Relevance of the ADAM and UK Small Aneurysm Trial Data in the Age of Endovascular Aneurysm Repair

Madhukar S. Patel, ScM; David A. Brown, PhD; Samuel E. Wilson, MD

Hypothesis: Neither the ADAM nor the UK Small Aneurysm trials showed an advantage for early open surgical repair of abdominal aortic aneurysms (AAAs) smaller than 5.5 cm in diameter. The rigorous exclusion criteria of these studies, however, limited surgery to low-risk patients. We tested the hypothesis that endovascular aneurysm repair (EVAR) has been successfully used for higher-risk patients, thus questioning the utility of the ADAM and UK Small Aneurysm trials exclusion criteria in EVAR patient selection.

Design: Retrospective case review.

Setting: An urban Veterans Affairs Medical Center.

Patients: Forty-four consecutive cases of patients with AAA who received EVAR.

Main Outcome Measures: Electronic medical records were accessed for 11 high-risk conditions that would have excluded patients from the open surgery trials, and 30-day interventional morbidity and mortality data were collected.

Results: The mean (SD) age of patients who underwent EVAR was 73.2 (10.3) years, with a mean (SD) AAA diameter of 5.8 (1.6) cm. Of 44 patients, 19 (43%) met at least 1 exclusion criterion that would have prevented randomization in the small AAA trials. Significant perioperative complications occurred in 14 patients (32%) and 1 death occurred at home within 30 days of the procedure.

Conclusions: Patients receiving EVAR at an urban Veterans Affairs Medical Center had a greater prevalence of high-risk conditions than patients included in the ADAM and UK Small Aneurysm trials, and overall perioperative morbidity and mortality were lower. Endovascular aneurysm repair has extended aneurysm repair to a higher-risk population with greater safety.

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More than 30,000 North Americans undergo elective surgical repair of abdominal aortic aneurysms (AAAs) each year, and aneurysm rupture accounts for more than 9000 deaths per year in the United States. Despite advances in emergency systems, surgical treatment, and postoperative care, the mortality rate of all ruptured AAAs approaches 80%. Epidemiological studies of AAAs showed that when discovered, more than 90% are considered small (<5.5 cm) and only 0.4% attain a size of more than 6.0 cm. Additionally, the rate of rupture increases with aneurysm size. Because open surgical repair of AAAs is associated with a mortality rate of 3% to 12%, the decision to operate has been based largely on the size, and thus risk of rupture, of the aneurysm. Neither the UK Small Aneurysm Trial nor the ADAM Trial showed an advantage of open surgical repair over observation for AAAs less than 5.5 cm. However, the rigorous exclusion criteria of these trials limited participation to patients with low risk for operative mortality.

In this report, we tested the hypothesis that endovascular aneurysm repair (EVAR) was safely performed in an urban Veterans Affairs (VA) medical center on higher-risk patients usually excluded from open surgical repair, thus questioning the utility of the ADAM and UK Small Aneurysm trials exclusion criteria in EVAR patient selection.

Methods:

The computerized medical records of 44 consecutive patients with AAA who received EVAR at an urban VA medical center (VA Long Beach Medical Center) were reviewed. These cases
were identified using Current Procedural Terminology codes, fourth edition, pertaining to endovascular repair of AAAs (codes 34800 and 34802-5). Data on patient risk factors and surgical outcomes were collected using a computerized medical records system.

The presence or absence of 11 high-risk conditions that would have excluded patients from previous open surgery trials was noted. These 11 factors adopted from the ADAM and UK Small Aneurysm Clinical Trial Design are listed in Table 1. Four of these high-risk cases met 2 of the exclusion criteria and 2 of these high-risk cases met 3 of the exclusion criteria. The remaining 25 cases (57%) were considered non–high risk since they did not meet any of the exclusion criteria.

The characteristics of all patients receiving EVAR are shown in Table 2. Mean diameters were obtained from the latest computed tomographic scan reports prior to surgical intervention. For the 1 patient needing reoperation for claudication, an angioplasty was done 5 months after the initial repair.

Data regarding postoperative events are presented in Table 3. None of the cases had graft infection, wound infection, stroke, ischemia of the colon or mesentery, or amputation. Additionally, of the 4 patients who had transient deterioration in renal function, likely contrast related, none required dialysis. One patient in the non–high-risk group had a 4-mm enlargement of aneurysm on follow-up computed tomography a month after surgery; an endoleak was not apparent on subsequent imaging. One patient in the high-risk group who initially presented with a 13 cm–diameter aneurysm had 6.4-cm residual dilatation 3 months postoperatively but

### RESULTS

Of the 44 consecutive EVAR cases that were reviewed, 19 (43%) were considered high risk because of the presence of at least 1 of the 11 exclusion criteria listed in Table 1. Four of these high-risk cases met 2 of the exclusion criteria and 2 of these high-risk cases met 3 of the exclusion criteria. The remaining 25 cases (57%) were considered non–high risk since they did not meet any of the exclusion criteria.

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### Table 1. Number of Patients Meeting Exclusion Criteria Derived From the ADAM and UK Small Aneurysm Clinical Trial Design

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
<th>No. of Patients Who Met Exclusion Criteria and Underwent EVAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous AAA repair or other aortic surgery</td>
<td>0</td>
</tr>
<tr>
<td>Symptomatic AAA or radiologic evidence of rupture</td>
<td>5</td>
</tr>
<tr>
<td>AAA expansion exceeding 1.0 cm in past year</td>
<td>1</td>
</tr>
<tr>
<td>AAA expansion exceeding 0.7 cm in past 6 mo</td>
<td>0</td>
</tr>
<tr>
<td>Severe pulmonary disease</td>
<td>0</td>
</tr>
<tr>
<td>Serum creatinine level ≥2.5 mg/dL</td>
<td>0</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0</td>
</tr>
<tr>
<td>Liver disease</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction within previous 6 mo</td>
<td>0</td>
</tr>
<tr>
<td>Major surgical procedure or angioplasty within proceeding 3 mo</td>
<td>0</td>
</tr>
<tr>
<td>Reversible defect or large fixed defect on thallium scan, unless cardiology consultation determines the patient not to be at high surgical risk</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 2. Clinical Characteristics of 44 Patients Who Had Endovascular Aneurysm Repair

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Entire Study Group</th>
<th>High-Risk Patients</th>
<th>Non–High-Risk Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>44</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Age, y, mean (SD)</td>
<td>73.23 (10.25)</td>
<td>74.26 (10.01)</td>
<td>72.40 (10.61)</td>
</tr>
<tr>
<td>Initial diameter of aneurysm, cm, mean (SD)</td>
<td>5.77 (1.64)</td>
<td>6.11 (1.86)</td>
<td>5.51 (1.44)</td>
</tr>
<tr>
<td>Perioperative death</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Reoperation</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

### Table 3. Postoperative Events in High- and Low-Risk Patients Who Had Endovascular Aneurysm Repair

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Entire Study Group</th>
<th>High-Risk Patients</th>
<th>Low-Risk Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative bleeding</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Endoleaks (type II)</td>
<td>8</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Postoperative mortality</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

### Abbreviations: AAA, abdominal aortic aneurysm; EVAR, endovascular aneurysm repair.

a Defined as in the ADAM Trial: dyspnea at rest, home oxygen use, or forced expiratory volume in the first second of expiration less than both 1.5 L and 50% of predicted value.

b Congestive heart failure was not evaluated using New York Heart Association Functional Class scoring as in the ADAM Trial but was considered a risk if noted as a diagnosis in the medical record.

c Thallium scan results were only available for 16 patients.

**SI conversion factor:** To convert creatinine to micromoles per liter, multiply by 88.4.
no endoleak was present. Two type II endoleaks reported in Table 3 were detected on follow-up computed tomographic angiogram at 33 and 35 days. No type I endoleaks occurred. Postoperative mortality was noted in 1 high-risk patient who died at home 4 days after surgery; myocardial infarction was the cause of death. Although not our primary outcome objective, we obtained complete follow-up data on all patients. During the interval of review, 4 patients died more than 30 days after discharge. The mean follow-up period was 1.2 years, with a range of 1 month to 4.8 years. The causes of death were known in 3 patients: ischemic bowel at 4 months, bronchopneumonia at 3 months, pneumonia at 5 months, and an unknown cause at 14 months. Three of these 4 patients who died were in the high-risk category. No statistical difference (P<.05) was noted in postoperative events in the high-risk group compared with the non–high-risk group but the possibility of type II limitations with our relatively small population is recognized.

In recent years, progress in endovascular techniques has allowed aneurysm repair with fewer of the associated risks of open surgery. Three major prospective trials conducted in Europe (EVAR 1,9 EVAR 2,10 and DREAM11) have compared EVAR vs open repair in both high– and low–operative risk patient populations. While the perioperative mortality rates after EVAR are consistently lower than those after open repair, a consensus on the long-term benefit of EVAR has not been reached during this transitional era.12

The low overall 30-day perioperative mortality rate (1 of 44) described in this study (2.3%) is comparable with that experienced in the low-risk patients of previous trials. The British EVAR 1 trial9 and the Dutch DREAM trial,11 both enrolling only patients at low perioperative risk, reported 30-day mortality rates of 1.7% and 1.2%, respectively. Patients excluded from the EVAR 1 trial (based on suggested criteria but ultimately dictated by physician discretion) were considered high risk and enrolled in the EVAR 2 trial.10 The study returned an unexpected high 30-day mortality rate of 9% in EVAR patients, but 27% of the surveillance group crossed over into the treatment group and these patients demonstrated an unexplained mortality rate of just 2%. Nevertheless, to our knowledge, the EVAR 2 trial is the only major prospective clinical trial with EVAR in high-risk patients, and the data remain the best evidence-based standard in this population.

Retrospective reviews of EVAR outcomes for both low- and high-risk patients in US hospitals have reported mortality rates akin to the low-risk patients in the EVAR 1 and DREAM trials. Bush and colleagues,13 examining a surgical procedures database of 123 participating VA hospitals, reported a 30-day mortality rate of 3.1% in all patients receiving EVAR and 3.4% in higher–risk patients receiving EVAR.14 The risk classification in the VA study was based on age older than 60 years, American Society of Anesthesiology class 3 or 4, and a number of comorbidity variables. Using similar criteria, a review of the Swedish Vascular Registry found a 30-day mortality rate of 4.6% in high-risk EVAR patients.15 Additionally, a study of the US Food and Drug Administration investigational device exemption trials showed a 30-day mortality rate of 2.9% in patients who met the EVAR 2 high-risk demographic.16

Two important questions arise. First, the 30-day mortality rates of high-risk patients undergoing EVAR vary by a factor of 3 in the literature. Whether EVAR stands as a safe procedure in patients unfit for open repair cannot be appropriately answered with current data and must be addressed by future prospective trials.

Second, the current evidence-based risk guidelines for AAA intervention are based on the ADAM and UK Small Aneurysm data, which showed no survival benefit in performing open repair in patients with aneurysms smaller than 5.5 cm.17 This guideline represents a trade-off between risk of death from rupture and from surgery. In the current era of EVAR and open repair, the 5.5-cm guideline and the low-risk status of the patients no longer reflect current practice. Our report, with 43% of patients meeting exclusion criteria for the ADAM trial, exemplifies the trend toward intervention for higher-risk patients. Intuition suggests that the 5.5-cm threshold could be reduced if EVAR emerges as a safer procedure than open repair, although the need for any intervention in smaller aneurysms must be considered as well. We realize that it is conceivable, indeed likely, that the majority of patients with small aneurysms, especially those at high risk, would not benefit from any procedure, regardless of the operative risk, because the probability of death from aneurysm-unrelated causes is significantly greater than either the risk of death from rupture or surgery. Nevertheless, it is possible that the growth characteristics of small aneurysms are different (eg, more rapid enlargement) in debilitated patients.

We recognize that the long-term success of EVAR remains controversial; there have been no systematic reviews or meta-analyses to date that demonstrate a clear late, overall survival benefit. While EVAR has been shown to reduce aneurysm-related deaths in the long-term, all-cause mortality appears similar.18 However, long-term survival is a meaningless concept for the patient who does not survive immediate intervention.

The UK Small Aneurysm and ADAM trials are credited with establishing the 5.5-cm guideline as the threshold for open AAA repair. With the success and proliferation of EVAR since publication of these studies, patients of higher perioperative risk are offered EVAR, and the balance of surgical risk vs aneurysmal rupture risk no longer reflects current practice. Our study demonstrates a large high-risk patient cohort (43%) and low all-cause perioperative mortality rate (2.3%) from review of EVAR practices at an urban VA medical center. The current evidence for long-term benefits of EVAR over open repair or surveillance is unclear, as are the appropriate criteria to select patients for this technique. Future efforts are needed for revision of the risk classification for EVAR pa-
patients, reassessment of the 5.5-cm guideline for all patients with AAA, and prospective trials comparing EVAR vs surveillance in high-risk cohorts.

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REFERENCES


DISCUSSION

Cornelius Olcott, MD, Stanford, California: Dr Wilson and his colleagues have brought to our attention an important question which crosses all disciplines of surgery: should technological advances which result in less invasive interventions for the treatment of a disease change or alter the indications for the surgical treatment of that disease. This paper specifically addresses the case of endovascular vs open repair of AAAs and raises the question as to whether we should reevaluate the indications for surgical intervention for AAAs, especially in high-risk patients or with small aneurysms. As the authors point out, much of our present decision making is based on studies comparing open repair to surveillance, and that may not be appropriate with the presumed lower risk of the less invasive endovascular repair.

This is such an important question that several clinical trials have attempted to help us gain insight into the issue. Two trials—the CAESAR trial [Comparison of Surveillance vs Aortic Endografting for Small Aneurysm Repair] in Europe and the PIVOTAL trial [Positive Impact of Endovascular Options for Treating Aneurysms Early] in the US—are presently ongoing to see if EVAR should be offered to patients with smaller AAAs. Just this month the Mayo Clinic published a paper in the Journal of Vascular Surgery comparing the results of EVAR and open repair for small aneurysms.

To put this discussion about EVAR in perspective, I refer you to a paper by Ron Dalman and John Harris that was published in 1998. They reported on 90 consecutive elective AAA open repairs performed at the Palo Alto VA Medical Center. In a high-risk group by any criteria, they had no operative deaths.

The study presented today includes a relatively small number of patients with a short follow-up of 30 days. Most trials are now looking at midterm results in the 3- to 5-year range. To date, none of the major trials have shown definite superiority of either open or endovascular repair of AAAs at midterm evaluation, nor has any trial to date definitively concluded that EVAR should be offered to patients with small aneurysms. The EVAR 2 trial, which compared EVAR to surveillance in higher-risk patients unfit for open repair, did not show any survival benefit for EVAR over no intervention. Paradoxically, however, I should state that almost every trial dealing with endovascular vs open repair or endovascular repair vs no intervention has engendered some controversy within the vascular community regarding its methodology.

I have several questions for the authors:

You list only 1 death within 30 days, which occurred in your high-risk group. However, in an earlier copy of your manuscript, you describe 3 deaths, 2 of which occurred after 30 days but while the patients were still in the hospital. I believe most surgeons would consider these operative deaths. The final draft lists 4 patients that died after 30 days, 3 within the first year. While these deaths occurred after the 30-day window, this is still a significant mortality rate—9.1% at the end of 1 year. Were these aneurysm-related deaths? Does this high mortal-

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ity rate temper your enthusiasm for operating on high-risk patients?

Almost all studies to date have shown better morbidity and mortality rates with EVAR vs open repair at 30 days. However, most studies are now showing similar or slightly better mortality rates with open repair at the midterm time frame. Do you believe that data recorded at 30 days can safely be used to determine or change the indications for intervention for AAAs?

In addition to mortality and morbidity, quality of life and cost should be considered. Most studies show better quality of life with EVAR initially but no difference after 1 to 2 years. Cost appears to be greater with EVAR, primarily because of the cost of the device, mandated postoperative imaging, and reinterventions. Certainly, cost has to be considered in any discussion about lowering the bar for indications. Did you look at either quality of life or cost in your study?

The authors quite correctly conclude that a good randomized clinical trial is needed to help answer the questions posed by this study, and in fact, many are ongoing. Unfortunately, due to the limitations of study size and follow-up, I don’t believe that we can make a decision regarding changing the indications for repair of AAAs based solely on the results of this study. It remains the responsibility of the surgeon to properly evaluate each individual patient with special attention to the operative risk, the risk of aneurysm rupture, and the life expectancy and quality of life. Whenever we consider broadening the indications for surgery, we need to be sure that the morbidity and mortality of the treatment do not exceed those of the natural history of the disease.

Dr Wilson: Large studies of patients in the thousands by necessity rely on administrative databases, often making do with seconhand clinical information entered by nonprofessionals or commercial enterprises primarily interested in calculation of costs. I am not sure they offer the same accuracy in detail that one can obtain from a smaller study of carefully reviewed patient records. In this study, we had the advantage of electronic medical records to find out exactly what happened to the 44 patients with complete follow-up to December 31, 2008, as detailed in the manuscript.

We measured neither costs nor quality of life, although the tated patient is more prone to rupture and more likely to enlarge. But we need to have that natural history before we advocate repair for high-risk patients.

We have shown that almost half of our patients coming to intervention for aneurysm by EVAR are, by strict definition, in a high-risk group. The definition of high risk differs among studies and databases. For example, the highly regarded NSQIP [National Surgical Quality Improvement Program] database was reported as having 721 ASA [American Society of Anesthesiologists] class 4 patients in 2966 who had elective repair, either open or EVAR [Bush RL, Johnson ML, Hedayati N, Henderson WG, Lin PH, Lumssden AB. Performance of endovascular aortic aneurysm repair in high-risk patients: results from the Veterans Affairs National Surgical Quality Improvement Program. J Vasc Surg. 2007;45(2):227-233, discussion 233-235]. In ASA category 4, “severe systemic disease is a constant threat to life,” and yet I would not consider 25% of the patients we operate upon electively for aneurysm to have that degree of risk. So much depends on subjective interpretation of data, beginning with a precise definition of risk and accurate application of the criteria to the medical record.

Our 1-year all-cause mortality after EVAR is similar to the 9% to 12% in other studies of aneurysm disease [eg, Bush RL, Johnson ML, Collins TC, et al. Open versus endovascular abdominal aortic aneurysm repair in VA hospitals. J Am Coll Surg. 2006; 202(4):377-387]. None of the deaths after 30 days was related to the aneurysm. But the major question is whether we should be intervening on such high-risk patients at all because their ultimate survival is probably unrelated to the intervention but to the nature of their systemic disease. Further, how do we assess the long-term results, which often show that no matter what we do, open or EVAR or how safe the procedure, it all works out the same 5 years later. If you don’t survive 30 days, however, you won’t have a chance to find out what happens 5 years later. So I think that argument is not appealing to the individual who has an aneurysm. As a patient, I would not want to be told in the informed consent that even though the mortality is 3 times higher at 30 days with the open method, after all, there is no difference in survival at 5 years. My response would likely be, “I won’t have a chance to make it to 5 years unless you get me through the 1-month interval.”

We measured neither costs nor quality of life, although the latter is likely enhanced by the minimally invasive process.

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