What Randomized Controlled Trials Tell Us About Endovascular Repair of Abdominal Aortic Aneurysms

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Endovascular aneurysm repair (EVAR) has been a revolutionary development in the treatment of abdominal aortic aneurysms (AAA). However, EVAR has been rapidly embraced by both physicians and patients despite the paucity of Level I evidence demonstrating the long-term benefit of EVAR. The result of the two randomized controlled trials (RCTs) comparing EVAR versus open repair for the treatment of AAAs has provided some insight to the questions surrounding the utility of EVAR. The data and conclusions of these EVAR-related RCTs are briefly reviewed and discussed in this manuscript.

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Abbreviations: AAA = abdominal aortic aneurysm, EVAR = endovascular aneurysm repair

BACKGROUND

IN 1999, the Food and Drug Administration approved two stent-graft systems for endovascular repair of abdominal aortic aneurysms (AAAs). The application of endovascular aneurysm repair (EVAR) techniques expanded rapidly despite the lack of robust outcomes data. Most studies were based on industry-sponsored clinical trials, registries, retrospective single-institution experience, and expert opinion. No level 1 randomized controlled trial data were available before 2004. Very limited level 2 and level 3a evidence was in the literature. The majority of reports involving EVAR had level 3b, 4, or 5 evidence (1–3) (**Table**). In 2002, Adriaensen et al (4) published a metaanalysis comparing the short-term results of nine studies of elective EVAR versus open repair of AAAs with a random-effects model to pool the data. This metaanalysis included studies with level 2, 3, and 4 evidence published in the English language. A total of 687 patients underwent EVAR and 631 open repair. Based on this metaanalysis (4), EVAR was associated with significantly less blood loss ($P = .003$), fewer days in the intensive care unit ($P = .04$), fewer hospital days ($P = .02$), improved mortality rates at 30 days ($P = .03$), and fewer systemic complications ($P < .001$). However, no long-term outcomes data were assessed. A metaanalysis published in 2003 (2) involved 11 studies with level 2b and 2c evidence and compared EVAR versus open surgical repair. This metaanalysis (2) again demonstrated that EVAR was associated with less blood loss, a shorter intensive care unit stay, and fewer systemic complications. However, no difference in 30-day mortality rate or survival at 2, 3, and 5 years was demonstrated. In addition, the costs associated with EVAR were more than those associated with open surgical repair. Increased local and vascular complications (ie, endoleaks) were also seen with EVAR. Although expert opinion and practice trends have suggested that EVAR is superior to open AAA repair, before 2004, there was a paucity of meaningful outcomes data to unequivocally support this opinion or trend. In an effort to better address some of the skepticism surrounding EVAR, several randomized controlled trials comparing EVAR and open AAA repair were initiated in 1999 and 2000.

RANDOMIZED CONTROLLED TRIALS

In theory, evidence-based data should provide information relevant to individual patients in an answerable and focused format. The evidence should be critically appraised for validity, strengths, and biases. The results must be able to be applied to patients and show usefulness in clinical practice. In addition, a clear idea of the statistical significance of the clinical reports and their results should be evident (5). As a general rule, a well conceived, prospective randomized controlled trial provides the most valid data with a minimum of bias.

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Levels of Evidence (1)

Level of Evidence	Type of Study
1	Prospective, randomized controlled trials
2a	Systematic review of homogenous, prospective cohort studies
2b	Prospective individual cohort studies
2c	Prospective "outcomes" studies
3a	Systematic retrospective review of homogenous case-controlled studies
3b	Individual retrospective cohort studies
4	Case series or poor quality cohort studies
5	Expert opinion without explicit critical appraisal

DREAM Trial

Conducted in the hopes of accomplishing the aforementioned tasks, the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial was published in 2004 (6). The DREAM trial was a multicenter, randomized controlled trial involving 24 centers in the Netherlands and four centers in Belgium. The study evaluated patients with AAAs 5 cm or larger in diameter who were considered good candidates for open surgical repair. Patients were accrued from November 2000 through December 2003. A total of 345 patients—174 who received open repair and 171 who received EVAR—were randomized and assessed. The primary endpoint was the combined 30-day mortality and severe complication rate. Clinical sites performing EVAR were required to have experience performing a minimum of five EVAR cases, and if they had experience with fewer than 20 cases, the EVAR procedure was proctored. Of the 345 patients, 339 (98.3%) received their planned treatment. Six patients crossed over to the other treatment arm: five to EVAR and one to open surgery. Endovascular devices used in the study were second- or third-generation devices: Zenith (Cook, Bloomington, Indiana) in 33.3%, Talent (Medtronic, Minneapolis, Minnesota) in 27.7%, Excluder (W.L. Gore & Associates, Flagstaff, Arizona) in 20.9%, AneuRx (Medtronic) in 6.8%, and others in 11.3%. Therefore, more than 60% of the devices used in the DREAM trial (6) are currently Food and Drug Administration–approved and available for use in the United States.

The results of the DREAM trial revealed that there was no major difference in terms of sex, age, and comorbidities of patients undergoing open repair and EVAR. As expected, more patients in the open repair group received general anesthesia ($P < .001$) and a tube graft ($P < .001$). The 30-day mortality rates were 4.6% for patients who underwent open repair and 1.2% for those who underwent EVAR ($P = .10$), with a relative risk of 3.9. The combined incidences of mortality and severe complications at 30 days were 9.8% in the open repair group and 4.7% in the EVAR group ($P = .10$), with a relative risk of 2.1. The combined incidences of mortality and moderate or severe complications at 30 days were 23.6% in the open repair group and 18.1% in the EVAR group ($P = .23$), with a relative risk of 1.3. The 3-year survival rates for open repair and EVAR were 89.6% and 89.7%, respectively.

The conclusion of the DREAM trial was that "EVAR is preferable to open repair over the first days in patients with an AAA [at least] 5 cm in diameter. Long-term follow-up is needed." Unfortunately, the conclusions of the DREAM trial were affected by one of the limitations of the trial; that is, patient accrual was 12% lower than planned and the incidence of the composite endpoint of 30-day mortality and moderate or severe complications was higher than predicted for the EVAR group (18.1% vs 10% predicted), which affected the number of patients needed to be enrolled into the trial to demonstrate a significant difference in the primary endpoint. However, what was clearly demonstrated by the DREAM trial was that EVAR was significantly better than open surgery when evaluating for periprocedural blood loss, systemic complications, intensive care unit and hospital stay, and the need for postoperative mechanical ventilation.

EVAR 1 Trial

In 2005, the Endovascular Aneurysm Repair versus Open Repair—or EVAR 1—trial (7) was published. The EVAR 1 trial was a randomized controlled trial performed at 34 centers in the United Kingdom. All clinical investigative sites had experience performing at least 20 EVAR procedures. Patients enrolled in this trial were older than 60 years of age and had an AAA at least 5.5 cm in diameter. The patients had to be good candidates for EVAR and open repair. If patients were believed unfit for open repair, they were referred to the EVAR 2 trial (8) (as described later). A total of 4,799 patients were screened between September 1999 and December 2003. Of the patients screened, 1,082 were randomized to undergo open repair ($n = 539$) or EVAR ($n = 543$). All patients had a minimum follow-up period of 1 year, with an average follow-up of 3.3 years and a median follow-up of 2.9 years. The primary endpoint was all-cause mortality, with secondary endpoints being aneurysm-related mortality, health-related quality of life, complications, and hospital costs. Patients undergoing EVAR were treated with bifurcated (90%) or aortouniiliac (10%) devices. The endografts used included a Zenith device in 51%, Talent in 33%, Excluder in 7%, AneuRx in 4%, and others in 5%. Again, more than 60% of the devices used in this trial are currently Food and Drug Administration–approved.

The results of the EVAR 1 trial showed no major difference in sex, age, or comorbidities between the patients undergoing open repair and those undergoing EVAR. The 30-day mortality rates were 4.7% for the open repair cohort and 1.7% for EVAR patients ($P = .009$). The health-related quality of life assessment revealed no differences between groups at 12 and 24 months. However, complication rates were 9% for the open group and 41% for the EVAR group ($P < .0001$). The significantly higher complication rate in the EVAR group is a reflection of the need for secondary interventions (ie, endoleak treatment). In addition, the mean hospital cost per patient