveillance Group</th>
<th>Early-Surgery Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>254</td>
<td>242</td>
</tr>
<tr>
<td>Cardiovascular causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cardiovascular causes</td>
<td>172 (68)</td>
<td>149 (60)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>48 (19)</td>
<td>42 (17)</td>
</tr>
<tr>
<td>Stroke</td>
<td>12 (5)</td>
<td>9 (4)</td>
</tr>
<tr>
<td>Ruptured thoracic aortic aneurysm</td>
<td>11 (4)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Ruptured AAA</td>
<td>21 (8)</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Secondary AAA rupture</td>
<td>5 (1)</td>
<td>0</td>
</tr>
<tr>
<td>AAA repair</td>
<td>25 (10)</td>
<td>27 (11)</td>
</tr>
<tr>
<td>Other</td>
<td>52 (20)</td>
<td>53 (22)</td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cancer</td>
<td>44 (17)</td>
<td>56 (23)</td>
</tr>
<tr>
<td>Lung</td>
<td>13 (5)</td>
<td>20 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>31 (12)</td>
<td>36 (13)</td>
</tr>
<tr>
<td>Other</td>
<td>37 (15)</td>
<td>38 (16)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (&lt;1)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

*Autopsies were performed in 130 cases (26 percent). AAA denotes abdominal aortic aneurysm.
†In a minority of patients the diameter of the aneurysm exceeded 5.5 cm and the patient had either refused surgery or become unfit for surgery; this was the case for 7 of the 21 in the surveillance group and 3 of the 10 in the early-surgery group.
‡Data are for ruptures after repair of an abdominal aortic aneurysm.
§Repair was considered the underlying cause of death, which occurred within 14 days after repair.
¶Data are for patients who died abroad.

DISCUSSION

Discussions between clinicians and patients concerning the prognosis of patients with life-threatening disorders, such as abdominal aortic aneurysm, commonly focus on the five-year survival rate. Neither our trial nor the Aneurysm Detection and Management Study demonstrated that early surgical intervention for small abdominal aortic aneurysms improved five-year survival. Both trials showed that eventually about three quarters of the patients in the surveillance group undergo aneurysm repair. Does improvement in survival depend on the timing of surgery?
the smaller number of deaths from myocardial infarction and stroke in the early-surgery group. Moreover, patients who reported that they were former smokers had a lower risk of death than those who reported that they were current smokers. Favorable biologic results of early surgery could include a reduction in circulating interleukin-6, a marker of cardiovascular risk.14 Two thirds of the 496 deaths were attributed to a cardiovascular cause. The diameter of the aneurysm is an independent marker of the risk of cardiovascular disease.15 Thus, a combination of lifestyle-related and biologic effects of early repair of an abdominal aortic aneurysm could underlie the long-term survival benefit of early surgery.

Patients with small abdominal aortic aneurysms, like surgeons, need information to guide decisions about the timing of surgery. Early surgery is associated with a significant risk of operative death, although taking this risk could lead to a long-term survival advantage. However, neither five-year survival nor the mean duration of survival is improved by early surgery. Given these findings, patients are likely to inquire about their own risk of death after surgery and the surgeon’s audited outcome data. However, there is no prospectively validated, simple means of assessing the risk associated with surgery to repair an abdominal aortic aneurysm that would permit the confident identification of patients with a low risk of death.

Coexisting conditions are important in patients with abdominal aortic aneurysms. Comparison of the patients enrolled in the British and U.S. small aneurysm trials reveals that the British patients had significantly worse lung and renal function (mean FEV1, 0.38 liter lower; mean serum creatinine concentration 0.08 mg per deciliter [7.1 μmol per liter] higher) as well as significantly higher systolic blood pressure and serum cholesterol than the U.S. cohort.2 The overall survival among the British patients was worse than that in the U.S. cohort. Lung and renal function have important effects on the risk of postoperative death9

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**Table 3. Crude Death Rates and Adjusted Hazard of Death According to Baseline Factors.**

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>DEATHS</th>
<th>CRUDE DEATH RATE</th>
<th>ADJUSTED HAZARD RATIO (95% CI)</th>
<th>ADJUSTED P VALUE</th>
<th>FACTOR</th>
<th>DEATHS</th>
<th>CRUDE DEATH RATE</th>
<th>ADJUSTED HAZARD RATIO (95% CI)</th>
<th>ADJUSTED P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–64 yr</td>
<td>124/354</td>
<td>5.4</td>
<td>1.06 (1.03–1.09) per 1-yr increment</td>
<td>&lt;0.001</td>
<td>67–71 yr</td>
<td>170/353</td>
<td>8.0</td>
<td>1.25 (1.01–1.53) per 1-yr increment</td>
<td>0.06</td>
</tr>
<tr>
<td>72–76 yr</td>
<td>202/353</td>
<td>9.9</td>
<td></td>
<td></td>
<td>77–80 yr</td>
<td>213/353</td>
<td>10.2</td>
<td>1.30 (1.08–1.52) per 1-yr increment</td>
<td>0.002</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>411/902</td>
<td>7.7</td>
<td>1.33 (0.94–1.60)</td>
<td>0.14</td>
<td>Female</td>
<td>85/188</td>
<td>7.8</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Smoking status</td>
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<td>1.46 (1.15–1.86)</td>
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<tr>
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<td>117/313</td>
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*Hazard ratios and P values were determined by Cox proportional-hazards regression analysis and were adjusted for baseline age, sex, smoking status, aneurysm diameter, average of left and right ankle–brachial pressure index, forced expiratory volume in one second (FEV1), and use or nonuse of aspirin, as well as for the source of referral (general practice, other clinic, or other), regional center, type of hospital (teaching or district general), and treatment-group assignment. For age, diameter of the aneurysm, ankle–brachial pressure index, and FEV1, the patients were divided into three groups of approximately equal size. CI denotes confidence interval.

†Data are for the average of the left and right ankle–brachial pressure indexes.
and might affect outcomes in both treatment groups.

Since the publication of the results of our trial,13 surgical practice in much of Europe has changed in favor of refraining from the prophylactic repair of small abdominal aortic aneurysms. Results from the Aneurysm Detection and Management Trial support this change in practice: even with low operative mortality among low-risk patients, early surgery did not improve five-year survival. Unlike the U.S. trial (conducted through Veterans Affairs medical centers), the United Kingdom trial included a considerable proportion of women (17 percent), for whom the threshold of 5.5 cm in diameter for the repair of an aneurysm may have been too high, although our data do not enable us to specify the diameter at which surgery should be recommended. At least for men, surveillance remains a justifiable policy until the threshold of 5.5 cm in diameter is reached.

Supported by grants from the Medical Research Council and the British Heart Foundation to Imperial College and the University of Edinburgh and by the BUPA Foundation.

APPENDIX

The following centers and investigators participated in the trial (the number of patients enrolled at each center is given in parentheses): Southwestern England and South Wales — Royal United Hospital (29); M. Horrocks (regional trial director); J. Budd; Bristol Royal Infirmary (22): R.N. Baird, P. Lamon; Derriford Hospital (9); D.C. Watkins, S. Ashley; Dorset County Hospital (9); K. Flowerdew; Frimley Hospital (7); A. Baker; Gloucester Royal Infirmary (7): J. Earnshaw, B. Heath; Horton Hospital (14); C. Gibbons; Nevile Hall Hospital (8); R.L. Blackett; New Royal Bournemouth General Hospital (50); S.D. Parvin; North Devon General Hospital (1); D.R. Harvey; Princess of Wales Hospital (1); R. Hedges; Princess Margaret Hospital (8); D. Finch, D.B. Hooken; Southampton General Hospital (3): G.E. Morris, C.P. Shearman; Southmead Hospital (4); P. Lear, Torbay Hospital (5); P. Lewis; Yeovil District General Hospital (3): R.J. 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REFERENCES


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DETECTION AND MANAGEMENT OF SMALL AORTIC ANEURYSMS

ABDOMINAL aortic aneurysms arise through a chronic degenerative process that produces localized weakening of the aortic wall. They have a natural history characterized by progressive expansion and eventual rupture. Population-based screening studies reveal that up to 9 percent of persons over 65 years of age have an unsuspected and asymptomatic abdominal aortic aneurysm, and it is estimated that ruptured abdominal aortic aneurysms cause at least 15,000 deaths each year in the United States.

The principal goal of treatment for these aneurysms is to extend life by preventing the rupture of the aneurysm. There is long-standing evidence that elective surgical repair improves survival for patients with large abdominal aortic aneurysms; with operative mortality rates reported to be as low as 2 percent in some centers, approximately 50,000 operations are performed annually for this condition in the United States. The success of surgical repair has also led some to advocate elective intervention for patients with smaller abdominal aortic aneurysms. The optimal treatment strategy for such patients is not known. However, since it is known that there is a low risk of rupture for abdominal aortic aneurysms less than 5.0 cm in diameter, it has been proposed that watchful waiting with the use of imaging might be a better long-term treatment strategy than early surgical repair for small aneurysms.

In this issue of the Journal, Lederle et al. report the final results of the Aneurysm Detection and Management (ADAM) Veterans Affairs Cooperative Study, a prospective, randomized trial comparing the outcomes associated with immediate surgical repair with those associated with long-term surveillance (by means of ultrasonography or computed tomography [CT]) in patients with asymptomatic abdominal aortic aneurysms less than 5.5 cm in diameter. The primary finding of their study is that there was no significant difference in overall survival between the two treatment groups after a mean of 4.9 years of follow-up. There was also no difference in survival between groups defined according to the age of the patient or the initial size of the aneurysm, and the results were unaffected by adjustment for baseline clinical variables that were significant independent predictors of death.

It is evident that the results of the ADAM Study were achieved by a combination of close clinical follow-up, careful medical management, and superb surgical care. In the immediate-repair group, the 30-day operative mortality rate was 2.1 percent — lower than would be expected in most clinical settings — and only 1.7 percent of patients required reoperation because of complications. In the surveillance group, there was complete clinical and radiographic follow-up in over 85 percent of patients, and the rate of rupture (0.6 percent per year) and the median rate of expansion of aneurysms (0.32 cm per year) were both quite low.

The results of this study are remarkably similar to those of the previously reported United Kingdom Small Aneurysm Trial, which also demonstrated no survival advantage for early surgical repair over imaging surveillance after five years of follow-up. However, because the operative mortality rate in the United Kingdom Small Aneurysm Trial was 5.8 percent, it was suggested that there might have been a difference in survival if the outcome of surgery had been better.

The major strength of the ADAM Study is that it has effectively overcome this concern, allowing Lederle et al. to conclude that “survival is not improved by elective repair of abdominal aortic aneurysms smaller than 5.5 cm, even when operative mortality is low.”

Do the results of the ADAM Study mean that the threat of rupture of aneurysms has been previously overestimated and that no patient should undergo repair of an abdominal aortic aneurysm less than 5.5 cm in diameter? Unfortunately, the answer is not that simple. For example, the trial was designed with rigorous surveillance by CT or ultrasonography for patients who were not assigned to undergo immediate repair, coupled with prompt surgical intervention if and when it became necessary. It is notable that 61 percent of the patients in this group underwent elective repair of an abdominal aortic aneurysm within 4.9 years, with the rate of repair corresponding to the size of the aneurysm at the time of randomization: 27 percent for aneurysms 4.0 to 4.4 cm in diameter, 53 percent for aneurysms 4.5 to 4.9 cm in diameter, and 81 percent for aneurysms 5.0 to 5.4 cm in diameter. These operations were performed because the aneurysm had gradually expanded to 5.5 cm or more in diameter, rather than because of rapid enlargement, development of symptoms, or frank rupture.

It is comforting to note that there was no increase in either operative mortality or the overall rate of complications among patients in the surveillance group who underwent delayed repair. Nonetheless, one caveat is that patients with a gradually expanding but asymptomatic abdominal aortic aneurysm might be overlooked in practice settings outside a carefully conducted clinical trial; if appropriate long-term follow-up cannot be ensured, a recommendation for ultrasonographic or CT surveillance might be associated with shorter survival than immediate repair. A second limitation of the ADAM Study is that the population of patients consisted almost entirely of men. The impor-
tance of this disparity arises from the observation that there may be a higher risk of rupture and a higher mortality rate associated with ruptured abdominal aortic aneurysms in women than in men—a difference that limits our ability to generalize from these results.

Complicating these issues further is a second report in this issue of the *Journal describing the long-term outcomes for patients enrolled in the United Kingdom Small Aneurysm Trial*. Although there had been no survival advantage for immediate surgery over surveillance in the initial study, further evaluation after nine years has revealed a small but statistically significant difference in total mortality that favors early surgery (45 percent survival in the surveillance group vs. 53 percent in the early-surgery group). Although the survival curves for the two groups appear to cross at about 3 years, the survival advantage was not associated with a significant difference in the number of life-years gained (mean survival after 9 years of follow-up was 6.5 years with surveillance vs. 6.7 years with early surgery).

The possible improvement in long-term survival associated with early surgery is quite difficult to explain, since it was not attributable to a higher incidence of ruptured aneurysms or higher surgical mortality in the surveillance group. The authors demonstrate, however, that the rate of smoking cessation was substantially higher in the early-surgery group than in the surveillance group. The findings of this study thus reinforce the notion that the choice of ultrasonographic surveillance must be accompanied by strong efforts by patients affected by abdominal aortic aneurysms to improve lifestyle-related factors and general health measures, and especially to quit smoking.

What recommendations can be made for the detection and management of small, asymptomatic abdominal aortic aneurysms? First, it is increasingly clear that any attempt to reduce the overall number of deaths from ruptured abdominal aortic aneurysms will depend on earlier diagnosis in the population at risk. Although routine physical examination is insensitive for the detection of aortic aneurysms, ultrasonographic screening in patients over 65 years of age is likely to detect almost all of these lesions. Broader recommendations for routine ultrasonographic screening would therefore permit informed decisions to be made regarding management.

Second, the results of the ADAM Study and the United Kingdom Small Aneurysm Trial have provided solid evidence that surveillance with imaging is a safe and reasonable treatment strategy for patients with abdominal aortic aneurysms between 4.0 and 5.4 cm in diameter, with surgical repair reserved for lesions that have expanded to 5.5 cm in diameter or have become symptomatic. Although surveillance will clearly be the preferred treatment strategy for many patients, it must be carried out with vigilant clinical evaluation and radiographic imaging at six-month intervals, since 50 to 80 percent of these patients can be expected to require surgical repair within several years.

It might still be reasonable to recommend repair of abdominal aortic aneurysms less than 5.5 cm in diameter, particularly in women, in the face of a strong preference by the patient, a long life expectancy, and a low risk associated with surgical repair, but this recommendation must be accompanied by an estimated operative mortality rate well below 5 percent; among patients or in practice settings in which low operative mortality rates cannot be ensured, recommendations for elective repair should be more restrained than they have been in the past. Indeed, existing data indicate that operative mortality associated with the repair of abdominal aortic aneurysms in the "real world" is closer to 5 to 8 percent and that surgical results are strongly influenced by the number of repairs performed by a given surgeon or in a given hospital, the specialty training of the surgeon, characteristics of the practice, and the geographic region where the repair is performed. On the basis of currently available evidence, there is no reason to expect that these recommendations should be any different for the endovascular repair of abdominal aortic aneurysms.

Surveillance should therefore be viewed as only one of the management options to be considered for patients with small abdominal aortic aneurysms, and it should be recognized that some carefully selected patients will still benefit from early surgical treatment. One hope for the future is that increased interest in the pathophysiology of aneurysmal disease will lead to further improvements in the management of small abdominal aortic aneurysms through the identification of biologic markers that are better predictors of which patients are likely to have expansion of an aneurysm and through the development of pharmacologic strategies by which to suppress the progression of aneurysmal degeneration.

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**REFERENCES**


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PHEOCHROMOCYTOMA — DEATH OF AN AXIOM

MEDICAL students often learn axioms in order to remember the key features of a disorder. The "rule of 10" used to describe pheochromocytomas is a good example: 10 percent are extraadrenal, and of those, 10 percent are extrabdominal; 10 percent are malignant; 10 percent are found in patients who do not have hypertension; and finally, 10 percent are hereditary.1 Familial pheochromocytoma is inherited as an autosomal dominant trait alone or as a component of the multiple endocrine neoplasia type 2 syndromes (MEN-2A and MEN-2B), von Hippel-Lindau disease, or, in rare cases, neurofibromatosis type 1.2 The remaining 90 percent of pheochromocytomas are classified as sporadic or nonsyndromic. In this issue of the Journal, a report by Neumann et al.3 on the screening of a large cohort of patients with sporadic pheochromocytoma and no family history of the disorder has dashed the rule of 10. Approximately 25 percent of the screened population had germ-line mutations of one of four susceptibility genes for pheochromo-
cytoma.4 Molecular analysis has advanced the knowledge that came from clinical observation.

The adrenal medulla and ganglia of the sympathetic nervous system are derived from the embryonic neural crest. The endocrine cells of this sympathoadrenal system synthesize and secrete catecholamines and exhibit a characteristic histochemical (chromaffin) reaction when treated with oxidizing agents. Pheochromocytomas, rare neoplasms that produce catecholamines, usually arise from the adrenal medulla. If they arise in extraadrenal chromaffin tissue, they are called paragangliomas or extraadrenal pheochromocytomas. Patients with pheochromocytomas may present with sustained hypertension that is resistant to conventional treatment. A classic clinical feature is a paroxysm resulting in the triad of episodic headache, sweating, and palpitations as a result of the release of stored catecholamines from the tumor. An unrecognized pheochromocytoma may lead to death as a result of a hypertensive crisis, arrhythmia, or myocardial infarction. After biochemical confirmation of catecholamine excess, radiographic imaging of the abdomen reveals an adrenal pheochromocytoma in the majority of cases. Demonstration of normal adrenal glands points toward a diagnosis of paraganglioma, which arises from sympathetic ganglia in the abdomen, chest, head, and neck.5 Nonchromaffin paragangliomas (chemodectomas) arise from parasympathetic ganglia in the head and neck and include the carotid-body and glomus jugulare tumors of the 9th and 10th cranial nerves. Paragangliomas below the head and neck are often functional, and patients with these tumors present with signs of catecholamine excess. The predominant clinical manifestation of tumors of the head and neck is a mass effect, such as cranial-nerve palsy and tinnitus, but a small proportion of such tumors may secrete catecholamines.6

Recently, the gene encoding succinate dehydrogenase subunit D (SDHD) was identified as a susceptibility gene for autosomal dominant familial paraganglioma (glomus tumor).5 Since pheochromocytomas and glomus tumors are both derived from neural-crest tissue, analysis of SDHD as a susceptibility gene for sporadic pheochromocytoma was performed in several small studies, with both positive6 and negative7 results. In the report by Neumann et al., a large cohort of patients with nonsyndromic pheochromocytoma from two registries in Freiburg, Germany, and Warsaw, Poland, were screened for germ-line mutations of four pheochromocytoma-susceptibility genes.8 These included the proto-oncogene RET (MEN-2), the tumor-suppressor gene VHL, and two novel genes that confer a predisposition to the development of pheochromocytomas and glomus tumors: SDHD and the gene encoding succinate dehydrogenase subunit B (SDHB). Of 271 patients, 66 (24 percent) had germ-
line mutations. Of these, 30 had mutations of \textit{VHL} (45 percent), 13 of \textit{RET} (20 percent), 11 of \textit{SDHD} (17 percent), and 12 of \textit{SDHB} (18 percent). Retrospective identification of clinical clues to the presence of a hereditary syndrome included multifocal and extraadrenal tumors and a young age. However, these features were noted to be disease-specific. For example, 80 percent of probands with the newly identified mutations of \textit{SDHD} and \textit{SDHB} presented with solitary pheochromocytomas, and 40 percent were older than 30 years of age.

Previously identified germ-line mutations that confer a predisposition to pheochromocytoma involve both proto-oncogenes and tumor-suppressor genes (Table 1). Activating mutations of the \textit{RET} proto-oncogene in the MEN-2 syndromes act as gain-of-function mutations, causing constitutive activation of the receptor tyrosine kinase.\textsuperscript{5} As a result of tissue-specific expression, calcitonin-producing parafollicular cells and adrenomedullary chromaffin cells initially undergo hyperplasia, with a high rate of subsequent neoplastic transformation. In contrast, von Hippel–Lindau disease results from loss-of-function (i.e., inactivating) mutations of the \textit{VHL} suppressor gene. The \textit{VHL} protein regulates the normal degradation of proteins such as hypoxia-inducible factor, which is implicated in the response to low oxygen tension.\textsuperscript{6} \textit{SDHD} and \textit{SDHB} are part of mitochondrial complex II, which regulates oxygen sensing and signaling.\textsuperscript{10,11} Therefore, patients with a predisposition to pheochromocytoma or paragangioma due to mutated \textit{VHL}, \textit{SDHD}, or \textit{SDHB} may share a defect in the oxygen-sensing system. It is postulated that this abnormality would result in activation of hypoxic signaling pathways that may be associated in some way with malignant proliferation. Finally, these same genes with germ-line mutations have also been found to be somatically mutated (i.e., in the tumor only) in sporadic cases of pheochromocytoma.\textsuperscript{3}

The clinical implications of the germ-line mutations described by Neumann et al in cases of pheochromocytoma that were thought to be sporadic are clear-cut for both the proband and the family. For the proband, there may be a lifelong risk of component tumors (Table 1). For example, in patients who had mutations of \textit{SDHD} or \textit{SDHB}, there was a 20 to 30 percent likelihood of the subsequent development of a glomus tumor. Periodic physical and ultrasonographic examinations of the neck should be performed in affected patients, since these neoplasms are difficult to treat surgically when they are advanced. In the case of von Hippel–Lindau disease and MEN-2, some of the component tumors are clearly life-threatening, such as hemangioblastoma of the central nervous system and medullary carcinoma of the thyroid, respectively. In addition, since all four of these disorders are inherited in an autosomal dominant fashion, it is important to screen first-degree relatives in order to detect new cases and identify patients who should undergo biochemical and radiographic monitoring for the development of component tumors.

On the basis of the finding that 25 percent of screened patients had germ-line mutations, Neumann et al conclude that routine analysis for mutations of \textit{RET}, \textit{VHL}, \textit{SDHD}, and \textit{SDHB} in apparently sporadic cases of pheochromocytoma should be consid-

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<td>\textit{SDHD}, \textit{SDHB}</td>
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</table>

*\textit{MEN-2A} denotes multiple endocrine neoplasia type 2A, \textit{MEN-2B} multiple endocrine neoplasia type 2B, CNS central nervous system, \textit{SDHD} the gene for succinate dehydrogenase subunit D, and \textit{SDHB} the gene for succinate dehydrogenase subunit B.
ered as the clinical standard of care. One cautionary note is the limited geographic area of this study; whether the results can be extended to populations in other regions is unknown. For example, in a previous study in Germany, performed by some of the same authors, a high proportion (20 percent) of patients with von Hippel-Lindau disease were found to have pheochromocytomas.12 There is considerable genetic variability among kindreds with von Hippel-Lindau disease, and certain mutations lead to a high frequency of pheochromocytoma. Thus, it is possible that specific pheochromocytoma-predisposing mutations were predominant in the two registry populations studied by Neumann et al. On the other hand, it is possible that additional pheochromocytoma-predisposing genes will be found, further reducing the percentage of pheochromocytomas currently classified as sporadic.

What is a reasonable strategy for the diagnosis of these hereditary syndromes in a patient with a newly discovered pheochromocytoma? Although clinicians can screen for the RET mutation, screening is not easily available for the other three mutations. However, clinicians should now have a higher index of suspicion for familial syndromes in patients with apparently sporadic pheochromocytoma. A young age and multiple extraadrenal neoplasms are diagnostic clues that should prompt clinicians to obtain a complete family history, particularly a history of component tumors in first-degree relatives. Moreover, a careful physical examination may be diagnostic. The presence of cutaneous or mucosal neurofibromas, a thyroid mass or carotid-body tumor, or a retinal angioma provides strong clinical evidence of a hereditary syndrome. Until genetic testing for SDHD becomes commercially available, a high index of suspicion and clinical evaluation are appropriate.

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