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Randomized EVAR Trials and Advent of Level I Evidence: A Paradigm Shift in Management of Large Abdominal Aortic Aneurysms?

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The recent endovascular aneurysm repair (EVAR) 1 and 2 and Dutch Randomized Endovascular Aneurysm Management (DREAM) trials addressed management of abdominal aortic aneurysms (AAAs) larger than 5.5 cm in diameter. The DREAM and EVAR 1 trials randomized patients appropriate for open repair between endovascular repair (EVAR) and open repair (OR), and the EVAR 2 trial randomized patients unfit for OR between EVAR and conservative nonoperative management (No Rx). The EVAR 1 trial showed a 3% lower initial mortality for EVAR, with a persistent reduction in aneurysm-related death at 4 years. Improvement in overall late survival was not demonstrated. Similarly, the DREAM trial observed an initial mortality advantage for EVAR, but overall 1-year survival was equivalent in both groups. Both trials found significantly higher complication and intervention rates and higher hospital costs with EVAR, and by 1 year a quality of life (QOL) benefit was not evident. The EVAR 2 trial did not demonstrate a survival advantage of EVAR with respect to nonoperative management, while noting that EVAR was associated with greater likelihood of treatment complications, subsequent interventions, and threefold higher costs. Both EVAR trials were limited by long delays between randomization and treatment. Moreover, 27% of patients in EVAR 2 crossed over from nonoperative to endovascular repair, and these patients had a lower procedure mortality from EVAR than those originally assigned to it (2% *v* 9%). These 47 cases, and the exclusion of 14 patients dying while waiting for EVAR, appears to confer a survival advantage to those receiving EVAR over those receiving no treatment in a post-hoc analysis, but per-protocol analysis of the EVAR 2 trial data performed by the EVAR investigators did not show a significant difference in either all-cause or aneurysm-related mortality. Thus, outcomes of the EVAR 2 trial have not settled the choice between EVAR and no treatment in this scenario to everyone's satisfaction. In patients with large AAAs who are fit for OR, EVAR offers an initial mortality advantage over OR, with a persistent reduction in AAA-related death at 4 years. However, EVAR offers no overall survival benefit, is more costly, and requires more interventions and indefinite surveillance with only a brief QOL benefit. It may or may not offer a mortality benefit over nonoperative management in patients with large AAAs who are unfit for open repair, but the statistical significance of this comparison is inconclusive.

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IN THE MIDDLE of 2005, three randomized trials of endovascular aneurysm repair (EVAR) were published. Each involved large (>5.5 cm) infrarenal abdominal aortic aneurysms (AAAs). These were the first randomized trials of EVAR and they present us with the first level I evidence regarding this new technique. It has been suggested that the findings of these EVAR trials justify a paradigm shift in management of AAAs. The purpose of this article is to examine that evidence and discuss its appropriate impact on AAA management.

Review of the Status of EVAR Prior to Publication of Randomized Trials

Prior to publication of these European randomized trials, our information regarding EVAR came from institutional experiences, registry reports, and US Food and Drug Administra-

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tion (FDA) device trials, particularly Phase II or pivotal trials of various devices conducted in the United States. The statistically significant advantages of EVAR over open repair (OR) established by these trials included (1) reduced cardiac and pulmonary morbidity, (2) decreased length of stay in the hospital and in intensive care units, and (3) reduced blood loss and transfusion requirements. The hoped-for mortality advantage was not shown. Indeed, no significant difference was observed in 30-day operative mortality.[1] In fact, combined mortality mean data favored OR (0.93% OR *v* 1.64% EVAR). Only one device trial reported a significant initial mortality advantage for EVAR over OR, but this was noted in only one subgroup (Zenith, standard risk group). In addition, late survival after EVAR has been no better, and more often worse than that after OR, possibly due to the frequent need for reintervention in EVAR. There had been suggestive, though not conclusive, data indicating that EVAR offers an advantage in reducing AAA-related deaths.[2] This endpoint eliminates the overwhelming effect on overall late mortality due to associated comorbidities.

Other Problems Limiting Acceptance of EVAR

In addition to an absence of an overall survival benefit, either early or late, for EVAR, there are a number of complications and other problems that are specific to EVAR, which continue to be of concern. The problem of endoleak remains, although its apparent incidence had been reduced by more aggressive intervention at the time of endograft implantation. The true prevalence of endotension and the significance of this effect on outcomes are still unresolved, and there is a small but definite risk of device migration, leading to late type II or III endoleak, and even AAA rupture. These combined to produce the need for indefinite surveillance and a significantly greater need for secondary procedures. Subsequent interventions, mandatory surveillance, the imaging requirements to evaluate patients prior to and during EVAR, along with the considerable cost of the device, have overwhelmed the initial cost savings resulting from shorter hospitalization and reduced use of hospital resources and blood transfusion. All told, this has led to significantly higher overall costs for EVAR.[3,4] Finally, studies now show that beyond the initial treatment period, EVAR does not improve quality of life.[5]

Recent Progress: An Improving Prospective

As one might expect with any new technology, the early years are full of problems, with first-generation devices falling by the wayside, and others withdrawn because of legal concerns or inadequate demand. Most current commercial endografts have been modified and new devices introduced in response to detected failure modes and perceived limitations of first-generation systems. In addition, newer devices have reduced profiles and their deployment systems have been improved. Adjunctive devices, such as extenders, and rescue techniques have been developed and refined. Considerable progress has been made, with current devices reporting steadily improving initial outcomes. For most institutions involved in performing EVAR, the learning curve has passed and technical mishaps have been greatly reduced. The technical success rate for EVAR has risen from less than 90% to over 97%. The need for conversion to OR had been reduced substantially. A recent analysis of the European Collaborators on Stent-Graft Techniques for Abdominal Aortic Aneurysm Repair (EUROSTAR) data, with withdrawn devices excluded, has confirmed these trends.[6-8] Recently, Anderson et al[9] and Lee et al[10] have shown an initial mortality advantage for EVAR over OR (3.8% *v* 1.4%, combined data). While the durability of new or modified endografts remains to be established, the effects of improving technology and operator skills have had a significant impact.

Indications for EVAR Before European Trials

Both the UK small AAA trial[11] and the Aneurysm Diagnosis And Management (ADAM) trial[12] failed to demonstrate a long-term survival advantage for early surgical intervention when compared with continued ultrasonography observation for small aneurysms in the range of 4 to 5.5 cm. These trials have reinforced conservative nonoperative management as appropriate for aneurysms of this size. A recent review of EVAR versus OR[1] concurred with these recommendations for small aneurysms, but also concluded that "using EVAR in patients who are quite fit for OR and have an otherwise reasonable longevity outlook when EVAR's durability has not been well-established, seems imprudent, at least at this point in the evolution of this new technology. On the other hand, EVAR is an appropriate elective treatment for patients with AAAs who have significant comorbidities and suitable anatomy and for patients with relatively limited life expectancy *and* larger or enlarging AAA's." The guidelines of a subcommittee of the American Association for Vascular Surgery and the Society for Vascular Surgery[13] concluded, among other things, that EVAR should be limited to large aneurysms with suitable anatomy in those unfit for OR. A recent FDA analysis of available EVAR devices with long-term data drew similar conclusions.[14] Finally, a decision-model analysis of data from the EUROSTAR registry also suggested that while EVAR is preferred for older patients with higher operative risk, open repair is preferred for younger patients with low operative risk.[15] These positions reflect both the apparent lack of a mortality benefit for EVAR and concerns over the durability of this treatment. While these positions may seem appropriate, it bears noting that in the US device trials, patients were not randomized, concurrent open surgical controls often consisted of patients who had unsuitable anatomy for EVAR, and the majority of patients treated with endovascular devices had aneurysms less than 5.5 cm in diameter. In contrast, the three recent European trials of EVAR involved only large aneurysms (>5.5 cm) and were randomized, so their results provide level I evidence for those

patients who are likely in greatest need of intervention. The publication of these trials in 2005 has generated considerable discussion as to their implications regarding AAA management. EVAR trial investigators suggest that data from the EVAR 1 trial supports endovascular management of large AAAs even in patients fit for OR. However, before accepting this recommendation, the evidence from these trials deserves close scrutiny, which is the intent of this article.

Dutch Randomized Endovascular Aneurysm Management Trial

The Dutch Randomized Endovascular Aneurysm Management (DREAM) trial was a multicentered randomized trial of EVAR versus OR, in which 351 patients were randomized with aneurysms larger than 5.5 cm. Patients were enrolled if considered fit for OR and had suitable anatomy for EVAR. Initial results were reported in 2004[16] and revealed a 30-day mortality rate in favor of EVAR (1.2% EVAR *v* 4.6% OR). Two-year follow-up results were reported in 2005[17] and demonstrated that all-cause mortality was not significantly different between the two approaches (20.4% EVAR *v* 20.3% OR). Although a trend toward reduced aneurysm-related death was noted for EVAR (2.1% EVAR *v* 5.7% OR), this difference was not statistically different. Quality of life (QOL) improved initially for EVAR, but after 6 months it was equivalent for both groups. Substantially higher hospital costs were also documented. The authors concluded that the initial mortality advantage of EVAR over open surgical repair was lost by 1 year because of the contribution of nonaneurysm-related deaths.

EVAR 1 and 2 Trials

In the United Kingdom, two EVAR trials have been conducted in which patients were enrolled with large AAAs with suitable anatomy for EVAR. In the EVAR 1 trial,[18] like the DREAM trial, patients with large (>5.5 cm) AAAs who were considered fit for surgery were randomized between EVAR and OR. Of the 4,799 screened patients, 22 refused enrollment, 273 dropped out during evaluation, 286 were eliminated because of missing computed tomography data, and 313 had AAAs less than 5.5 cm. Significantly, 1,795 (54%) were eliminated due to unsuitable EVAR anatomy and another 457 (1.4%) patients were excluded because they were considered unfit for OR. The latter were recruited into the EVAR 2 trial.[19] Thus, 1,423 patients were eligible for inclusion in this study. Of these, an additional 341 refused randomization or preferred other treatment or no treatment, leaving 1,082 patients for randomization. A total of 543 were assigned to EVAR, but 10 died before receiving treatment (3 ruptured AAA). Fifteen others had OR and the remaining 517 underwent EVAR. Of the 539 randomized to OR, 13 died before receiving this treatment (7 ruptured AAA), 500 received OR, and 18 received EVAR.

EVAR 1

The primary endpoint of EVAR 1 was all-cause mortality and at 4 years there was no advantage to either form of repair with approximately 28% mortality in both treatment groups.[18] However, as a secondary endpoint, aneurysm-related death was significantly reduced among patients treated by endovascular repair. An initial 3% perioperative mortality advantage for EVAR (1.7% EVAR *v* 4.7% OR) was maintained at 4 years in aneurysm-related death (26% EVAR *v* 29% OR; $P = .04$). Compared with OR, disadvantages in three other secondary endpoints were observed for those treated with EVAR. Complication rate for EVAR was 41% compared with 9% for surgical repair. Reintervention rate for EVAR was 20% as opposed to 6% for open surgery and hospital costs were one-third higher for EVAR. There was no difference in QOL by 12 months. The conclusions of this report emphasized that the 3% perioperative mortality advantage was maintained at 4 years in terms of aneurysm-related death.

A number of key observations of the EVAR 1 trial deserve comment. First, the significant preoperative death and rupture rate is cause for concern and may well be related to the considerable delay from randomization to treatment (mean 57 days), despite a mean aneurysm diameter of 6.7 cm. This might have accounted for 10 preoperative aneurysm ruptures. In fairness, removing these preoperative deaths does not alter the advantage for EVAR in AAA-related death. Second, it might seem disappointing that only 23% of those assessed were eligible for randomization. However, two-thirds of those eliminated had very valid reasons, including small aneurysms (9%), anatomic unsuitability (54%), or unfit for OR (1.5%). In addition, only 24% of patients had reached the 4-year endpoint for analysis, with 72% of the remaining cohort alive. Clearly, longer follow-up observations will be important and might modify the conclusions of this study. Finally, hospital costs were only roughly estimated from use of key resources, questionnaires, and trial records. Out-of-hospital costs (eg, expense of preoperative and surveillance imaging) and the costs of later reinterventions and complications were not included.

On the positive side, it is fair to note that the intent-to-treat analysis did not favor either group, a variety of present-day endografts were used, and the results were probably not at odds with recent reports showing improved results with current endografts. The one thing that would not be generalizable, at least to US practice, were the significant treatment delays for large AAAs. An average wait of 2 months for treatment of AAAs of this size is much too long.

EVAR 2

The EVAR 2 trial pitted EVAR against no intervention (No Rx) for those patients unfit for OR.[19] The trial randomized 338 patients, many of whom were identified during the EVAR 1 recruitment. A total of 166 were randomized to EVAR, but 20 patients did not receive this treatment; 14 died awaiting EVAR (with 6 AAA ruptures), there was one conversion, the procedure was abandoned in one patient, and four received OR. Of the 172 randomized to no treatment, 47

crossed over to receive intervention. Thirty five received EVAR but 12 received open surgical repair. A 9% 30-day mortality rate was observed for EVAR and this included 14 deaths that occurred during the period *before* treatment. The overall mortality was 40% (68 of 172) for those enrolled in the no-treatment arm and 45% (74 of 166) for EVAR. A total of 64% of all patients died during follow-up with no significant difference between groups (62% *v* 66%). Aneurysm-related death was 14% for EVAR, 19% for No Rx. A crossover was observed at 2 years with a late trend, though not statistically significant, in favor of EVAR. Interventions were greater for EVAR (43% *v* 26%) and hospital costs were over three times higher for EVAR than No Rx. Of interest, patients crossing over to interventional treatment displayed an initial mortality of 2% and a late overall mortality of 23%.

EVAR 2 was criticized because of the large number of patient crossovers from the no-treatment group and long delays in treatment. The per protocol analysis reported by the EVAR investigators, using hazards ratios, showed no significant difference in all cause or aneurysm related deaths ($P = .7$, $P = .43$, respectively). Presumably, their analysis included the 14 who died while awaiting EVAR in the EVAR treatment group. However, if patients who died awaiting treatment (n = 14) are eliminated from the EVAR group and 47 patients who crossed over to repair are included in this modified "treatment" group, a 36% mortality (71 of 197) is observed and this is significantly less than the 46% mortality (57 of 125) of those patients in the No Rx arm. However, 16 of the crossover patients received OR, not EVAR, reducing the denominator to 181 for a 39% mortality, which does *not* reach statistical significance compared to the 46% mortality of those staying with No Rx. So post hoc analyses of these suggestive data do not really support EVAR over No Rx.

Of significance, however, the 23% mortality for those patients receiving EVAR or OR after leaving the no-treatment group and crossing over to receive an intervention is clearly significantly different than the 40% mortality for those initially assigned to EVAR.

As Cronenwett[20] whimsically commented in his accompanying review of these two trials in *Lancet*, that this result could be taken to show that in this setting physician/patient decision is superior to randomization. Paraphrasing this, being assigned to EVAR carried a greater risk than subsequently choosing an intervention. It is worth pointing out that the reasons for crossover to EVAR in this trial were analyzed and, although varied, were quite unlike those experienced in the surveillance groups in the UK small aneurysm trial, where roughly two-thirds of patients crossed over to surgery because of symptoms or aneurysm enlargement. Crossover in the EVAR 2 trial was attributed in a small proportion of patients to fast growth (n = 5), but in the majority of crossovers the decision for repair was a result of patient choice or unknown reasons (n = 28) or "tenderness" (n = 11).

Impact of Trials on AAA Management

How should these trials affect the process of deciding between endovascular, OR, and conservative management? First, these trials apply to only two of the four large aneurysm categories. Specifically, patients who may or may not be suitable for open surgery, but who have a large aneurysm and are anatomically appropriate for EVAR. OR for those with a large aneurysm who are fit for surgery but have unsuitable anatomy for EVAR goes unchallenged. Management of those patients who are high risk for OR but have unsuitable anatomy for EVAR remains a dilemma. Certainly, if patient risk can be reduced or should the aneurysm become symptomatic, OR seems a reasonable approach. The informed patient can help in this decision.

Observation with ultrasonography surveillance of small aneurysms seemed justified on the basis of the UK and ADAM small AAA trials. There are two randomized trials addressing the role of EVAR versus surveillance in small aneurysms (PIVOTAL and CEASAR), but each of these is supported by the manufacturer of the single device employed in the trial. Admittedly, because EVAR has been shown to achieve better results in smaller, as compared with larger, AAAs[21,22] it is conceivable that endovascular intervention could be shown to be superior to a surveillance program, particularly if the endpoint is aneurysm-related death. Against this is the lack of a mortality advantage for EVAR over OR in FDA trials, which were predominantly small aneurysms, with the aggregate procedural mortality for EVAR in these trials of 1.64% being greater than the annual mortality for a surveillance strategy in the UK and ADAM small aneurysm trials ($\leq$1% per year). If an advantage for EVAR in an aneurysm-related mortality is demonstrated, it would be of interest to reanalyze the UK and ADAM trial data using the same AAA-related mortality endpoint applied to open repair. It is conceivable that all-cause mortality in those trials was dominated by death from comorbid conditions and obscured any late advantage for early surgical repair in terms of reducing aneurysm-related death. This may be particularly valuable to do in the ADAM trial because it was associated with a low perioperative mortality for OR. Use of AAA-related death rather than all-cause mortality as an endpoint is a key issue here, and in many other observations, and this will be discussed further.

Before accepting the conclusions of the EVAR 1 and 2 and DREAM trials, each physician needs to address the following questions, not necessarily in agreement with the author's comments.

1. Is a 3% reduction in aneurysm-related death associated with endovascular repair of large aneurysms worth the higher costs in the absence of an improvement in overall late mortality or a sustained benefit in quality of life?

The answer to this must be an individual one for physician and patient, but should be part of any informed consent. A comprehensive statement could include that "this procedure carries a lower initial morbidity and mortality and will also protect you from late aneurysm-related death. However, current data does not support that this procedure will prolong your overall life expectancy. While endovascular repair does provide an initial advantage in terms of quality of life, when compared with treatment by open surgery, this benefit is limited to the first few months after repair. When compared with open surgery, endovascular repair is associated with a

greater need for subsequent catheter-based procedures with an attendant risk of complications, requires indefinite CT scan surveillance, and costs more."

Two additional perspectives are added here for the reader's consideration. The choice between aneurysm-related death and all-cause mortality is more than just a question of whether the goal of treatment is just to prevent death from aneurysm rupture or to prolong life. In principle, AAA-related death seems like a fairer endpoint, intended as it is to avoid penalizing EVAR for deaths from comorbidities that it is not designed to prevent. The author supports this principle, but in practice this endpoint appears to favor EVAR. Lederle[23,24] has pointed out that, unless the cause of death is accurately documented by an autopsy or a physician in attendance aneurysm-related death is not as accurate as all-cause mortality in comparing aneurysm management strategies. Obviously, one must attribute 30-day perioperative mortality to an intervention, but most deaths thereafter are attributed to nonaneurysm-related causes in the absence of a witnessed fatal rupture. In the present era of infrequent autopsies, this favors EVAR over OR by sustaining its initial mortality benefit. There is an observed tendency whenever the 30-day mortality significantly favors EVAR, for this advantage to be sustained if AAA-related death is the late endpoint. Because neither endpoint is perfect, both should be reported to give the reader the full perspective. Both the DREAM and EVAR 1 trials did this, but in drawing their conclusions the DREAM trialists emphasized their primary endpoint and the EVAR trialists emphasized this secondary endpoint.

Costs are also worth considering and are a necessary concern in countries or regions with limited resources. A recent cost analysis, modeled after the EVAR 1 and EVAR 2 trial scenarios,[25] found that EVAR for a 70-year-old patient with a 5.5-cm AAA who was otherwise fit for surgery would provide an estimated benefit of only 0.10 quality adjusted life years (QALYs) when compared with open surgery at an incremental cost-effectiveness ratio of close to $200,000 (10,000 UK pounds sterling) per QALY. For an 80-year-old with a 6.5-cm AAA who was unfit for open repair, EVAR would produce an estimated benefit of 1.64 QALYs compared with conservative management at an incremental cost-effectiveness ratio of roughly $15,000 (8,579 UK pounds sterling) per QALY, which is much more acceptable.

2. Should EVAR be chosen over OR for all "fit" patients with large AAAs (>5.5 cm) or only for older patients with limited longevity where an absolute survival advantage from endovascular repair may be apparent? Are the underlying considerations of durability, increased reinterventions, and costs valid concerns?

An analysis of long-term EVAR 1 data anticipated in 2010 may, in large part, answer this question. Because 72% of patients entered into this trial remain alive at 4 years, this late analysis could even modify the original conclusions of the study. It would seem appropriate at present to offer EVAR to patients with large AAAs whose comorbidities preclude longevity well beyond the proven durability of current endograft devices, some of which have been modified to overcome failure modes only within the last 2 to 3 years. Then, until follow-up proves the durability of current devices and/or the EVAR 1 results hold up, one would be justified in offering OR to relatively younger patients with no or minor comorbidities, for whom an extended longevity can be expected. The latter scenario would seem to represent the minority of those presenting for intervention because of large AAAs.

3. Has EVAR 2 satisfactorily solved the treatment choice for those "unfit" for OR? The potential advantage of EVAR may have been obscured in the EVAR 2 trial, for the reasons given above. If EVAR indeed has no advantage over conservative management for patients with large aneurysms and who are at high risk for OR, it would be a great pity because these are precisely the patients for whom EVAR was designed to offer a low-risk alternative. Even if the benefit of EVAR over no treatment is slim, the author personally would favor EVAR in this situation, after intensive in-hospital treatment of their comorbidities. However, healthcare organizations and funding agencies may not accept this choice if EVAR does not extend survival and is three times more expensive.

Conclusions

It is heartening to have level I evidence to assist in decisions regarding the application of EVAR and we should be grateful to our European colleagues and their healthcare systems for carrying out these studies. The climate in the United States, with patients exposed to so much hype for EVAR almost precludes proper randomized trials, as has been the case for device-specific FDA trials. Nonetheless, even level I evidence should be examined closely, to determine if it draws valid conclusions and can be generalized to one's own practice. It is hoped that the above in-depth analysis will be helpful to the readers in that regard.

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