True Long-Term Results: What Have We Learned?

A discussion of updated long-term data from randomized studies and their implication on the approach to endovascular aneurysm repair.

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Since its introduction, endovascular aneurysm repair (EVAR) has become the gold standard for elective repair of infrarenal abdominal aortic aneurysms (AAAs). The outcomes after open and endovascular repair are well documented, and follow-up of the major trials comparing both procedures has recently been updated.[1,2] The need for long-term results has been addressed in several publications.[3] It has been suggested that the continued rate of secondary interventions after EVAR provokes an overall survival disadvantage over a longer follow-up period.[4,5]

In an attempt to prove this hypothesis, follow-up results for the EVAR 1 and DREAM trials have been published inclusive of up to 15 years after patient randomization. Because the number of patients surviving in the trials is decreasing with prolonged follow-up, analysis of bundled data may be needed to determine the cumulative effect of stent graft durability issues on overall survival after EVAR.[6,7] This article discusses the long-term results from randomized clinical trials in light of outcomes learned from population-based studies. The real lessons learned after 2 decades of performing EVAR are also described.

DATA REVIEW

Perioperative and Short-Term Outcomes

Initially, three out of four major trials reported a survival benefit with EVAR (the exception was the French ACE trial).[8-11] However, this advantage was not seen until 2 years in the EVAR 1 and DREAM trials.[7,12] The OVER trial showed equivalent survival rates between open and endovascular repair at 9 years.[13] Similar to registries that began before the start of the randomized controlled trials, a need for close observation of stent grafts was argued.[4,5] Although similar survival rates were seen in the mid to long term, a decline in freedom from secondary interventions was seen in both EVAR 1 and DREAM.[7,12] However, the OVER trial did not find an increased rate of secondary procedures after EVAR.[13] The ACE trial observed an even bigger difference in the rate of secondary procedures; however, it has been criticized that interventions related to open repair were not included and therefore overestimate the difference in survival free from secondary procedures.[14]

Updates on Survival From Long-Term Data

In the latest update, the EVAR 1 study group described survival and secondary intervention rates up to 15 years after randomization.[1] An analysis was performed on all surviving patients at the time of the former investigation in 2009. Follow-up was completed for 98.2% of patients after 15 years, with 25 patients lost to follow-up and only four of these patients lost due to mortality. The median follow-up period was 12.7 years. After 15 years, the cumulative overall survival after open repair was 14.8% (95% confidence interval [CI], 10.3–19.9) as compared to 23.8% (95% CI, 19.4–28.4) after EVAR, for a difference of 11%. There was a significantly increased rate of aneurysm-related mortality after EVAR (83%; 95% CI, 76.4%–94%) as compared to open surgical repair (87.9%; 95% CI, 76.2%–88%) for a difference of 4.9% over the entire follow-up period.

Interestingly, half of patients treated for infrarenal AAAs were still alive 10 years after aneurysm repair.

Furthermore, data indicated an increased rate of death beyond 8 years of follow-up after EVAR. A detailed analysis to determine the cause of this mortality increase revealed an increased rate of aneurysm-related deaths due to secondary aneurysm sac rupture beyond 8 years, which contributes to diverging Kaplan-Meier curves after 8 years of follow-up. The authors described an increased rate of late deaths per 100 person-years due to malignant disease in the time interval beyond 8 years after randomization, suggesting a relationship between increased radiation exposure from close surveillance after EVAR and the development of malignancies.

The DREAM trial collaborators presented similar overall survival rates compared to EVAR 1 at the 2016 Society for Vascular Surgery (SVS) annual meeting.[2] The DREAM trial updated outcomes in all 233 patients surviving at the time of the last analysis in February 2009.[2] Follow-up was completed for 98.2% of patients over a median follow-up period of 10.1 years. Twelve years after randomization, the cumulative overall survival rates were 42.2% after open repair and 38.5% after endovascular repair (difference, 3.7%; 95% CI, -6.7–14.1). Identical to EVAR 1, the investigators observed half of the patients surviving for over a decade after randomization; however, increased aneurysm-related mortality after EVAR over the long term was not found in DREAM. In an earlier publication of DREAM results, the catch-up mortality after 6 years was mainly explained by cardiovascular and miscellaneous causes.[7] A detailed analysis of the DREAM trial related to all causes of death and event rates per 100 person-years will be forthcoming.

Updates on Secondary Procedures From Long-Term Data

At 15-year follow-up for patients randomized in EVAR 1, survival free from secondary interventions was 79.8% (95% CI, 72.7–85.2) after open repair compared with 65.2% (95% CI, 59.1–70.6) after EVAR.[1] At the SVS annual meeting, the DREAM trial investigators reported cumulative rates of survival free from reintervention 12 years after randomization. At this time point, survival free from secondary procedures was 78.9% after open repair and 62.2% after EVAR (difference, 16.7%; 95% CI, 5.8–27.6). Therefore, both the EVAR 1 and DREAM trials demonstrated a nearly twofold risk of secondary intervention after EVAR for up to 15 years after randomization. Nonetheless, in both trials, an even bigger difference was found in the total number of reinterventions required after both procedures. Indications for reintervention for the DREAM trial will be addressed in an upcoming publication.

In EVAR 1, 258 reinterventions were performed in 165 patients after EVAR, and 105 reinterventions were performed in 74 patients following open repair. The rates of survival free from a first reintervention, life-threatening reintervention, second reintervention, or subsequent reinterventions per 100 person-years diverged most between 4 and 6 years after randomization. Durability of stent grafts was considered to be an underlying cause of the necessity for secondary procedures after EVAR.[1]

Data From Population-Based Studies

A comparison of data from a large study of a propensity score–matched cohort of Medicare patients by Schermerhorn et al demonstrated an initial survival benefit for EVAR as compared with open repair.[15] In this study, the perioperative advantage was maintained over a period of 3 years. Overall survival rates were approximately 45% after 8 years of follow-up.

The Swedish Vascular Registry study performed between 1987 and 2005 compared survival rates between open repair and EVAR in different time intervals.[16] In the entire cohort, no difference in overall survival was observed after 5 years. However, higher overall survival rates were observed in patients who underwent AAA repair between 2000 and 2005 as compared to those who underwent repair before 2000. The 10-year survival rate was 39.3% on average; however, data collection for patients who underwent AAA repair after 2000 was not completed.

A single-center observational study performed in Australia reported survival rates up to 15 years after aneurysm repair and showed no significant difference in overall survival.[17] The cumulative survival rate after open repair was 31% as compared with 33% after EVAR ($P = .75$). Interestingly, survival rates were close to 49% 10 years after aneurysm repair, comparable with overall mortality rates found in randomized trials. However, patient follow-up was incomplete in this study, with the median follow-up of 6.5 years after open repair as compared to 4 years after EVAR.

DISCUSSION

Both the EVAR 1 and DREAM trials showed equivalent survival rates over the long term, despite a continued decline in freedom from secondary intervention. This might be explained by the relative minor nature of most of the secondary interventions in both trials. Hence, the combined impact on overall survival was not detected, given the relatively small number of reinterventions required. In addition, the authors of EVAR 1 described a change in the approach of stent-related complications, especially for type II endoleak. Over the years, evidence for a more reserved approach to type II endoleak without sac expansion has grown,

whereas more aggressive treatment was chosen in the early years of the trials. As a result, reinterventions for benign type II endoleak are relatively overreported in both EVAR 1 and DREAM.

When comparing the results of randomized trials to population-based studies, the overall survival is remarkable. Schermerhorn et al demonstrated overall survival rates close to 45% after 8 years; at the same time point, EVAR 1 and DREAM showed cumulative survival rates in the range of 60%.[1,2,15] The same statement on overall survival can be made for the Swedish Vascular Registry study, where the mean 10-year overall survival rate was 39.3% in patients who underwent AAA repair before 2000.[16] In comparison, both randomized trials showed that about half of the patients survived at the 10-year mark. The single-center Australian study was the only study to demonstrate a survival rate equivalent to the 10-year outcomes from randomized trials; however, the completeness of follow-up was doubtful.[17]

The difference in overall survival between these population-based studies and randomized trials can be related to the patients' general health prior to initial surgery. The fact that patients from the randomized trials were considered suitable for both procedures indicates that they were relatively healthy compared to the general population, especially those undergoing surgery for infrarenal AAA. Furthermore, the difference in overall survival could also be attributed to the strict follow-up protocol in randomized trials. In this way, complications might be detected at an earlier stage, which could have reduced the risk of secondary rupture and death.

By design, prospective studies are prone to selection and information bias. Because these studies are not randomized, the preferences of surgeons and patients, as well as the concern regarding suitability might have a significant effect on overall survival and reintervention rates. On the other hand, the estimated short- and long-term risks of death for each patient are considered while determining the approach of aneurysm repair in modern-day medicine. Therefore, the results from population-based studies might reflect a more realistic view regarding daily practice.

Despite equivalent overall survival rates over the long term, EVAR 1 showed a significantly increased rate of aneurysm-related deaths, whereas DREAM did not. Especially beyond 8 years of follow-up, EVAR 1 showed an increased rate of death related to secondary aneurysm sac rupture, which might be explained by the overall health of both trial groups. Although patients in both trials were comparable in terms of history of cardiac disease, diabetes, and statin use, the age at surgery was slightly higher in EVAR 1.[8,9] An extensive discussion of the differences between both trial populations will be addressed in the upcoming publication of the DREAM trial results.

In succession to the reintervention rates reported after 6 years, freedom from secondary procedures continued to decline in both trials. A nearly twofold risk of secondary interventions was shown following EVAR for up to 15 years after randomization.[1,2] Compared to these rates, the rate of secondary procedures after 8 years of follow-up in a Medicare-based study was almost 80% after open repair and 70% after EVAR (estimated risk ratio, 1.5).[15] This difference might be prompted by the increased follow-up intensity of the trial protocols, leading to detection of benign indications for reintervention. In a population-based study, these interventions might not have arisen during regular follow-up.

In both EVAR 1 and DREAM, the highest rate of reinterventions was seen between 4 and 6 years. Based on the indications for reintervention, this effect was related to stent graft durability. The investigators of the EUROSTAR database previously concluded that the rate of secondary sac rupture after EVAR was initially low but increased after 4 years. After this initial period, complications arose in 25% to 40%, and reinterventions were required in 15%.[4] The EUROSTAR investigators recommended lifelong surveillance, especially in those with known sac expansion.[4] A similar increased rate of secondary procedures was seen in patients undergoing EVAR in both EVAR 1 and DREAM. As a result of this advised close surveillance, more minor complications could have been detected.

It must be addressed that the stent grafts used in the clinical trials are from an earlier generation,[18] and it has been suggested that early generation stent grafts are inferior to the currently used stent grafts with respect to durability.[11-14] Therefore, reintervention rates might have been higher then compared to current ongoing studies investigating newer-generation stent grafts. A recent study comparing long-term outcomes with newer and older stent grafts demonstrated similar perioperative and long-term mortality.[19] On the other hand, late conversion rates, secondary procedures, and aneurysm sac expansion were significantly lower when using the newer-generation stent grafts.[19] Thus, progression of stent graft durability might be beneficial to patients suitable for EVAR. Still, the long-term survival rates did not indicate a harmful effect of secondary procedures on overall survival.[1,2]

In recent years, more stent grafts have been placed outside the instructions for use (IFU) in order to enable an endovascular approach in patients with challenging

aneurysm neck anatomy. Earlier studies have demonstrated an increased risk of stent graft–related complications and graft failure in patients treated outside the IFU. An increased risk of migration, type I endoleak, occlusion, and eventual secondary rupture was reported.[20] As a result, more secondary interventions might be required in these patients. Future studies need to determine whether the increased risk of graft failure from stent grafts placed outside the IFU could lead to a long-term survival disadvantage. A retrospective cohort study comparing stent grafts that were deployed off-label to those placed according to the IFU showed similar long-term survival rates in 566 patients who underwent elective EVAR between 2003 and 2014.[21] In the entire cohort, 31.1% of patients fit the IFU. There was no difference in cumulative overall survival between stent grafts placed according to the IFU or those placed off-label at 10 years after aneurysm repair. At that time, the reported survival rates were in the range of 40%.

In general, patients who are unfit for open repair tend to undergo treatment via an endovascular approach, even if the IFU discourages EVAR. The results of a single-center trial investigating outcomes in patients not meeting the IFU found no overall short- or long-term survival benefits after EVAR as compared to no intervention.[22] On the contrary, data from a retrospective analysis showed that patients considered unfit for open repair were more likely to develop postoperative major complications and had worse 5-year survival rates.[23]

Although the importance of close surveillance has been proven on several occasions, annual CT is discouraged in order to reduce radiation exposure. Nevertheless, Garg et al demonstrated a great variability in postoperative surveillance, and fewer than half of the patients treated for AAA had complete postoperative surveillance as recommended in the SVS guidelines.[24] The actual effect of incomplete surveillance on overall survival was not described.

Despite the majority of studies pointing in a similar direction, it is suggested that new trials comparing open surgical repair to EVAR might be beneficial. The existing body of evidence is sufficient to assess the short-term survival and reinterventions following EVAR[25]; however, larger patient cohorts and more consistent follow-up might be beneficial to detect the effectiveness of EVAR over the long term. Future trials should investigate the approach of stent-related complications and the effectiveness of new-generation stent grafts,

although this presents ethical dilemmas because EVAR has a proven initial survival benefit and endovascular repair is constantly improving. Because the OVER trial was conducted between 2002 and 2008 with newer-generation stent grafts, the long-term results might add to the weight of this ongoing discussion.

CONCLUSION

Based on the initial survival benefit in combination with an equivalent long-term survival to open repair, EVAR is currently the method of choice for treating infrarenal AAAs. Considering the continued risk of secondary interventions after EVAR, close surveillance is required, although total radiation exposure should be kept in mind. Still, in a patient survey, EVAR proved to be comparable to open repair in terms of health-related quality of life, and the majority of patients highly preferred EVAR over the conventional open procedure.[26] Because EVAR is used in a broader range of anatomy, the experience in open surgical repair of AAAs has decreased, and a more centralized health care method is indispensable. ■

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