

# EVAR on Trial: What We Have Learned

Professor Roger M. Greenhalgh, MD, FRCS, discusses the progress made in studying endovascular AAA repair, its current global applications, and what the future has in store for evaluating this procedure.



**Endovascular Today:** How would you describe the lasting impact of the EVAR trials in the UK, Europe, and the US?

**Dr. Greenhalgh:** The EVAR trials were the first properly powered trials in the world to evaluate the efficacy of endovascular repair. They were published in the *Lancet* simultaneously in the UK and in the US by design, so they were aimed at both audiences from day one. The results were also presented in front of the senior officers of the National Institute of Clinical Excellence, and thus having been funded by the Department of Health, which is an arm of the British government, they had the stamp of officialdom in that country. The impact of the EVAR trials has not been especially British; it has been British, European, and American.

However, the responses to the findings of the data were different in different parts of the world. In the UK and in many parts of Europe, I believe the findings of EVAR-2 were surprising, but they were accepted. In the US, the environment is much more commercially driven, and the practice is much more responsive to promotional advertising and to patient orientation. There has been a succession of presentations at international meetings questioning the data from the EVAR trials. There were few concerns about EVAR-1, which showed EVAR to be superior to open repair. Many in the US—not anywhere else in the world—have questioned EVAR-2. The EVAR-2 results were surprising, as were the different reactions to data across the Atlantic.

The findings of the trials were not predictable. We had no idea what they were going to show. Whenever I

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consider a trial, I make my mind up what the uncertainty is but then have an open mind and let the data speak for themselves. The one thing that I was fairly certain would emerge was that endovascular repair would be the only and obvious mortality beneficial option for patients who were so unfit for open repair. After all, those are the patients that Parodi and his colleagues introduced EVAR for. They demonstrated in the early 1990s that patients unfit for open repair were the very ones that we would be able to perform EVAR on. I expected and powered EVAR-2 to show a dramatic reduction in mortality rates from EVAR; I was very surprised when that did not happen.

**Endovascular Today:** What shortcomings do you feel are inherent in randomized, controlled trials aimed at gaining commercial approval, as opposed to the trials that you designed?

**Dr. Greenhalgh:** I am not an expert on US clinical trials; I have never performed one. Unlike many people who comment on my trials, it is not usual for me to comment on other people's work—certainly the pivotal trials. The pivotal trials are designed with a view toward satisfying the FDA; that is a very American need. The FDA is a regulatory body; every part of the world has its

own regulatory body, and the FDA is very specific about what it requires to be satisfied before approval is given for a device to be used. The FDA clinical trials are not really trials in the sense that they are not randomized controlled trials—they are not the same level. They are designed to satisfy that organization for the safety of the patient; they are not the same as showing that something works better than something else. In a randomized, controlled trial, there is a question asked, and the trial is only as good as the question. If you ask a bad question, you will get a worthless result. If you ask a very good question, a randomized, controlled trial will answer it.

**Endovascular Today:** Which unanswered questions must be evaluated in future randomized, controlled trials?

**Dr. Greenhalgh:** The most unanswered question at the moment pertains to EVAR-2 itself because EVAR-2 is the only trial of its type; nobody has tried to repeat it. One or two colleagues have not grasped that there is a group of patients that can be defined in any population that are so sick that the majority of them are dead in a few years. In EVAR-2, only 36% were alive at 4 years. The patients were dying. It is alleged that EVAR-2 has an unacceptably high operative mortality rate; 9% is high, but any intervention on patients as sick as that will have a high operative mortality. What I would like to see most of all is an equivalent population to EVAR-2 in a separate part of the world checking the results. I think that would settle a lot of scores. You would need a population in some part of the world that agreed to define patients equivalent to EVAR-2. Thus far, so-called high-risk groups have been defined with superior results to EVAR-2, but when you perform the Kaplan-Meier survival curves for the “high risk,” they are shown to be equivalent to the poorest patients in EVAR-1.

There has been no series in which intervention has been contemplated for patients as sick as those in EVAR-2. That is the big question. It not only requires a transatlantic approach; it requires any other group to do it properly. I would like to see the US do this. I think the US has a vested interest in it because, at the moment, the EVAR-2 trial data are out. A vote at ISET 2008 has suggested that the EVAR trial and even the EVAR-2 trial data are believed. I have said that I am very surprised; the British are not proud of EVAR-2 in the sense of a contribution to practice. We expected an endorsement—an obvious benefit of endovascular repair. Our data have shown that the patients who are anatomically suitable for endovascular repair have a

lower rupture rate, and therefore, the urgency to deploy an endovascular device is not as great as we thought originally. I would like a truly equivalent population managed optimally in terms of whether EVAR can affect the mortality rate. I had always predicted that it would, but EVAR-2 suggested that it would not. At the moment, I am endorsing and recommending EVAR as opposed to open repair in patients who are high risk and almost unfit for open repair.

**Endovascular Today:** Do you think that device innovations could tip the scales more in favor of the endovascular approach? If so, what device innovations would help?

**Dr. Greenhalgh:** The EVAR trials show that 54% of aortas are suitable for endovascular repair. Some parts of the world regard that as a very high figure. Belgium, for example, says that figure is very high and would put it much lower—around 30%. I think it is obvious that the higher the proportion that can be safely fixed, the better, but it could be that if we apply the endovascular treatment too frequently, there will be patients who run the risk of not doing as well as they would have with open repair. Endovascular device innovation is crucial, but I am not sure how far it can safely go. I would expect the proportion to go up and up and up, but it will not reach 100%.

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We need to address difficult angulations of the neck and short necks; we have already applied fenestrated and branched grafts. I think that with the anchoring systems and device modification, more patients will be able to be treated safely by infrarenal repair. I do not think we should race ahead of the safety. We must be very careful.

**Endovascular Today:** As of January 2008, how would you define the ideal patient for endovascular repair?

**Dr. Greenhalgh:** The best candidate is one who could tolerate open repair as well as endovascular repair, who is anatomically suitable for endovascular repair, with a satisfactory neck, parallel sides of the neck, good land-

ing sites above and below, no thrombus in the wall, little calcification, and an ability to have a good grasp of the artery wall at the top and bottom. Those are ideal circumstances that will beat open repair. But, EVAR will be available over a much wider range than that, to the very high-risk patients and will be used in high-risk patients; it just will not be surprisingly as obviously superior to open repair. The worst thing that could happen, almost, is an endovascular repair, which requires further interventions, particularly conversion to open repair in a high-risk patient.

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Patients we would not treat endovascularly would be those such as the worst type of EVAR-2 patients, whose customized probability score would indicate a high risk of mortality. Anesthetists are inclined to use customized probability scores, adding together all the various factors that are screened to show the risks of mortality. These patients have very poor scores.

As few patients as possible should not receive any treatment. Once a patient knows he has an aortic aneurysm, he has a sense that he has a time bomb. During a screening program, it is terrible to find an aortic aneurysm that the patient knew nothing about that you cannot fix. It is awful to inform someone of the time bomb inside them and do nothing about it. The problem with a trial such as EVAR-2 is that you have to investigate the patients, and often, the data suggest that there is very little chance of improvement with performing endovascular repair. That is why I want to see those data checked. There are some patients so unfit for surgery according to these scores that every effort should be made to improve their fitness. They should undergo cardiologic assessment; they should have ventricular ejection fractions, necessary coronary intervention, and whatever it takes to help their fitness improve before anything. Once their customized probability index is improved, including the chest, heart, kidneys, lungs, etc., then you can reconsider intervention—not when they are desperately sick with a poor score for fitness.

**Endovascular Today:** Having conducted both EVAR trials and seen so many of those patients, if you were to

design those trials retrospectively, is there anything you would change or would you leave it just as is?

**Dr. Greenhalgh:** I would leave the trials exactly as they were and let the data speak for themselves. It is a question that we had plenty of time to decide on when we first performed endovascular repair in 1993. We started to design the trials in 1996 and commenced in 1999. There were three populations of patients in which endovascular repair was a possibility: (1) patients very fit and suitable for open repair, which is EVAR-1; (2) patients unfit for open repair, which is EVAR-2; and (3) patients with ruptured aneurysms (eEVAR). I would have predicted that the result would most likely be positive in ruptured aneurysms, followed by the patients in EVAR-2, and finally those in EVAR-1. Look what happened. The result became positive in EVAR-1, before the other two. That surprised me, but that is what the data showed. The vast number of aortas are suitable for EVAR and often can be repaired under local anesthesia; sometimes, these procedures can be performed almost as an outpatient. But the surprise remains that we have controversy about EVAR-2, which needs to be resolved, and we still have uncertainty about ruptured aneurysms.

**Endovascular Today:** What advancements must be made in order for EVAR to become the standard of care in more patients?

**Dr. Greenhalgh:** It is more than the trials; in certain parts of the world, not so much in the US, it is necessary to consider the appraisal of the procedure, the number of reinterventions, and the complications after EVAR, which do not occur after open repair, and compare the two procedures. When there is a 3% operative mortality benefit for EVAR in EVAR-1, it is fine, but it is not great. If there are a lot of complications and need for reinterventions, that clinical improvement, being small over time against complications, has a deleterious effect: what is called *cost effectiveness*. Cost effectiveness is a modeling tool, and it is unlikely under current analysis that endovascular repair will be cost effective to the satisfaction of the health economists, so it is relevant to ask ourselves what would have to happen for it to be cost effective. First, the sale price must not go up; second, device modification needs to reduce the need for reinterventions and the number of complications; and third, it would be better to have more knowledge of whether the procedure would work with ruptures and patients such as those in EVAR-2. For the cost effectiveness to work in much of the world, there would have to

be device modification and control of the sale price. It would be important to know whether the mortality benefit is maintained over the years. At 4 years, the EVAR trials show a 3% aneurysm-related mortality benefit, significant over open repair. The question is whether it will translate to all-cause mortality during the follow-up. If there is a clinical benefit in the long term and if there are reduced complications, that would make the widespread acceptance of EVAR much more likely.

**Endovascular Today:** What do you think the standard practice for follow-up should be?

**Dr. Greenhalgh:** No practitioners or patients enjoy the annual CT follow-up. The CT follow-up is performed during the trial period, and I do not believe that it will be standard practice for the future. Efforts are being made to develop ultrasound and also to try to establish criteria for when CT angiography will be required. There is much less radiation, which is better for the patients, and it will be much less costly.

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**Endovascular Today:** How would you say that transatlantic collaboration, such as you highlight at the Charing Cross and ISET meetings, makes an impact on both sides of the ocean?

**Dr. Greenhalgh:** The transatlantic consensus approach is a concept that Barry Katzen, MD, and I championed because we are both inclined to look beyond our own populations, and we are interested to know what the view of treatment is on both sides of the Atlantic. At ISET 2008, we did it for the first time, and using the audience's responses to approximately give questions, we compared the American opinions with the opinions given at Charing Cross in April 2007. We shared these results, and for the majority of questions, we were in agreement. One question struck me as greatly different and made me very delighted that we had undertaken this Charing Cross/ISET consensus. It was the question on venous intervention, which showed that in the US, a vast majority of interventionists were interested in endovenous surgery ahead of

open surgery. This tells me that in the audience of ISET, a much larger group of specialists are using endovenous methods. My own persuasion is that is right, and I was surprised that in my country, there is still a conservative, prosurgical lobby; I was extremely interested to see the difference. There are two possible explanations. One could be that the ISET meeting is attended primarily by radiologists, who would perform interventions and would not do surgery. The other explanation is that in the US, there is an inclination to embrace the office-based treatment of tumescent anesthesia and venous correction and the avoidance of the patient going for an unnecessary open surgical procedure. I do not think that has caught on in Europe quite to the same extent.

One question Dr. Katzen and I asked was about the use of the stents with angioplasty in the superficial femoral artery. Audiences on both sides of the Atlantic were quite convinced the stent was a benefit, but they had the benefit of knowing data from trials in the last 12 months. It would be interesting to know what the audience thought a year ago, before those trials were published. I think they have a massive impact, and I am not a person who is obsessed with clinical trials. As I said at ISET, I started to learn how to conduct clinical trials properly halfway through my clinical academic life because I saw the power of high-quality multicenter, randomized, controlled trials to alter clinical practice. The NASCET trial in the mid-1980s was a big trial, and I saw the impact of that. Because of NASCET, neurologists started to refer patients for carotid intervention. Here again, I suspect the RESILIENT and other trials have changed practice so that the stent has become an accepted part of the reconstruction of the superficial femoral artery. ■

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