

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 sig-

nificant 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

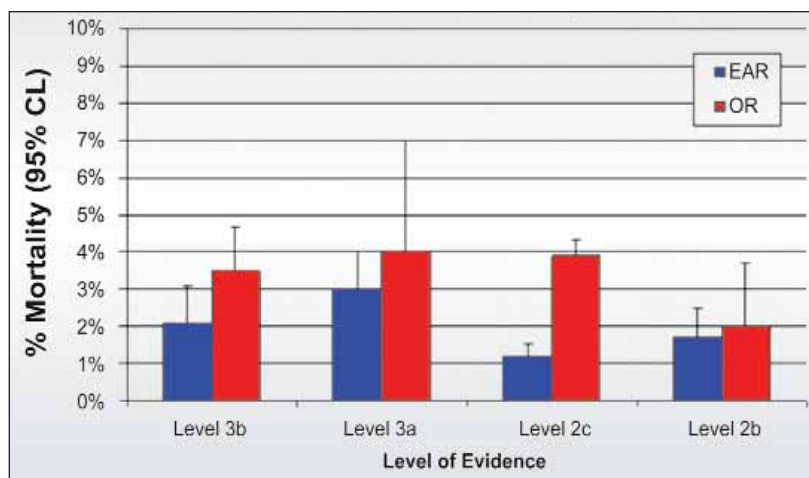


Figure 1. The reported 30-day mortality rates for EVAR (blue) and OR (red) before the randomized trials.

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 reg-

istry 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

Indications

The AneurX Stent Graft System is indicated for the endovascular treatment of infrarenal abdominal aortic or aorto-iliac aneurysms having:

- adequate iliac/femoral access;
- infrarenal non-aneurysmal neck length of greater than 1 cm at the proximal and distal ends of the aneurysm and an inner vessel diameter approximately 10-20% smaller than the labeled device diameter;
- morphology suitable for endovascular repair;
- one of the following:
 - aneurysm diameter of >5 cm
 - aneurysm diameter of 4-5 cm which has also increased in size by 0.5 cm in the last 6 months; or
 - aneurysm which is twice the diameter of the normal infrarenal aorta.

Contraindications

There are no known contraindications currently associated with this device.

Warnings and Precautions

FDA approval of the AneurX device on September 28, 1999 was based upon 1 year follow up data. The clinical information in this Brief Statement has been updated from the information originally submitted to the FDA for approval to include updated clinical information available to Medtronic as of August 1, 2003 (the clinical data freeze date for the 2003 PMA Annual Report).

The AneurX Stent Graft is intended to prevent rupture of abdominal aortic aneurysms. However, this risk is not completely eliminated. Based on reports received for patients enrolled in all phases of the clinical study, through August 1, 2003, ruptures have occurred in 2/1193 (0.167%) patients during the operative period; in 3/1193 (0.251%) patients within 30 days of treatment; and in 15/1193 (1.257%) patients greater than 30 days after treatment. The one year freedom from rupture rate for patients enrolled in all phases of the clinical study is 99.5%; the two year freedom from rupture rate is 98.6%; the three year freedom from rup-

ture rate is 98.5%; the 4 year freedom from rupture rate is 97.2%, and the 5 year freedom from rupture rate is 97.2%.

The long term safety and effectiveness of this implant has not been established. All patients with endovascular aneurysm repair must undergo periodic imaging to evaluate the stent graft, aneurysm size, and occlusion of vessels in the treatment area. Significant aneurysm enlargement (>5 mm), the appearance of a new endoleak, evidence of perigraft flow, change in aneurysm pulsatility, or migration resulting in an inadequate seal zone should prompt further investigation and may indicate the need for additional intervention or surgical conversion.

Exercise care in the handling and delivery technique to aid in the prevention of vessel rupture. If an AneurX Stent Graft is placed with less than one centimeter length of non-aneurysmal tissue at the proximal or distal attachment sites, there is potential for leaking or migration due to inadequate apposition of the stent graft.

Inappropriate patient selection may contribute to poor device performance. Preliminary data indicate that patients with an aortic neck angle >45 degrees may have a higher likelihood of suboptimal outcomes compared to patients with an aortic neck angle <45 degrees. The same data indicate that patients with an aortic seal length of <15 mm and an iliac seal length of <25 mm may also have a higher likelihood of suboptimal outcomes.

This device should only be used by physicians and teams trained in vascular interventional techniques, including training in the use of the device.

Do not use the AneurX Stent Graft in patients unable to undergo the necessary preoperative and postoperative imaging and implantation studies.

The results of the clinical studies indicated that patients who experience an unsuccessful endovascular

repair attempt, and as a result undergo conversion to surgical Abdominal Aortic Aneurysm (AAA) repair, are likely to have increased complications arising from both procedures (i.e., cardiac complications, fever, infection, musculoskeletal complications, neurological complications, pulmonary complications, vascular disease, vessel dissection, wound healing issues, and mortality).

The safety and effectiveness of the AneurX Stent Graft System for the treatment of abdominal aortic aneurysms has not been evaluated in patients: • with connective tissue disorder • with hypercoagulability • with mesenteric artery occlusive disease • with ilio-femoral, thoracic, or inflammatory aneurysms • with juxtarenal AAA • with pararenal AAA • with suprarenal or thoracoabdominal aneurysms • who are morbidly obese • pregnant or nursing • less than 18 years old • with less than one-year life expectancy.

Always have a vascular surgery team available at institutions performing endovascular grafting in the event that conversion to open surgical repair is required.

Patient Selection, Treatment and Follow-up

Do not use this device in patients having an active systemic infection.

Do not use this device in patients with sensitivities or allergies to the device materials. The materials include: polyether block amide (PEBA); polyether block amide (PEBA) with tungsten filler; polyether block amide (PEBA) with barium sulfate filler; acrylonitrile-butadiene-styrene (ABS) copolymer; glass-filled acrylonitrile-butadiene-styrene (ABS) copolymer; polyetheretherketone (PEEK); polyvinyl chloride (PVC); stainless steel; ethylene propylene rubber; Nylon; silicone; polycarbonate; cyanoacrylate; nickel/titanium (nitinol); tantalum; and polyester. The AneurX Stent Graft with Xcelerant Delivery System is latex-free.

The results of the clinical study indicate that women treated with this device may have a higher mortality rate as compared to their male counterparts.

The use of this device requires administration of radiographic agents. Patients with preexisting renal insufficiency may have an increased risk of renal failure postoperatively.

Proper use of this device requires accurate fluoroscopic imaging. This device is not recommended for patients whose weight exceeds 350 lbs (150 kg) or whose weight may impede accurate fluoroscopic imaging.

Regular follow-up including imaging of the device should be performed every 3 to 6 months for patients in the enhanced surveillance group and at least every 6 to 12 months for patients in the routine surveillance group (see IFU for patient follow-up recommendations). During the recommended follow-up imaging schedule, patients should be monitored for aneurysm size, occlusion of vessels, change in pulsatility, migration, leaks, and device integrity.

Additional treatment including endovascular treatment or surgical conversion should be strongly considered in the following cases:

- Aneurysm growth >5 mm (with or without leak) since last follow-up
- Change in aneurysm pulsatility (with or without growth or leak)
- Persistent endoleak with or without aneurysm growth
- Stent graft migration resulting in an inadequate seal zone

The results of the clinical study indicate that subjects experiencing reduced blood flow through the graft limbs and/or leaks may be required to undergo secondary interventions or minor surgical modifications.

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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 three-fold 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 far-fetched 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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