Impact of the EVAR-1 and DREAM Trials

Is endovascular aneurysm repair better than open repair, or is the race still on?

BY JAN D. BLANKENSTEIJN, MD

Recently, two independent randomized trials, the Endovascular Aneurysm Repair Trial1 (EVAR-1) and the Dutch Randomized Endovascular Aneurysm Management Trial (DREAM) have reported lower operative mortality rates after endovascular aneurysm repair (EVAR) as compared to open repair (OR).[1,2]

Regardless of what some in the vascular field may want us to believe, operative mortality rates are compelling arguments from a patient's perspective. But is EVAR really preferable if both procedures are optional? And how do we convince patients with the trial results at hand otherwise?

Some claim that conclusions of EVAR-1 and DREAM differ dramatically.[3] But do they really? And if so, is this based on differences in trial design, outcome, or interpretation of data? Are there any solid conclusions to be drawn from the currently available data? Do we really need to wait for years until the long-term results of the trials are published before we can convincingly advise patients on the best treatment option?

BEFORE THE RANDOMIZED TRIALS

It is interesting to note that until recently, none of the controlled studies comparing EVAR with OR showed significant improvement in operative mortality rates. In 2004, two population-based studies demonstrated reduced operative mortality for EVAR as compared to OR, with figures close to those of the randomized trials.[4,5] The available controlled studies are listed according to their level of evidence in Table 1, and the weighted averages of reported operative mortalities are given in Figure 1. Despite lack of convincing evidence of EVAR's superiority over OR with respect to operative mortality, in almost all studies, EVAR was associated with shorter hospital and ICU stay, reduced blood loss and transfusion, quicker recovery, and improvement of other soft endpoints. Considering the fact that

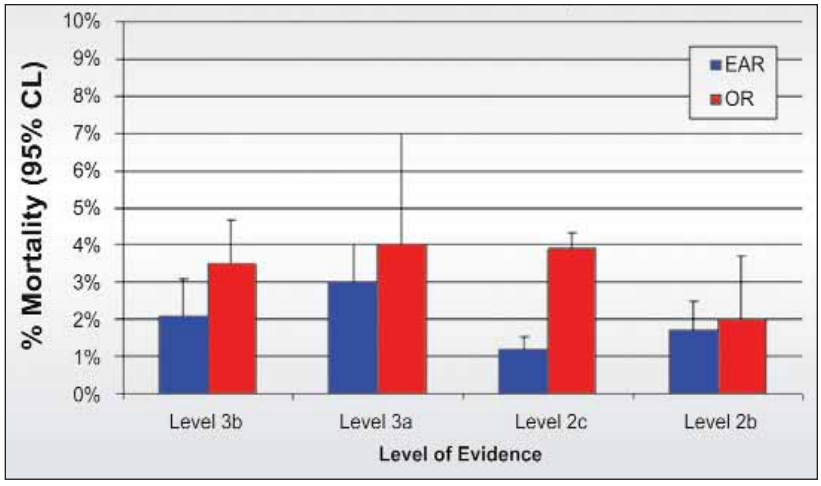

Figure 1. The reported 30-day mortality rates for EVAR (blue) and OR (red) before the randomized trials.

TABLE 1. NUMBER OF PUBLICATIONS ON EVAR AND OPEN ANEURYSM REPAIR BEFORE THE RANDOMIZED TRIALS ACCORDING TO LEVEL OF EVIDENCE (OCTOBER 2004)

Level	Type	Number
1	Randomized controlled trials (RCT)	0
2	Prospective, nonrandomized controlled trials (cohort studies)	
2a	Systematic review of prospective cohort studies	0
2b	Individual prospective cohort studies[6-9]	4
2c	Population 'outcomes' studies[4,5]	2
3	Retrospective cohort studies	
3a	Systematic review retrospective cohort studies[10,11]	2
3b	Individual retrospective cohort studies	10 (-2)*
4	Case series (no control or historical control group)	>100
5	Expert opinion (without critical appraisal)	>100

**Of 10 Level 3b publications, two reported on the same cohort of patients.*

these studies include endografts for high-surgical-risk patients and open repairs in patients with unsuitable anatomy, the similarity in outcome between the population-based registries and the randomized trials is more likely a matter of coincidence.

EVAR-1 AND DREAM DATA

The trial designs of DREAM and EVAR-1 are almost identical. Because the DREAM trial was powered to show a difference in combined operative mortality and moderate or severe morbidity, a smaller number of patients (n=400) was scheduled for inclusion. The EVAR-1 trial was based on hypothetical annual mortality rates of 7.5% after OR and 5% after EVAR, requiring 450 patients in each arm with at least 3-year follow-up for the analysis. It is unclear why the EVAR-1 trial investigators decided to publish operative mortality data prematurely—the primary endpoint was long-term all-cause mortality. Clearly, operative mortality was not considered as a stopping rule for the interim analysis because the trial would have been stopped long before 1,000 patients were randomized.

Despite the difference in power analysis and primary endpoints, both trials reported on operative mortality. DREAM defined 30-day mortality as deaths occurring within 30 days of surgery, or after 30 days but during the same admission (in-hospital mortality). EVAR-1 also reported in-hospital mortality. When comparing both trials based on outcome-by-protocol analysis, the in-hospital mortality for DREAM was 4.6% for OR and 1.2% for EVAR (risk ratio = 3.9), whereas the in-hospital mortality for EVAR-1 was 6% for OR and 1.6% for EVAR (risk ratio = 3.9). The risk ratios were identical. Not surprisingly, both trials showed significantly better outcomes in terms of the soft endpoints listed previously.

CLINICAL EQUIPOISE?

The EVAR-1 trial concluded: "Results are a license to continue scientific evaluation of EVAR, but not to change clinical practice." This translates into stating that there is still clinical equipoise between EVAR and OR for patients suitable for both procedures. The conclusion of the DREAM trial was: "… in patients who are candidates for both techniques, endovascular repair is preferable to open repair." At first glance, it is rather surprising that the larger (EVAR-1) trial seems to be more reluctant in putting forward clinical advice than the smaller DREAM trial. Taking into account that the DREAM trial was designed to show a difference in early outcome, whereas the underlying hypothesis of the EVAR-1 trial was based on all-cause long-term mortality, the only real surprise is the EVAR-1 trial publishing 30-day results. Both trials stressed the fact that long-term evaluation is needed to determine whether the early advantage of EVAR is sustained.

The Veterans Affairs Open Versus Endovascular Repair (OVER) trial, and the French Anévrisme de l'aorte Abdominale: Chirurgie Versus Endoprothèse (ACE) trial are currently recruiting patients. The EVAR-1 trial is also still randomizing patients. Considering the primary endpoint of the trial (long-term, all-cause mortality), continued randomization clearly makes sense but it may become

increasingly hard to convince patients to sign the informed consent. The ethical implications of this situation in which reimbursement issues also come into play are discussed in a recent editorial of the *European Journal of Vascular and Endovascular Surgery*.[12]

In his editorial accompanying the DREAM trial publication in the *New England Journal of Medicine*, Frank Lederle, MD, supports the view of the EVAR trialists.[13] He concludes: "If the patient is a candidate for either open or endovascular repair, referral to a randomized trial is the best option." This statement is based on the concept that a less-invasive treatment can only be proven superior to a more risky procedure if long-term results are known. For instance, the same dilemma arises in trials comparing PTCA with CABG and carotid endarterectomy with carotid artery stenting. Intuitively, this premise makes sense, but there are several issues limiting its relevance for AAA patients.

In this relatively frail population, considerable long-term risks are required to balance off the added perioperative mortality of open repair. And when addressing these endograft-durability issues, the only real long-term data source is Eurostar.[14] One obvious disadvantage of this registry is that most of the long-term data apply to preceding generations of endografts that are no longer available. There is little doubt that long-term results of the newer endografts have improved. Also, it is not unlikely that long-term results after OR are less favorable than expected when these patients are scrutinized using the vigorous follow-up protocols designed for surveillance of EVAR. Finally, when incorporating long-term results into the debate on EVAR versus OR, it should be realized that "long-term" is not an issue in a large subset of patients, even though objectively they may be candidates for OR.

The bottom-line question then becomes whether the perioperative mortality gain of the less-invasive technique is large enough to sustain survival benefit for the remaining life years, despite the potential increased risk of long-term, disease-specific complications. Clearly, the answer to this question is different for a relatively old and high-risk patient as compared to a relatively young and low-risk patient.

Another approach of interpreting the randomized trial results is one based on the principle *primum non nocere* (first do no harm). Along those lines, doing as little intervention as possible has almost become a code in vascular

surgery. Should we apply this code to AAA repair? From that point of view, the EVAR-1 and DREAM trials certainly provide justification to offer endovascular repair to all AAA patients. The only remaining question with this approach is how much of an increase in long-term AAA-related mortality after EVAR can be accepted before it balances out with OR outcomes.

An important issue is patient selection. Obviously, both trials only included patients suitable for OR but, nevertheless, a wide range of surgical risks, as well as ages, were represented in the trial arms. Consequently, if EVAR is threefold better than OR for the average patient, then for the relatively old AAA patient with increased surgical risk but who is still suitable for OR, the choice between EVAR and OR becomes even less difficult. Moreover, for this group of patients, long-term data are also less important.

More caution is necessary at the other end of the age and risk spectrum. The relatively young patient with good surgical risk and still many years to live may end up sacrificing more in the long run than EVAR can avoid perioperatively. It seems that long-term data of the trials are particularly relevant for this subset of patients.

According to the EVAR-1 trialists and Dr. Lederle, we should wait before changing clinical practice. There are no scientific reasons to disagree. But, is there really nothing we have learned from these trials? Is it hard to predict what the 1-year results will be and how these will affect our clinical management of AAA patients?

We already know that there is little quality-of-life and sexual function advantage, and that this is of short duration after EVAR as compared to OR.[15,16] With respect to survival, the 30-day advantage of EVAR patients theoretically will taper off in the first year because the less-invasive treatment is most likely to have prevented death in those patients at risk of dying in the first year. Conversely, the patients surviving 30 days after the more invasive OR procedure are more likely to survive the first year than the remaining EVAR patients. The effect of this proportional-hazards problem can be expected to play an important role in the first year. Consequently, a large part of the early survival advantage of EVAR over OR will be lost in that period. Whether survival rates of EVAR patients will continue to decline after meeting the OR curve is debatable, but it seems unlikely that the differential late mortality after EVAR will be so extreme that long-term OR outcome will prevail for all elective AAA-repair patients.

A new challenge is to preoperatively identify patients who would survive EVAR, but not the first postoperative year. These patients probably should not be operated on for their AAA at all. Another strategy could be to develop medical treatment strategies that help to maintain the perioperative survival advantage of EVAR.[17,18]

CONCLUSION

In the face of the currently available data, it seems farfetched to maintain clinical equipoise for all patients eligible for elective AAA repair. Although not entirely evidence-based, there is some justification for offering EVAR to all eligible patients, especially to those at the upper end of the age and surgical-risk spectrum. More randomized data with long-term follow-up are definitely needed. At the same time, however, the currently running randomized trials will be increasingly hard to complete, and ethical issues and stopping rules may need reconsideration. In any event, the clinical equipoise between EVAR and OR appears to have moved to younger and healthier patient strata. ■

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1. Dutch trial conclusions differ from those of EVAR trial 1. Vascular News (North American Edition). November 2004:1
2. Prinssen M, Verhoeven EL, Buth J, et al. A randomized trial comparing conventional and endovascular repair of abdominal aortic aneurysms. N Engl J Med. 2004;351:1607-1618.
3. Greenhalgh RM, Brown LC, Kwong GP, et al. Comparison of endovascular aneurysm repair with open repair in patients with abdominal aortic aneurysm (EVAR trial 1), 30-day operative mortality results: randomised controlled trial. Lancet. 2004;364:843-848.
4. Anderson PL, Arons RR, Moskowitz AJ, et al. A statewide experience with endovascular abdominal aortic aneurysm repair: rapid diffusion with excellent early results. J Vasc Surg. 2004;39:10-19.
5. Lee WA, Carter JW, Upchurch G, et al. Perioperative outcomes after open and endovascular repair of intact abdominal aortic aneurysms in the United States during 2001. J Vasc Surg. 2004;39:491-496.
6. Zarins CK. The US AneuRx clinical trial: 6-year clinical update 2002. J Vasc Surg. 2003;37:904-908.
7. Matsumura JS, Brewster DC, Makaroun MS, et al. A multicenter controlled clinical trial of open versus endovascular treatment of abdominal aortic aneurysm. J Vasc Surg. 2003;37:262-271.
8. Greenberg RK, Chuter TA, Sternbergh WC III, et al. Zenith AAA endovascular graft: Intermediate-term results of the US multicenter trial. J Vasc Surg. 2004;39:1209-1218.
9. Moore WS, Matsumura JS, Makaroun MS, et al. Five-year interim comparison of the Guidant bifurcated endograft with open repair of abdominal aortic aneurysm. J Vasc Surg. 2003;38:46-55.
10. Adriaensen ME, Bosch JL, Halpern EF, et al. Elective endovascular versus open surgical repair of abdominal aortic aneurysms: systematic review of short-term results. Radiology. 2002;224:739-747.
11. Maher MM, McNamara AM, MacEneaney PM, et al. Abdominal aortic aneurysms: elective endovascular repair versus conventional surgery—evaluation with evidence-based medicine techniques. Radiology. 2003;228:647-658.
12. Mavroforou A, Giannoukas AD, Gaines P, et al. Ethical dilemmas regarding treatment when recruitment ends in randomized trials. Eur J Vasc Endovasc Surg. 2004;28:571-572.
13. Lederle FA. Abdominal aortic aneurysm—open versus endovascular repair. N Engl J Med. 2004;351:1677-1679.
14. Harris PL, Buth J. An update on the important findings from the EUROSTAR EVAR registry. Vascular. 2004;12:33-38.
15. Prinssen M, Buskens E, Blankensteijn JD. Quality of life endovascular and open AAA repair. Results of a randomised trial. Eur J Vasc Endovasc Surg. 2004;27:121-127.
16. Prinssen M, Buskens E, Tutein et al. Sexual dysfunction after conventional and endovascular AAA repair: results of the DREAM trial. J Endovasc Ther. 2004;11:613-620.
17. Kertai MD, Boersma E, Westerhout CM, et al. Association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery. Am J Med. 2004;116:96-103.
18. Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. Circulation. 2003;107:1848-1851.