

# The Value of TEVAR Trials

Do we need more trials to tell us how and when to treat descending thoracic aortic aneurysms?

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Endovascular repair of the thoracic aorta (TEVAR) can be performed with relatively low perioperative morbidity and mortality and has been proven to be at least as effective in preventing aortic-related death as open surgical repair (OSR).<sup>1-5</sup> As a result, TEVAR is now considered to be a valid first-line therapy for many conditions, and there has been a steady increase in the number of thoracic endovascular procedures being performed over the last decade.<sup>6,7</sup>

The frequency of diagnosis of thoracic aortic disease has increased, potentially due to more axial imaging being performed in an aging population, and there has been a corresponding increase in the number of hospital admissions related to thoracic aortic pathology.<sup>6</sup> The relatively constant number of open surgical operations over this period suggests that TEVAR is offered to some patients who may have previously been deemed unfit for surgery and were being managed conservatively.<sup>8</sup>

The relatively poor long-term survival rates that have been observed in some groups of patients after TEVAR has led to some concern that the advantages of TEVAR over OSR are not as clear when considering overall survival gain as the main endpoint, and some have questioned the utility of TEVAR in certain groups of patients.<sup>1,8</sup> There are no equivalent studies to the randomized controlled trials that justified the adoption of infrarenal EVAR, and the uptake of TEVAR has been mainly based on early, smaller studies and ideas extrapolated from the EVAR trials.

## EXISTING EVIDENCE FOR THE USE OF TEVAR IN DESCENDING THORACIC AORTIC ANEURYSMS

The best quality evidence describing the use of TEVAR for the treatment of descending thoracic aortic aneurysms is derived from prospective trials that were aimed at determining the safety and efficacy of specific devices

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(Table 1). The Gore TAG trial recruited 140 patients to undergo implantation of the Gore TAG device (Gore & Associates), comparing outcomes with 94 retrospectively treated OSR patients. The 30-day death rate was 2.1% in the TEVAR group and 11.7% in the OSR group, with similar rates of midterm all-cause death rates.<sup>4</sup>

The VALOR trial similarly recruited 195 patients who had the Talent thoracic endograft (Medtronic, Inc.) implanted and identified an OSR control arm of 189 patients who were retrospectively matched as controls.<sup>2</sup> As with the Gore TAG device, a lower 30-day mortality rate was noted in the TEVAR groups when compared to the OSR group (2% vs 8%), and there were approximately half the number of major adverse events. There were significantly fewer aortic-related deaths in the TEVAR group at follow-up (3.1% vs 11.6%), but despite this, freedom from all-cause mortality was relatively poor (58.5%).<sup>9</sup>

The Zenith TX2 pivotal trial recruited 160 patients with thoracic aortic aneurysms to undergo treatment with the Zenith TX2 thoracic endograft (Cook Medical) with 70 historical open surgical controls.<sup>5</sup> The rate of perioperative adverse events was low in both groups, but there was significantly less-severe morbidity in the TEVAR group. The aortic-related death rate was 5.9% in the TEVAR group versus 12% in the OSR group, and freedom from all-cause death was 63% in both groups.

TABLE 1. PIVOTAL TRIALS INVESTIGATING THE USE OF A SINGLE STENT GRAFT IN TAA PATIENTS

Study	Length of Follow-Up	Study Arm	N	30-Day Mortality	30-Day Stroke	30-Day SCI	Major Morbidity	Freedom From Reintervention	Freedom From Aortic Death	Freedom From All-Cause Death
Gore TAG 1999–2001	60 mo	TEVAR	140	3/140 (2.1%)	5/140 (4%)	4/140 (2.9%)	NA	96.4%	97.2%	68%
		OSR	94	11/94 (11.7%)	4/94 (4%)	13/94 (14%)	NA	NA	88.3%	67%
VALOR I 2003–2005	60 mo	TEVAR	195	4/195 (2.1%)	7/195 (7%)	17/195 (8.7%)	80/195 (41%)	81.5% (91.6% at 1 y)	96.1% (96.9% at 1 y)	58.5% (83.9% at 1 y)
		OSR	189	15/189 (7.9%)	13/189 (7.3%)	29/189 (15.2%)	151/179 (84.4%)	NA	88.4% at 1 y	79.4% at 1 y
Zenith TX2 2004–2006	60 mo	TEVAR	160	3/160 (1.9%)	4/160 (2.5%)	9/160 (5.7%)	225/160 (15.6%)	92%	94.1%	62.8%
		OSR	70	4/70 (5.7%)	6/70 (8.6%)	6/70 (8.6%)	25/70 (44.3%)	88%	88%	62.9%

Abbreviations: NA, not available; SCI, spinal chord ischemia; TAA, thoracic aortic aneurysm.

## ARE THERE DISCREPANCIES BETWEEN TRIALS AND REAL-WORLD PRACTICE?

The results of these three trials seem to justify the increased use of TEVAR as the first-line therapy of choice in patients with suitable thoracic aortic pathology, but comparison with large administrative datasets suggests that the cohorts studied may not be reflective of real-world practice.

### Perioperative Mortality and Major Morbidity

The perioperative mortality rate reported for trial patients undergoing elective OSR was significantly higher than for TEVAR patients, with over a fourfold higher risk of death (odds ratio, 4.5; 95% confidence interval, 2.1–10;  $P < .001$ ) (Table 2). Analyses of hospital administrative databases do not show a clear difference in perioperative mortality (Table 3). Data from the US Nationwide Inpatient Sample of patients who underwent repair of thoracic aortic aneurysms showed that the mortality rate was 2.3% in both groups.<sup>10</sup> Analysis of US Medicare data from 1998 to 2007 showed that

30-day survival was slightly better in patients undergoing TEVAR,<sup>11</sup> and analysis of the UK Hospital Episode Statistics (HES) database showed similar early mortality rates of 6.5% versus 7.6% for those undergoing TEVAR and OSR, respectively.<sup>8</sup> This is probably explained by the fact that the patients in the trials were usually fit enough to have undergone OSR, if required, and it was noted in all of the administrative database analyses that the TEVAR cohort was generally more physically frail than the OSR group.

The rate of other serious morbidity among patients undergoing OSR was double of that in the TEVAR trial patients. This was 41% versus 84% in the VALOR trial and 15.6% versus 44.3% in the Zenith TX2 trial (Table 1). The OSR patients also had a > twofold risk of developing spinal cord ischemia (odds ratio, 2.4; 95% confidence interval, 1.5–4;  $P < .001$ ) (Table 2). This was borne out in the large datasets, which concluded that TEVAR can be performed in older, sicker patients with less perioperative morbidity and leads to a greater chance of timely discharge from the hospital.<sup>10,11</sup>

TABLE 2. COMPOSITE ADVERSE EVENT RATE

Adverse Events	TEVAR (n = 495)	OSR (n = 353)	OR (95% CI); P Value
30-day death	10 (2%)	30 (9%)	4.5 (2.1–10); P < .001
30-day spinal cord ischemia	30 (6%)	48 (14%)	2.4 (1.5–4); P < .001
30-day stroke	21 (4%)	23 (7%)	1.6 (0.8–3); P = .158

Abbreviations: CI, confidence interval; OR, odds ratio.

### Aortic-Related Death

Data from the EVAR I trial suggest that the early mortality benefit seen after endovascular repair of abdominal aortic aneurysms may be lost due to an excess of late aortic-related deaths.<sup>12</sup> This has not been seen so far in studies of TEVAR. Freedom from aortic-related death in the pivotal trials was 94% to 97% at 5-year follow-up, which is in agreement with other recent studies and is superior to that seen after OSR.<sup>1</sup> An important caveat to this is that there are very little 10-year follow-up data available for patients who have undergone TEVAR.

### All-Cause Mortality

Despite the protection that aortic repair confers against aortic-related death, freedom from all-cause mortality at midterm follow-up is fairly poor in both the trials and administrative datasets (Tables 1 and 3). The MOTHER (Medtronic Outcomes of Thoracic Endovascular Repair) registry, which contained the VALOR study cohort, as well as registry and high-risk arms, reported a midterm survival rate of 56%, with most patients dying of cardiovascular causes or malignancy.<sup>1</sup> The Medicare and HES studies showed a similarly poor rate of survival, with more patients in the TEVAR group dying of “cardiorespiratory” causes, probably leading to a higher attrition rate in the this group (Table 3).<sup>8,11</sup> Patients treated for thoracic aortic aneurysms

experience a high level of all-cause mortality that is often not related the primary treated condition. This can be seen in comparisons with matched control groups of the same age and sex who do not have aneurysmal disease.<sup>13</sup>

### DO WE NEED MORE TRIALS TO TELL US HOW AND WHEN TO TREAT DESCENDING THORACIC AORTIC ANEURYSMS?

Repairing aneurysms of the descending thoracic aorta prevents aortic-related death regardless of the method employed, although in comparative trials, there are substantial early benefits associated with the TEVAR in terms of perioperative morbidity and mortality. Reports from large administrative databases suggest that these early mortality benefits are less pronounced, probably due to a propensity to offer TEVAR to less-fit patients who may not have been treated at all when OSR was the only option. A trial to compare the early outcomes of TEVAR and OSR does not seem to be necessary given these existing data.

A study with the goal of determining the appropriate threshold to offer surgery when the risk of aortic-related death outweighs the risks of intervention would, however, be valuable. Ideally, this would also help to identify individuals who are likely to die due to unrelated causes regardless of undergoing aortic repair, rendering surgery potentially fruitless and subjecting them to the risk of perioperative morbidity and mortality. The best way to investigate this would be a “Small Thoracic Aneurysms” trial, similar in methodology to the UK Small Aneurysm trial.<sup>14</sup> Patients could be randomized into either a treatment or observation arm and then followed to compare life expectancy and potential cause of death in each group. It may then be possible to determine which patients should be managed conservatively and which should be treated with either TEVAR or OSR.

Descending thoracic aortic aneurysm is not a common condition, so a large number of participating centers recruiting over a long period of time would be required

TABLE 3. FREEDOM FROM ALL-CAUSE DEATH IN ADMINISTRATIVE DATABASE ANALYSES

Adverse Events	Study Arm	NIS (United States) N = 11,669	Medicare (United States) N = 15,305	HES (United Kingdom) N = 759
30-day death (%)	TEVAR	2.3	6.1	6.5
	OSR	2.3	7.1	7.6
Freedom from all-cause death at 5 years (%)	TEVAR	NA	62	54
	OSR	NA	72	66

Abbreviations: NA, not available; NIS, National in-patient sample; HES, Hospital Episode Statistics.

The use of large, well-run, prospective registries is likely to be a more appropriate way to study methods to improve outcomes after repair of descending thoracic aortic aneurysms.

to adequately power the study. Another significant issue would be the ethics of deciding on the patients who would be eligible for randomization. Randomizing patients with an aneurysm diameter of 5.5 to 6.5 cm may be appropriate for a study such as this, but many would be uncomfortable randomizing a patient with a 6.4-cm aneurysm to conservative management and observation. The most comprehensive work to date suggests that the aorta expands exponentially after reaching 6 cm, and at 7 cm, the rate of aortic-related complications increases rapidly to over 40% annually.<sup>15</sup> Based on this work, a conservative threshold for descending aortic repair has been suggested as 6.5 cm in an asymptomatic patient, with lower thresholds for those with connective tissue disease. Interestingly, approximately 50% of patients in the endovascular arm of the VALOR trial had an aortic diameter of < 6 cm, and in the Gore TAG and Zenith TX2 trials, the mean diameter was 6.4 and 6.1 cm, respectively, which means that the majority of patients in the 5.5- to 6.5-cm range are being routinely treated in clinical practice.

The use of large, well-run, prospective registries is likely to be a more appropriate way to study methods to improve outcomes after repair of descending thoracic aortic aneurysms. Although the natural history of untreated aneurysms is unlikely to be determined using a study of this kind, it may be possible to determine who does not appear to benefit from repair in terms of overall survival gain. Development of risk-stratification systems may help to balance the perceived risk of aneurysm-related mortality against perioperative mortality and identify those who have a poor life expectancy regardless of their aneurysm.<sup>16</sup> They could then either be treated conservatively or set a higher threshold for intervention. Such registries may also help to determine which patients, if any, should be offered OSR as opposed to TEVAR by directly comparing the perioperative and long-term results in each group.

## CONCLUSION

It has been established that TEVAR is a reliable way of preventing aortic-related death in patients with

thoracic aortic aneurysms and results in less major morbidity than OSR. Midterm follow-up suggests that midterm survival after repair of the thoracic aorta is poor, especially after TEVAR, which is mainly due to non-aortic-related death. A randomized controlled trial to determine the optimum conditions for intervention that maximized the subsequent survival benefit of surgery would be ideal, but this is unlikely to be practically achievable for a variety of reasons. Information from large prospectively collected registries may help to identify those who are likely to benefit most from interventional treatment, those in whom it would be of no benefit, and those it may harm. ■

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