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Endovascular Aortic Repair Versus Open Surgical Repair for Descending Thoracic Aortic Disease

A Systematic Review and Meta-Analysis of Comparative Studies

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Objectives The purpose of this study was to determine whether thoracic endovascular aortic repair (TEVAR) reduces death and morbidity compared with open surgical repair for descending thoracic aortic disease.

Background The role of TEVAR versus open surgery remains unclear. Metaregression can be used to maximally inform adoption of new technologies by utilizing evidence from existing trials.

Methods Data from comparative studies of TEVAR versus open repair of the descending aorta were combined through meta-analysis. Metaregression was performed to account for baseline risk factor imbalances, study design, and thoracic pathology. Due to significant heterogeneity, registry data were analyzed separately from comparative studies.

Results Forty-two nonrandomized studies involving 5,888 patients were included (38 comparative studies, 4 registries). Patient characteristics were balanced except for age, as TEVAR patients were usually older than open surgery patients ($p = 0.001$). Registry data suggested overall perioperative complications were reduced. In comparative studies, all-cause mortality at 30 days (odds ratio [OR]: 0.44, 95% confidence interval [CI]: 0.33 to 0.59) and paraplegia (OR: 0.42, 95% CI: 0.28 to 0.63) were reduced for TEVAR versus open surgery. In addition, cardiac complications, transfusions, reoperation for bleeding, renal dysfunction, pneumonia, and length of stay were reduced. There was no significant difference in stroke, myocardial infarction, aortic reintervention, and mortality beyond 1 year. Metaregression to adjust for age imbalance, study design, and pathology did not materially change the results.

Conclusions Current data from nonrandomized studies suggest that TEVAR may reduce early death, paraplegia, renal insufficiency, transfusions, reoperation for bleeding, cardiac complications, pneumonia, and length of stay compared with open surgery. Sustained benefits on survival have not been proven. (J Am Coll Cardiol 2010;55:986–1001)

Since the introduction of thoracic endovascular aortic repair (TEVAR) using stent grafts for complicated diseases of the descending thoracic aorta, there has been debate regarding the safety, efficacy, and durability of this approach. Until recently, options for the management of thoracic aortic disease were limited to open surgical repair or conservative medical management. After the first formal publication of a case series describing the outcome of 13 patients undergoing TEVAR for descending thoracic aneurysm in the early 1990s (1), the subsequent pace of uptake of TEVAR has outstripped adequate evaluation of the evidence for its benefits and risks.

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To date, no randomized trials of TEVAR versus open surgical repair for descending thoracic aortic disease have been performed. Most published reports describing TEVAR consist of uncontrolled retrospective cohorts or case series. Recently, a number of nonrandomized phase II studies have compared endovascular repair with a concurrent or historical open surgical group. In the absence of definitive randomized controlled trials, the value of TEVAR relative to conventional open surgical approaches will continue to be debated (2–4).

When randomized trials are unavailable, metaregression can be performed to maximize the knowledge gained from existing comparative studies in order to optimally direct future patient care decisions and need for further research. A methodologically rigorous meta-analysis with metaregression to account for baseline demographics is urgently needed to clarify the overall benefit-to-risk ratio of TEVAR versus open surgical repair for complicated diseases of the descending thoracic aorta, and to better inform further research in this area. Metaregression may also shed light on the balance of outcomes across various patient subgroups with differing pathologies of the aorta. Disease of the descending thoracic aorta requiring surgical or endovascular intervention may include degenerative aneurysm, dissection, traumatic rupture, intramural hematoma, and penetrating aortic ulcer. Previous meta-analyses of TEVAR assessed only noncomparative studies (5), did not include more recent studies (5–7), focused only on 1 pathology such as blunt injury (6–10), or selectively reported only 1 outcome such as death (10). This study was commissioned by the European Association of Cardiothoracic Surgery to address the current evidence for adoption of TEVAR. The objective was to perform a comprehensive meta-analysis with metaregression of available comparative studies to determine whether TEVAR improves morbidity, mortality, and resource-related outcomes compared with open surgery for adults presenting with thoracic aortic disease.

Abbreviations and Acronyms

CI = confidence interval
OR = odds ratio
TEVAR = thoracic endovascular aortic repair
WMD = weighted mean difference

Methods

This analysis was planned in accordance with current guidelines for performing comprehensive systematic reviews and meta-analyses with regression, including the PRISMA (Preferred Reporting Items for Systematic reviews Meta-Analyses) (11) and MOOSE (Meta-analysis Of Observational Studies in Epidemiology) (12) guidelines for randomized and nonrandomized studies, respectively. A protocol pre-specified outcomes, search strategies, inclusion criteria, and statistical analyses.

Search strategy. A search was performed by bibliographic experts to identify all studies in MEDLINE, Cochrane Central Register of Controlled Trials on The Cochrane Library, International Association of Health Technology Assessment (INAHTA), and EMBASE from 1990 to March 2009, as well as surgical meeting abstracts from 2006 to 2009. The Food and Drug Administration devices database was also accessed for additional unpublished data. Search terms included combinations and derivatives of the following as textwords and MESH terms: (thorac* AND aort*) OR aneurys* OR dissect* OR "penetrating atherosclerotic ulcer" OR "intramural hemorrhage" OR trauma* OR rupture*) AND (endovasc* OR endostent* OR surg* OR operat* OR TEVAR OR EVAR OR stent*). After the initial searches were completed and potentially relevant studies identified, additional tangential searches were conducted using related article links within MEDLINE. In addition, individual searches for specific names of commercial stents were performed to identify further TEVAR stud-

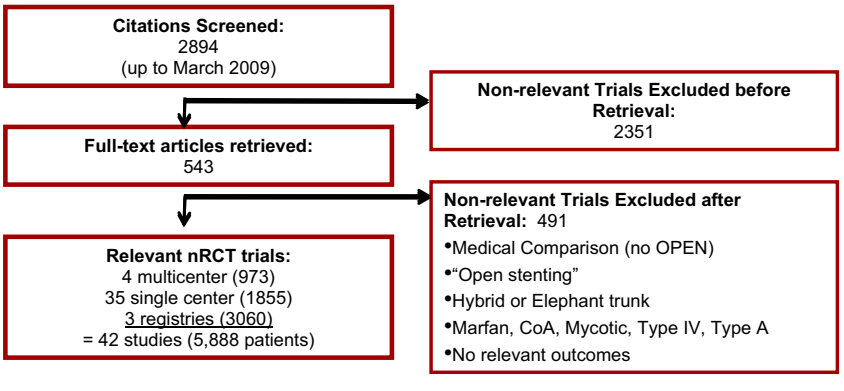

Figure 1 Results of Literature Search

The flow chart outlines the total number of potentially relevant citations reviewed and collected for full-text screening. Reasons for inclusion and exclusion are outlined. CoA = coarctation; nRCT = nonrandomized controlled trial.

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ies, including Gore TAG (Gore, Flagstaff, Arizona), Excluder (Gore), AneuRx (Medtronic, Sunnyvale, California), Talent (World Medical Manufacturing, Sunrise, Florida), Vanguard (Boston Scientific, Natick, Massachusetts), Zenith (Cook, Indianapolis, Indiana), Stentor (MinTec, La Ciotat, France), Relay (Bolton Medical, Barcelona, Spain), Endofit (Endomed, Inc., Phoenix, Arizona), E-Vita (Jotec, Heitchingen, Germany), and TX1 or TX2 (Cook). Reference lists of relevant studies and recent overviews were also reviewed for additional

Table 1 Characteristics of Included Comparative Studies for TEVAR Versus OPEN Surgery

Authors, Year (Study) (Ref. #)	n	Pathology	Type of Control	Location	Year	Stent Name*
Multicenter studies						
Bavaria/Makaroun (GORE TAG) (23–30)	234	Aneurysm	Overlapping	U.S.	1998–2001	Gore
Demetriades et al., 2008 (AAST) (35)	125	Trauma	Concomitant	U.S., Australia, Europe	~2006	Mixed (Gore Tag, Talent, Vanguard, Zenith)
Matsumura et al., 2008 (TX2) (51–54)	230	Mixed	Overlapping	U.S., Canada	2004–2006	Zenith Cook
Fairman et al., 2008 (VALOR) (42,43)	384	Mixed	Concomitant	U.S.	2003–2005	Talent
Single-center studies						
Aasland et al., 2005 (19)	60	Mixed	Historic	Europe	1985–2003	Unspecified
Akowuah et al., 2007 (20)	15	Trauma	Concomitant	Europe	2000–2006	Talent
Amabile et al., 2004 (21)	20	Trauma	Historic	Europe	1998–2004	Talent or Gore
Andrassy et al., 2006 (22)	46	Trauma	Historic	Europe	1997–2005	Mixed (Talent, Excluder, Zenith)
Brandt et al., 2004 (31)	44	Mixed	Concomitant	Europe	1995–2003	Talent
Broux et al., 2006 (32)	30	Trauma	Concomitant	Europe	1995–2005	Mixed (Talent, Thoracic Excluder)
Buz et al., 2008 (33)	74	Trauma	Overlapping	Europe	1987–2007	Mixed (Talent [n = 27], e-Vita [n = 9], Relay [n = 3])
Chung et al., 2008 (34)	103	Trauma	Historic	Canada	1995–2003	Mixed (Talent, Zenith)
Cook et al., 2006 (36)	42	Trauma	Concomitant	U.S.	2000–2005	Mixed
Dick et al., 2008 (37)	136	Mixed	Concomitant	Europe	2001–2005	Mixed
Doss et al., 2005 (38,39)	54	Rupture	Concomitant	Europe	1999–2002	Talent or Gore
Ehrlich et al., 1998 (40,41)	68	Aneurysm	Overlapping	Europe	1989–1997	Talent
Geisbusch et al., 2009 (45)	28	Trauma	Overlapping	Europe	1990–2007	Gore Tag, Talent/Valiant
Glade et al., 2005 (44)	95	Aneurysm	Historic	Europe	1997–2003	Mixed
Kasirajan et al., 2003 (46)	27	Trauma	Concomitant	U.S.	1999–2002	Mixed (Talent [n = 3], Thoracic Excluder [n = 1], homemade graft [n = 1])
Keiffer et al., 2009 (47)	163	Aneurysm	Concomitant	Europe	1997–2005	Unspecified
Kokotsakis et al., 2007 (48)	32	Trauma	Concomitant	Europe	2002–2006	Mixed (Talent, Valiant, Relay)
Kuhne et al., 2005 (49)	42	Trauma	Concomitant	Europe	1998–2002	Mixed
Lebl et al., 2006 (50)	17	Trauma	Historic	U.S.	1997–2003	Mixed
McPhee et al., 2007 (55)	27	Trauma	Concomitant	U.S.	2000–2004	Mixed (Talent, Thoracic Excluder)
Midgely et al., 2007 (56)	28	Trauma	Overlapping	Canada	1994–2006	Talent
Moainie et al., 2008 (57)	52	Trauma	Historic	U.S.	2005–2007	Gore
Mohan et al., 2008 (58)	26	Trauma	Concomitant	Australia	2000–2007	Mixed
Morishita et al., 2004 (59,61)	29	Rupture	Concomitant	Asia	2001–2004	Homemade
Najibi et al., 2002 (60)	34	Aneurysm	Historic	U.S.	1996–2005	Talent or Gore
Nienaber et al., 2003 (63)	22	Dissection	Historic	Europe	1998–2002	Talent
Nienaber et al., 1999 (62)	24	Dissection	Concomitant	Europe	1997–1998	Talent
Ott et al., 2004 (64)	18	Trauma	Historic	Canada	1991–2002	Talent
Pacini et al., 2005 (65)	69	Trauma	Overlapping	Europe	1980–2003	Mixed (Talent, Gore Excluder)
Patel et al., 2008 (66,67)	93	Mixed	Overlapping	U.S.	1993–2007	Mixed
Reed et al., 2006 (68)	24	Trauma	Overlapping	U.S.	2000–2005	Mixed (Aneurx or Excluder)
Riesenman et al., 2007 (69)	62	Trauma	Overlapping	U.S.	1993–2006	Mixed (Gore TAG, Talent, Vanguard, Excluder extension cuffs)
Rousseau et al., 2005 (70)	64	Trauma	Historic	Europe	1981–2003	Mixed (Talent, Thoracic Excluder, Vanguard)
Stampfl et al., 2006 (71)	10	Trauma	Historic	Europe	1993–2004	Mixed (Talent or Gore)
Stone et al., 2006/Conrad et al., 2008 (72,76)	173	Mixed	Overlapping	U.S.	1996–2005	Mixed
Yamane et al., 2008 (77)	26	Trauma	Overlapping	U.S.	1999–2007	Mixed
Orandi et al., 2009 (AHRQ) (74)	1,030	Mixed	Concomitant	U.S.	2005–2005	Mixed
Reuben et al., 2007 (NTDB) (75)	1,788	Trauma	Concomitant	U.S.	1994–2003	Mixed
Tsai et al., 2006 (IRAD) (73)	242	Dissection	Concomitant	Europe, Canada, U.S.	1996–2003	Mixed

*Mixed = a variety of stents used; Homemade = custom-created stent described as homemade by the authors.

AAST = American Association for the Surgery of Trauma; IRAD = International Registry of Acute Aortic Dissection; TEVAR = thoracic endovascular aortic repair; VALOR = Evaluation of the Medtronic AVE Talent Thoracic Stent Graft System for the Treatment of Thoracic Aneurysms.

studies. Studies in any language, whether published or unpublished, were eligible for inclusion. Selected authors of clinical studies and experts were contacted to further identify unpublished studies of TEVAR versus open surgery management.

Study retrieval and selection criteria. Trials identified as potentially relevant on the basis of title or abstract were selected for full review. Two reviewers independently assessed these trials for eligibility based on prespecified inclusion criteria. Disagreement was resolved by consensus with third party adjudication.

For the primary analysis, all studies comparing TEVAR with open surgery were eligible if they enrolled at least 10 adults with descending thoracic aneurysm disease and reported at least 1 clinically relevant or resource-related outcome. Eligible aortic pathologies included thoracic aortic aneurysm, dissection, rupture, trauma, penetrating aortic ulcer, or intramural hemorrhage, whether chronic or acute, emergent or elective. Studies of coarctation or Marfan syndrome, hybrid procedures, Type A aneurysm, and combined thoracic and abdominal aortic disease were excluded. If studies provided outcomes across a number of thoracic aorta pathologies, only the relevant subgroups were included.

Data extraction and outcomes definitions. Two reviewers independently assessed studies for inclusion criteria, and data were extracted independently by the lead reviewer and at least 1 additional reviewer. Discrepancies were resolved by consensus with international authors at designated consensus meetings. Data were extracted onto standard forms, and included baseline demographics, aortic pathology, duration of follow-up study sites, study design, years of enrollment, whether patients were consecutively enrolled, and loss to follow-up. Studies from centers that included the same set of patients over different time frames were carefully evaluated to include only updated follow-up data.

For clinical outcomes, definitions provided by authors of the studies were generally used as provided. Death was defined as cumulative incidence of all-cause mortality. Incidence of paraplegia or paraparesis, whether permanent or temporary, was reported as an aggregate outcome, and only post-operative incidence of new paraplegia or paraparesis was considered (i.e., preprocedural paraplegia due to trauma was not considered relevant). Permanent paraplegia was defined as paraplegia persisting at the time of last study follow-up. Renal dysfunction was defined as per the authors' definition (increases in serum creatinine over baseline by more than 50% or need for renal replacement therapy). Incidence of transfusions was defined as the cumulative number of patients transfused blood products post-operatively. The composite outcome of any cardiac complications was recorded only when the study authors provided the number of patients experiencing any complication related to cardiovascular system post-operatively, typically defined as 1 or more episodes of ischemia, infarction, hemodynamic instability, low cardiac output syndrome, or arrhythmia. Endoleaks were classified according to the usual nomenclature (13). Early endoleak was defined as occurring within 30 days, and late endoleak as occurring or persisting at follow-up beyond 30 days.

Statistical analysis. Planned subanalyses included analysis by study design (single-center series, multicenter studies, and registries; unfortunately, randomized studies were unavailable), aortic pathology (degenerative aneurysm, dissection, trauma, rupture, and intramural hemorrhage/penetrating aortic ulcer), and by type of stent (commercial and noncommercial or homemade).

Potential confounding due to selection bias or differential intensity of follow-up in the observational studies was evaluated by measuring whether there were important differences between TEVAR and open surgical groups in baseline patient characteristics or study design characteristics including age, sex, aortic pathology, urgency of intervention, and comorbidities including smoking history, chronic obstructive pulmonary disease, diabetes, hypertension, coronary artery disease, and length of follow-up. Metaregression was performed to measure the impact of baseline characteristics and pathologies on the effect size for death, stroke, or paraplegia. To determine the impact of time and the learning curve, metaregression was also performed by year of patient enrollment defined for each study as the median year within the range of years during which patient data were collected. When date ranges for patient enrollment were not provided, the year was assumed to be 3 years prior to the date of publication. Sensitivity analysis was planned for the following indicators of study quality: prospective versus retrospective data collection, consecutive patient recruitment versus nonconsecutive patient inclusion, and historic versus concomitant control groups.

In evaluating multiple publications of overlapping patient populations, we classified all studies by the center(s) and dates of patient enrollment, and selected the most recent and/or most complete series from each center to extract as many relevant outcomes as possible. When the more recent series failed to report all outcomes

Table 2 Baseline Characteristics for Included Patients

	TEVAR	Open Surgery	p Value
Male	61.9	67.0	0.84
CAD	41.9	36.2	0.31
Diabetes	13.8	9.1	0.23
COPD	38.1	32.3	0.13
Smoker	76.0	71.1	0.21
Hypertension	79.6	78.3	0.84
Renal insufficiency	9.9	13.6	0.74
Age, yrs	54 ± 13	51 ± 13	0.001

Values are % or mean ± SD.

CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; TEVAR = thoracic endovascular aortic repair.

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Table 3 Clinical Outcomes for MC, SC, and All Studies

Design	n/N	TEVAR, %*	n/N	Open Surgery, %*	I^2, %	OR (95% CI)	p Value
Death, 30-day							
MC	18/676		41/421		0	0.24 (0.13–0.44)	<0.00001
SC	62/773		165/1,008		0	0.53 (0.38–0.74)	<0.0001
All	80/1,444	5.8	206/1,429	13.9	0	0.44 (0.33–0.59)	<0.00001
Death, 1-yr							
MC	44/352		49/259		0	0.68 (0.43–1.06)	0.09
SC	55/260		61/249		7	0.81 (0.49–1.32)	0.39
All	99/612	16.0	110/508	21.9	0	0.73 (0.53–1.02)	0.07
Death, 2- to 3-yr							
MC	36/140		26/94		0	0.91 (0.50–1.63)	0.74
SC	42/194		45/195		0	0.93 (0.63–1.33)	0.65
All	78/334	23.0	71/289	24.8	0	0.92 (0.63–1.33)	0.65
Paraplegia, paraparesis							
MC	31/620		48/411		28	0.44 (0.23–0.84)	0.01
SC	15/769		75/1,063		0	0.40 (0.24–0.68)	0.001
All	46/1,389	3.4	123/1,474	8.2	0	0.42 (0.28–0.63)	<0.0001
Permanent paraplegia							
MC	7/495		16/343		0	0.29 (0.12–0.71)	0.007
SC	2/215		15/282		0	0.31 (0.09–1.11)	0.07
All	9/710	1.4	31/625	4.9	0	0.30 (0.14–0.62)	0.001
Stroke							
MC	19/495		27/343		0	0.46 (0.25–0.85)	0.01
SC	34/539		35/669		10	1.12 (0.64–1.94)	0.70
All	53/1,034	5.0	62/1,012	6.2	23	0.75 (0.50–1.13)	0.17
AMI							
MC	3/495		11/343		0	0.26 (0.08–0.86)	0.03
SC	13/208		33/358		0	1.25 (0.59–2.66)	0.56
All	16/703	2.3	44/701	6.3	20	0.81 (0.43–1.53)	0.51
Renal dysfunction							
MC	39/615		76/410		66	0.36 (0.16–0.82)	0.01
SC	19/390		69/536		0	0.42 (0.24–0.72)	0.0001
All	58/1,005	5.9	145/946	15.7	0	0.40 (0.25–0.63)	<0.001
Ischemia, limb or gut							
MC	7/530		7/452		0	0.75 (0.25–2.70)	0.60
SC	5/117		3/130		13	1.29 (0.32–5.29)	0.72
All	12/647	1.9	10/582	1.7	0	0.92 (0.39–2.21)	0.86
Reoperation for bleeding							
MC	0/160		3/70		0	0.06 (0.003–1.18)	0.06
SC	4/304		27/392		0	0.30 (0.12–0.74)	0.009
All	4/464	0.01	30/462	6.5	0	0.26 (0.11–0.62)	0.002
Transfused patients							
MC	5/160		61/70		0	0.005 (0.002–0.015)	<0.0001
SC	2/17		16/22		0	0.04 (0.004–0.34)	0.004
All	7/177	3.9	77/92	83.7	23	0.01 (0.002–0.04)	<0.0001
Reintervention							
MC	13/298		4/164		57%	1.89 (0.18–19.0)	0.60
SC	40/389		44/413		0%	0.99 (0.62–1.58)	0.97
All	53/687	8.1	48/577	9.1	0%	1.01 (0.64–1.60)	0.95
Pneumonia							
MC	57/319		64/246		73	0.54 (0.23–1.23)	0.14
SC	15/134		66/207		22	0.32 (0.15–0.69)	0.003
All	72/453	15.9	130/453	28.7	44	0.14 (0.23–0.71)	0.002
Wound infections							
MC	20/300		18/164		0	0.70 (0.20–2.47)	0.58
SC	1/66		8/82		0	0.19 (0.03–1.11)	0.07
All	21/366	5.7	26/246	10.6	0	0.42 (0.16–1.27)	0.13

Continued on next page

Table 3 Continued

Design	n/N	TEVAR, %*	n/N	Open Surgery, %*	I^2, %	OR (95% CI)	p Value
Ischemia, limb or gut							
MC	5/335		6/273		14	0.62 (0.15–2.52)	0.51
SC	5/117		3/130		12	1.29 (0.32–5.29)	0.72
All	10/452	2.2	9/403	2.4	8	0.89 (0.33–2.41)	0.83
Neurologic complications							
MC	54/495		81/343		41	0.41 (0.24–0.68)	0.001
SC	2/140		22/207		0	0.22 (0.07–0.74)	0.01
All	56/635	8.9	103/550	18.7	5	0.37 (0.23–0.59)	<0.0001
Cardiac complications							
MC	78/495		139/343		0	0.29 (0.14–0.62)	0.001
SC	6/67		27/172		0	0.51 (0.21–1.28)	0.15
All	84/562	14.6	166/515	32.1	0	0.37 (0.20–0.66)	0.001
Respiratory complications							
MC	57/690		164/522		0	0.21 (0.15–0.29)	<0.0001
SC	39/213		120/338		39	0.50 (0.26–0.96)	0.04
All	96/903	11.1	284/860	33.2	48	0.25 (0.18–0.33)	<0.0001
Vascular complications							
MC	89/690		112/522		87	0.50 (0.15–1.60)	0.24
SC	1/8		0/5		0	2.20 (0.08–6.49)	0.65
All	90/698	13.0	112/527	21.9	83	0.58 (0.19–1.76)	0.34
Overall complications							
MC	240/620		295/411		88	0.16 (0.06–0.41)	<0.0001
SC	24/143		82/179		15	0.23 (0.10–0.53)	<0.001
All	264/763	41.4	379/590	69.3	63	0.19 (0.10–0.36)	<0.0001

*Incidence of events using weighted events across studies.

All = all studies combined; AMI = acute myocardial infarction; CI = confidence interval; MC = multi-center; OR = odds ratio; SC = single-center; TEVAR = thoracic endovascular aortic repair.

of interest, we referred to the next most current series from the same center, and extracted the remaining outcomes as far as possible. When it became apparent that a number of single-center experiences were published with overlapping patient datasets as those included in multicenter phase II trials or registries, we decided to present the data aggregated by each study type (consecutive series, multicenter trial, and registries), and to combine the results across multicenter and single-center studies only when the degree of overlap was likely to be low, if any. Registry data were not aggregated together with multicenter and single-center studies, since the degree of overlap was likely to be large, and since significant heterogeneity was detected between the registry aggregate data compared with nonregistry data.

Patient characteristics and outcomes were entered into a database, and analysed using Comprehensive Meta-Analysis Software version 2 (Biostat, Littlewood, New Jersey). For dichotomous variables, individual and pooled statistics were calculated as weighted odds ratios (ORs) with 95% confidence intervals (CIs). For continuous outcomes, individual and pooled statistics were calculated as weighted mean differences (WMD) and 95% CIs. Since heterogeneity was anticipated across the trials, the random effects model was used for all calculations to provide an overall conservative analysis (14). For the primary analysis, data were combined within each category of study type (single-center series, multicenter trials, registries), and presented by study subtype and in aggregate (for single-center and multicenter data only). For subanalyses by pathology, by study design, and by type of stent used, data were combined across subgroups using the mixed effects analysis. The test for interaction was employed to determine whether effect sizes differed significantly across subgroups. We preferentially captured intention-to-treat data whenever available (15).

Heterogeneity across trials was explored for each outcome by calculating I^2, which indicates the percent of heterogeneity across trials that cannot be explained by chance variation alone (16,17). I^2 >50% was considered to indicate high heterogeneity. Publication bias was assessed through funnel plots, and Egger's regression test was applied (18).

Results

In total, 2,894 abstracts were identified for screening, and a total of 42 studies reported in 59 papers involving 5,888 patients met the inclusion criteria for this analysis (19–77). Fifteen papers described 4 multicenter observational trials (23–30,35,42,43,51–54), 3 papers described 3 registries (73–75), and the remainder of papers described cohorts or series of patients undergoing TEVAR versus concurrent or historical control groups, from single centers. Figure 1 outlines the results of the search strategy, and Table 1 describes the included studies.

Weighted analysis across all studies showed that baseline characteristics were similar between TEVAR and open groups for the following: sex, hypertension, coronary artery disease, chronic obstructive pulmonary disease, and smoking status (Table 2). However, patients included in the TEVAR group were older on average by nearly 3 years than patients included in the open surgery group, and this difference was statistically significant (age 54 ± 13 years for TEVAR versus 51 ± 13 years for open surgery; p = 0.001), underscoring the need for metaregression analysis to assess the impact of age differences at baseline on outcomes estimates for TEVAR versus open surgery.

Clinical outcomes. Clinical outcomes are summarized in Table 3, subanalyzed by study category.

Operative death and all-cause mortality. Cumulative 30-day all-cause mortality was reduced for TEVAR versus open surgery (OR: 0.44, 95% CI: 0.33 to 0.59). Cumulative all-cause mortality at 1 year (OR: 0.73, 95% CI: 0.53 to 1.02; $I^2 = 0\%$) and at 2 to 3 years did not differ significantly between TEVAR and open surgery groups (OR: 0.92, 95% CI: 0.63 to 1.34; $I^2 = 0\%$).

The reduction in all-cause mortality at 30 days was greater in multicenter trials (OR: 0.24, 95% CI: 0.13 to 0.44) than for single-center series (OR: 0.53, 95% CI: 0.38 to 0.74), and the p value for interaction across study type was significant (p = 0.020). Mortality at 1 year and beyond was similar in multicenter and single-center studies. Figures 2 to 4 summarize the results for all-cause mortality at each period of follow-up. Funnel plots (not shown) did not indicate a significant risk of publication bias for the outcome of mortality.

Stroke. The overall risk of stroke was similar for TEVAR (single-center and multicenter studies combined) versus open surgery (OR: 0.75, 95% CI: 0.50 to 1.13; $I^2 = 23\%$). In subgroup analysis, stroke was significantly reduced in multi-

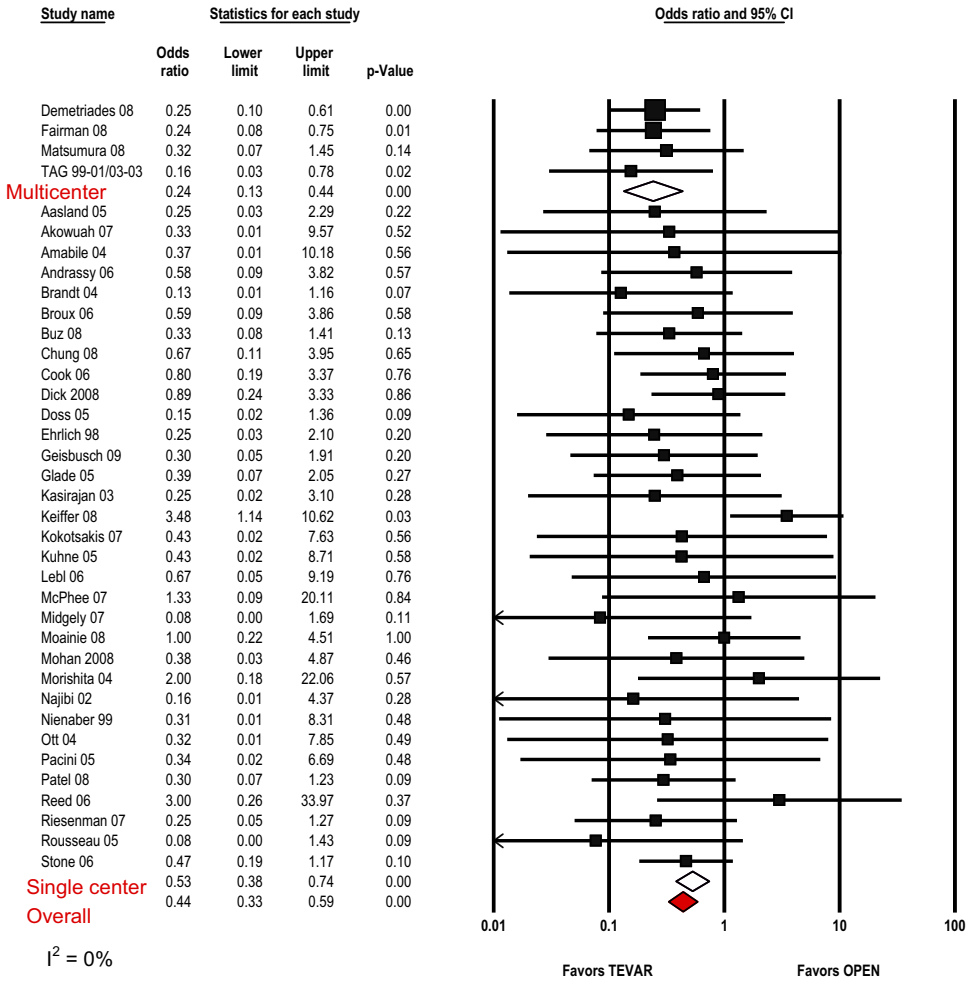

Figure 2 **Death at 30 Days for TEVAR Versus Open Surgery**

Meta-analysis comparing death at 30 days for thoracic endovascular aortic repair (TEVAR) versus open surgery. The odds ratio (OR) for death from each included study is plotted. A pooled estimate of overall OR **(diamonds)** and 95% confidence intervals **(width of diamonds)** summarizes the effect size using the random effects model. Effects to the **left** of 1.0 favor TEVAR; effects to the **right** favor open surgery. When the **horizontal bars** of an individual study, or the pooled **diamond width**, cross 1.0, the effect is not significantly different. The I^2 for heterogeneity was not significant, suggesting homogeneity in effect size across each study.

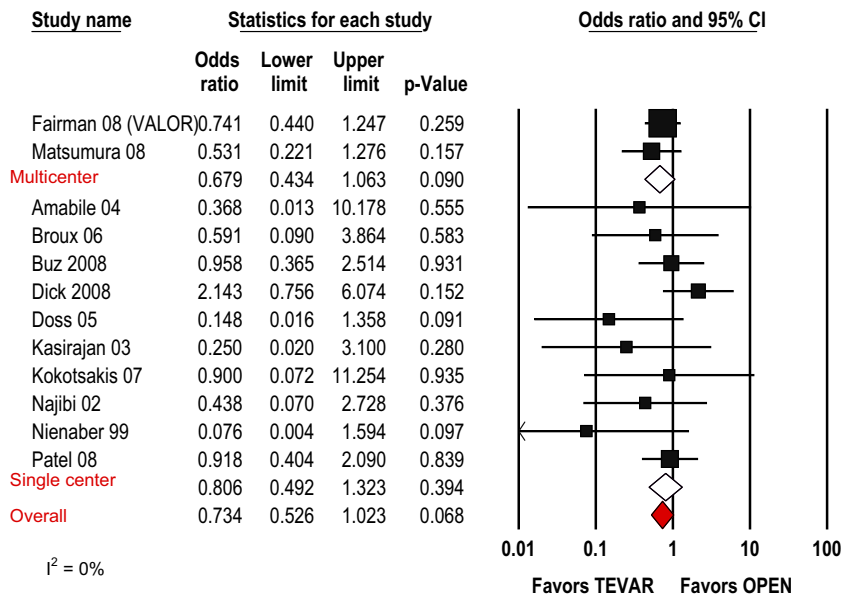

Figure 3 **Death at 1 Year for TEVAR Versus Open Surgery**

Meta-analysis comparing death at 1 year for thoracic endovascular aortic repair (TEVAR) versus open surgery. The odds ratio (OR) for death from each included study is plotted. A pooled estimate of overall OR **(diamonds)** and 95% confidence intervals **(width of diamonds)** summarizes the effect size using the random effects model. Effects to the **left** of 1.0 favor TEVAR; effects to the **right** favor open surgery. When the **horizontal bars** of an individual study, or the pooled **diamond width**, cross 1.0, the effect is not significantly different. The I^2 for heterogeneity was not significant, suggesting homogeneity in effect size across each study.

center trials of TEVAR versus open surgery (OR: 0.46, 95% CI: 0.25 to 0.85). Subanalysis of single-center series alone did not show significant reduction in stroke for TEVAR versus open surgery (OR: 1.12, 95% CI: 0.64 to 1.94). There was significant interaction across multicenter versus single-center subgroups ($p = 0.021$) (Fig. 5).

Paraplegia and paraparesis. Paraplegia or paraparesis (permanent or temporary) was significantly reduced for TEVAR versus open surgery (OR: 0.42, 95% CI: 0.28 to 0.63) (Fig. 6). Permanent paraplegia was also significantly reduced (OR: 0.30, 95% CI: 0.14 to 0.62; $I^2 = 0\%$). The magnitude of reduction in risk of paraplegia or paraparesis and permanent paraplegia was similar in multicenter and single-center studies (p values for interaction across studies were 0.83 and 0.92, respectively).

Other clinical outcomes. Compared with open surgery, TEVAR significantly reduced risk of renal dysfunction (OR: 0.40, 95% CI: 0.25 to 0.63), reoperation for bleeding (OR: 0.26, 95% CI: 0.11 to 0.62), and incidence of transfusion (OR: 0.01, 95% CI: 0.002 to 0.04). Other outcomes that were significantly improved with TEVAR included cardiac, pneumonia, and respiratory complications. TEVAR significantly reduced the composite outcome of any complication compared with open surgery (OR: 0.23, 95% CI: 0.12 to 0.44).

Hospital length of stay was significantly reduced (WMD: −7 days, 95% CI: −10 to −5 days). Similarly, total intensive care unit length of stay was significantly reduced by 4 days (−4 days, 95% CI: −5 to −3 days). Procedure time was significantly reduced by a mean of 140 min for TEVAR versus open surgery (WMD: −142 min, 95% CI: −200 to −87 min; $I^2 = 90\%$). The higher heterogeneity in length of stay and procedure time was due to difference in magnitude of effect across studies rather than due to differences in direction of effect or study design.

Clinical outcomes that did not differ between TEVAR and open surgery included myocardial infarction, ischemic complications (gut or limb), vascular complications, wound infections, aortoesophageal fistula, laryngeal nerve injury, phrenic nerve injury, post-operative dissection or rupture, and need for reintervention. These outcomes were less commonly reported in the trials, and power was inadequate to rule out the potential for clinically and statistically significant differences in future studies. Patient-reported outcomes such as pain, functionality, quality of life, and patient satisfaction were not reported in the trials.

Endoleaks. The reported incidence of endoleak was 12.1% (95% CI: 13.0 to 17.4%) when limited to studies in which endoleaks were definitively reported. However, this may be an overestimate, since many studies did not expressly report endoleaks, and we did not presume that the incidence was zero when endoleaks were not mentioned. Since most of the studies failed to provide sufficient details about the endoleaks, it was not possible to analyze the aggregate incidence of early versus late endoleak and the different subtypes of endoleaks. Stent fractures and migration were reported rarely.

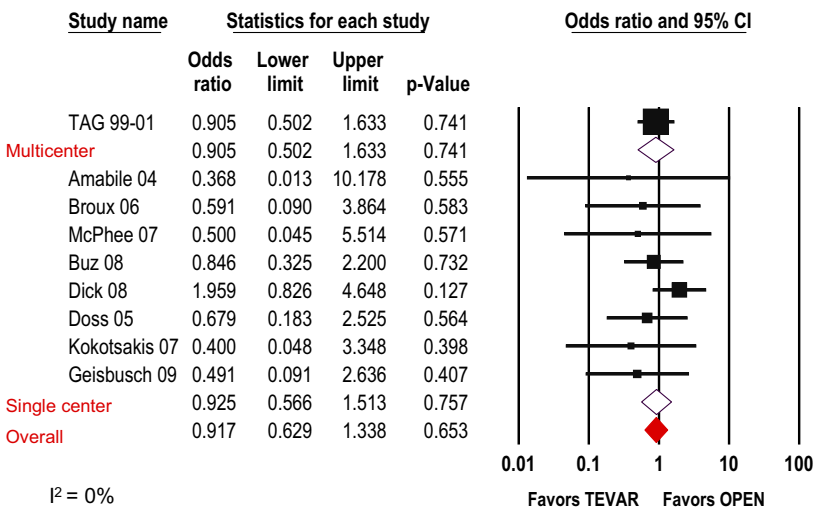

Figure 4 Death at 2 to 3 Years for TEVAR Versus Open Surgery

Meta-analysis comparing death at 2 to 3 years for thoracic endovascular aortic repair (TEVAR) versus open surgery. The odds ratio (OR) for death from each included study is plotted. A pooled estimate of overall OR **(diamonds)** and 95% confidence intervals **(width of diamonds)** summarizes the effect size using the random effects model. Effects to the **left** of 1.0 favor TEVAR; effects to the **right** favor open surgery. When the **horizontal bars** of an individual study, or the pooled **diamond width**, cross 1.0, the effect is not significantly different. The I^2 for heterogeneity was not significant, suggesting homogeneity in effect size across each study.

Metaregression and other subanalyses. Metaregression by baseline age did not impact the relative reduction in risk of death, stroke, and paraplegia for TEVAR versus open surgery (i.e., the results were consistent across age groups) (Fig. 7). Similarly, when the results for death, stroke, and paraplegia were analyzed by different aortic pathologies, the relative reductions for TEVAR versus open surgery were similar across subgroups (data not shown). Many comparative studies failed to report outcomes by specific type of pathology, and of those that did, only degenerative aneurysm and trauma were adequately represented in most subanalyses. In addition, ORs for death, stroke, and paraplegia did not differ by prospective versus retrospective design, historic versus concurrent control, consecutive versus nonconsecutive patient recruitment. Metaregression by year of patient recruitment showed that the results were similar over time since the slope of effect size over time was nonsignificant (Figs. 8 to 10).

Subanalysis by commercial and homemade stent was not possible due to very few patients receiving homemade stents in this analysis. Analysis of outcomes by different types of commercial stents was not possible since most studies used a variety of commercial stents, and few reported outcomes individually by type of stent used.

Examination of publication bias and funnel plots did not reveal a statistically significant risk of publication bias for any of the clinical outcomes, including death, paraplegia, stroke, cardiac complications, and renal dysfunction. For some outcomes, the paucity of data precluded adequate power for robust analysis of publication bias.

Registry data. Registry data showed significant reduction in overall complications with TEVAR versus open repair. In contrast to comparative studies, meta-analysis of data from published registries that compared TEVAR with open surgery failed to show significant reduction in all-cause mortality, stroke, myocardial infarction, and renal dysfunction with TEVAR. Paraplegia was not reported in these registries (Table 4). The apparent differences between registry results and clinical studies are not surprising since the registries reported on a small number of patients undergoing TEVAR, and generally included only traumatic aortic injury patients with short-term follow-up and nonconsecutive patient inclusion. In addition, few registries reported on clinical outcomes other than short-term survival. As a result, registry data are likely less reliable than the cumulative evidence from clinical studies of TEVAR versus open surgery.

Discussion

This meta-analysis of studies comparing TEVAR with open surgery for the management of descending thoracic aortic disease provides a comprehensive aggregate analysis of the available evidence to date. Given that there are no randomized trials of TEVAR versus open surgery for descending thoracic aortic intervention, the appropriate use of meta-analysis with metaregression represents an important method to extract the best possible information from existing data to examine the relative benefits and risks of TEVAR versus open surgery while account-

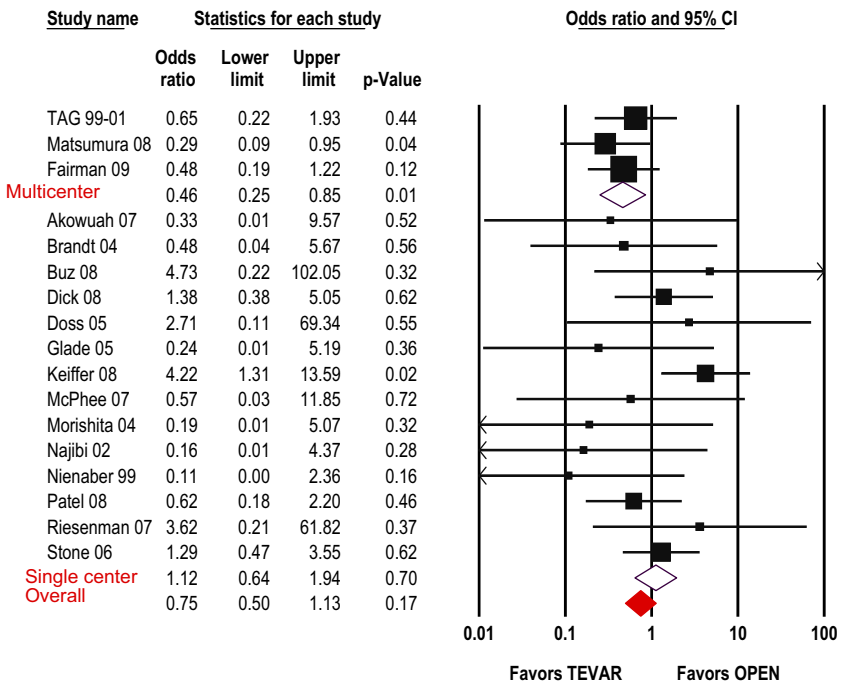

Figure 5 **Stroke for TEVAR Versus Open Surgery**

Meta-analysis comparing stroke for thoracic endovascular aortic repair (TEVAR) versus open surgery. The odds ratio (OR) for stroke from each included study is plotted. A pooled estimate of overall OR **(diamonds)** and 95% confidence intervals **(width of diamonds)** summarizes the effect size using the random effects model. Effects to the **left** of 1.0 favor TEVAR; effects to the **right** favor open surgery. When the **horizontal bars** of an individual study, or the pooled **diamond width**, cross 1.0, the effect is not significantly different. The I^2 for heterogeneity was not significant, suggesting homogeneity in effect size across each study.

ing for differences in patient characteristics inherent in the observational trials.

Overall, existing evidence suggests that TEVAR reduces the risk of all-cause mortality at 30 days. Survival at 1 year and beyond did not show a definitive benefit for TEVAR compared with open surgery; however, survival data after discharge were less commonly reported in the trials, and the trend was consistently in favor of TEVAR for the studies reporting 1-year cumulative all-cause mortality ($p = 0.07$), with no significant heterogeneity across the trials for this outcome. At minimum, the existing evidence shows that survival for TEVAR is not worse than for open surgery at midterm. Further studies, preferably randomized, with adequate power and complete follow-up will be needed to better define whether there are important long-term survival benefits for TEVAR over open surgery (78).

This analysis also shows that the risk of paraplegia/paraparesis is reduced for TEVAR versus open surgery. This has important implications for the long-term functionality and quality of life for patients undergoing thoracic aortic repair. Even when the definition was limited to permanent paraplegia, TEVAR provided significant benefit over open surgery. It is important to note that some trials employed protective techniques such as routine cerebrospinal fluid drainage, whereas others did not. Despite these practice differences, there was no detectable statistical heterogeneity across the trials for this outcome, and confidence in this result is heightened.

Other important benefits of TEVAR include reduction of renal dysfunction, transfusions, reoperation for bleeding, cardiac complications, neurologic complications, pneumonia, respiratory complications, reduced incidence of any complication, and shorter procedure time, and length of stay in intensive care unit or hospital.

Since there was generally low heterogeneity across trials, this lends credence to the robustness of the results across studies. Metaregressions and subanalyses of the results by various characteristics, including baseline characteristic differences and study design features, failed to show material changes in the results, again lending credence to the stability of the results across the studies.

Endoleaks and aortic graft reinterventions. There was a paucity of information on the true incidence of endoleaks and most studies limited their reporting, if any, to type I and II endoleaks since many had insufficient longitudinal follow-up to adequately ascertain type III and IV endoleaks. The incidence of endoleak was 12% overall; however, this value should be interpreted with caution since a number of trials did not report on endoleaks, and hence did not contribute to the summary estimate of incidence.

Study strengths and limitations. This study represents a comprehensive and rigorous systematic review with meta-

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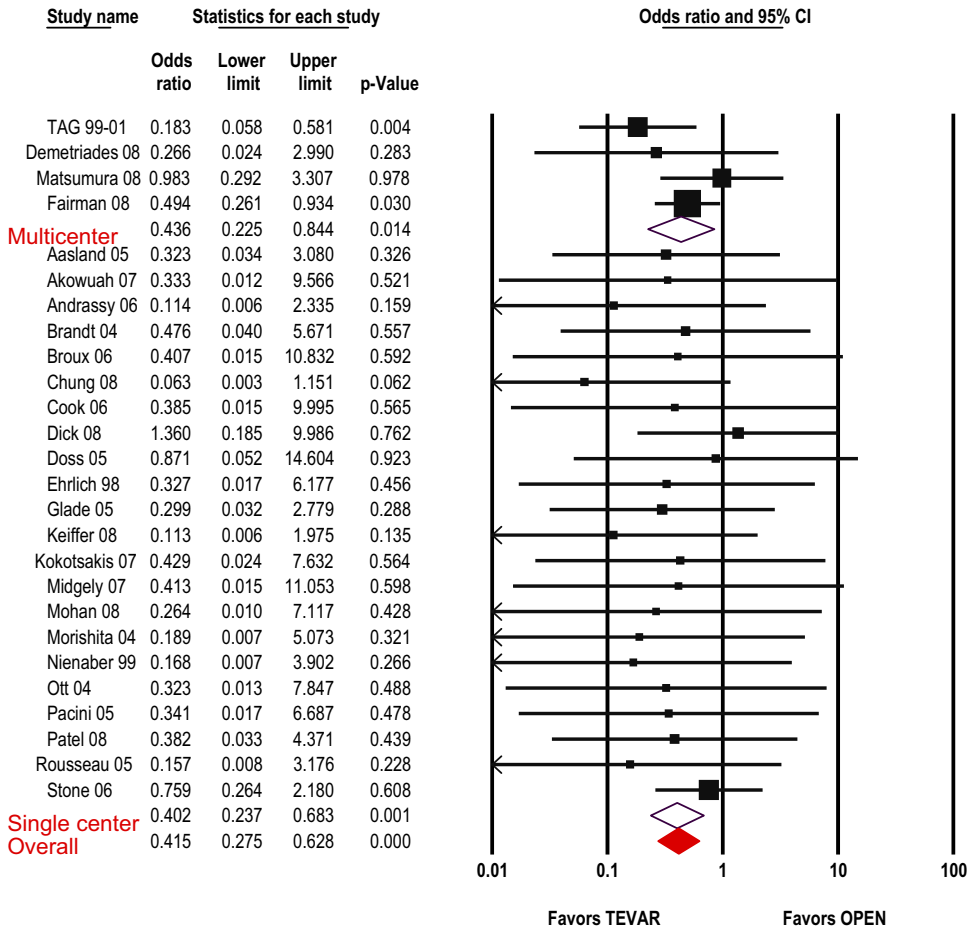

Figure 6 **Paraplegia or Pareparesis for TEVAR Versus Open Surgery**

Meta-analysis comparing paraplegia/pareparesis for thoracic endovascular aortic repair (TEVAR) versus open surgery. The odds ratio (OR) for paraplegia/pareparesis from each included study is plotted. A pooled estimate of overall OR **(diamonds)** and 95% confidence intervals **(width of diamonds)** summarizes the effect size using the random effects model. Effects to the **left** of 1.0 favor TEVAR; effects to the **right** favor open surgery. When the **horizontal bars** of an individual study, or the pooled **diamond width**, cross 1.0, the effect is not significantly different. The I^2 for heterogeneity was not significant, suggesting homogeneity in effect size across each study.

analysis of existing evidence for TEVAR versus open surgery in the management of descending thoracic aortic disease. Adherence to current guidelines for performing meta-analyses of observational studies was undertaken to ensure highest possible objectivity in analyses (11,12). Unlike previous systematic reviews in this area, this meta-analysis synthesizes all clinically relevant outcomes rather than a few selected outcomes, performs metaregression, and also included all major aortic pathologies rather than focusing on a single pathology only. This allows for comparisons of the balance of clinical outcomes across all pathologies. Where possible, methods to incorporate time-to-event data in the survival analyses were used to ensure best possible estimates of survival at each time point (79,80).

Despite the quality methodology used in this meta-analysis, this analysis should be interpreted in light of the shortcomings of the available data. The most important limitation is the absence of randomized trials comparing TEVAR versus open surgery, and the risks of systematic bias inherent to observational studies. In some studies, TEVAR was compared with a historical control. The historicity of the control group increases the risk of bias favoring TEVAR since outcomes of patients with descending thoracic aortic disease may be improving over time due to better contemporary detection and overall management of aortic disease. Nonetheless, in our regression analysis by historicity of control group, the ORs did not materially change for historical versus contemporaneous controls. In addition, analysis by various features of study design (consecutiveness of patient inclusion, retrospective vs. prospective) also failed to show material changes in the results.

In some studies, the duration of follow-up was longer for the open surgery group than the TEVAR group. This may bias the results against open surgery, since increased passage of time may reveal more adverse events than

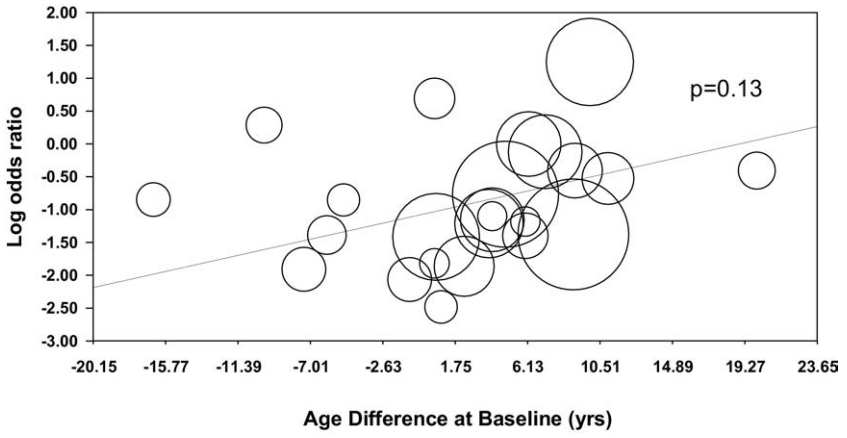

Figure 7 **Metaregression for Death by Age Differences at Baseline**

Metaregression of the effect of baseline age differences on the log odds ratio for the risk of death for thoracic endovascular aortic repair (TEVAR) versus open surgery. Each **circle** represents a study, telescoped by its weight in the analysis. The relationship was nonsignificant, suggesting that the impact of TEVAR on risk of death was consistent over the years (p = 0.13).

during shorter follow-up. In a post-hoc sensitivity analysis limited to studies with similar duration of follow-up between TEVAR and open surgery groups, the results for death at 1 year and 2 to 3 years were similar as in the original analysis.

There was inconsistency across studies in the description of criteria used to select patients for TEVAR versus alternative procedures. In some studies, TEVAR was reserved for patients unfit for open surgery, or with comorbidities that would place them at greater risk for complications with open surgery. In some studies, younger and fitter patients were selected for the newer procedure early in the surgeon's experience. Also, in the retrospective studies, it was generally unknown how many of the patients intended to undergo TEVAR were crossed over to open surgery due to difficult morphology or other reasons. If these cross-over patients were reported in the open surgical group, there may be slight overestimation of TEVAR benefit relative to open surgery since cross-over patients are likely to have worse outcomes and more complications than patients who were originally scheduled to undergo open surgery. Nonetheless, the total contribution of crossovers to the open group is likely small, and we used the more conservative random effects analysis to avoid overestimation of benefits.

Despite extensive efforts to systematically address the risk of including overlapping patient populations in this analysis, the authors acknowledge that there may be some remaining undetected overlap within the analysis since

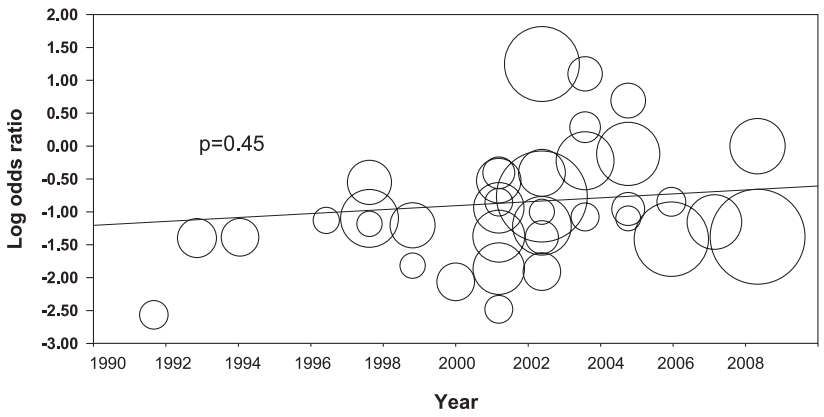

Figure 8 **Metaregression for Death at 30 Days by Enrollment Year**

Metaregression of the effect of enrollment year on the log odds ratio for the risk of death at 30 days for thoracic endovascular aortic repair (TEVAR) versus open surgery. Each **circle** represents a study, telescoped by its weight in the analysis. The relationship was nonsignificant, suggesting that the impact of TEVAR on risk of death was consistent over the years (p = 0.45).

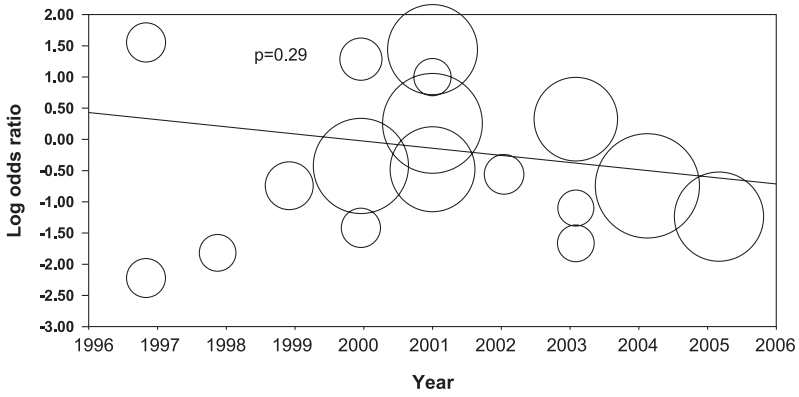

Figure 9 **Metaregression for Stroke by Enrollment Year**

Metaregression of the effect of enrollment year on the log odds ratio for the risk of stroke for thoracic endovascular aortic repair (TEVAR) versus open surgery. Each **circle** represents a study, telescoped by its weight in the analysis. The relationship was nonsignificant, suggesting that the impact of TEVAR on risk of stroke was consistent over the years (p = 0.29).

duplication and overlapping datasets are difficult to identify, particularly when authors' and centers' names do not exactly match from 1 patient series to the next overlapping series.

In order to maximally address the limitations inherent in nonrandomized studies, we performed metaregression analyses and subgroup analyses to determine whether key patient or study characteristics measurably affected outcomes estimates. Although patient-level data would have substantially improved the ability to evaluate confounders, using study-level data for metaregression allowed for maximal information to be derived from existing evidence in the absence of available patient-level data. It is encouraging that baseline characteristics such as age and aortic pathology were not found to significantly affect the overall estimate of relative benefit of TEVAR over open surgery for all-cause mortality, stroke, or paraplegia/paraparesis. Interestingly, since the relative benefit of TEVAR over open surgery did not differ significantly by year of enrollment, there was no statistically detectable learning-curve effect for earlier trials versus later trials, although, the analyses may be limited in power to detect small differences over time. Importantly, we should not discount the importance of interpreting these results in light of the fact that results of TEVAR and open surgery are inextricably dependent on the skills of the surgeons and their teams, and it is more likely for experienced centers to publish their results than those who are early in the learning curve. The results of this analysis also need to be interpreted with the knowledge that the patient

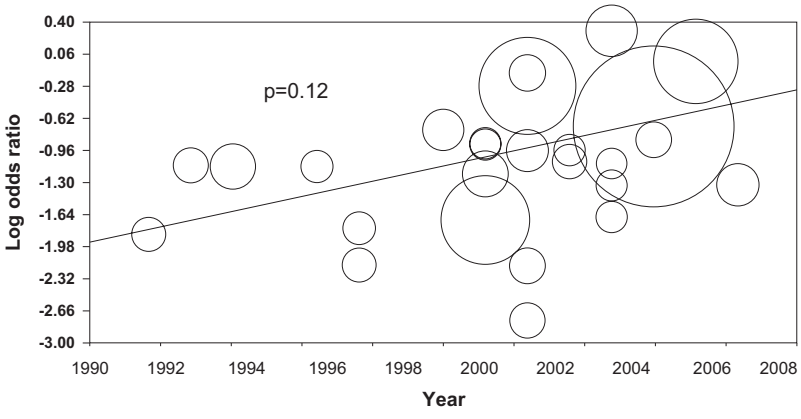

Figure 10 **Metaregression for Paraplegia by Enrollment Year**

Metaregression of the effect of enrollment year on the log odds ratio for the risk of paraplegia/pareparesis for thoracic endovascular aortic repair (TEVAR) versus open surgery. Each **circle** represents a study, telescoped by its weight in the analysis. The relationship did not reach significance, suggesting that the impact of TEVAR on risk of paraplegia/paraparesis was consistent over the years (p = 0.12).

Table 4 Clinical Outcomes for Registry Data

	n/N	TEVAR, %	n/N	OPEN, %	I^2, %	OR (95% CI)	p Value
Death, 30-day	26/332	7.9	398/2,563	15.2	73	0.48 (0.13–1.79)	0.27
Death, 1-yr	7/36	19.4	13/41	31.7	0	0.52 (0.18–1.49)	0.22
Death, 2- to 3-yr	10/36	27.8	16/41	39.0	0	0.87 (0.61–1.23)	0.30
Stroke	9/294	3.1	25/789	3.2	61	1.22 (0.18–8.05)	0.84
AMI	1/27	3.7	1/26	3.8	—	0.96 (0.06–16.2)	0.98
Renal	3/27	11.1	4/26	15.4	—	0.69 (0.14–3.42)	0.65
Ischemia, gut or limb	13/54	24.1	10/52	19.2	—	1.34 (0.52–3.44)	0.55
Overall complications	55/267	20.6	253/763	33.2	0	0.52 (0.34–0.73)	<0.0001

Abbreviations as in Tables 2 and 3.

selection for TEVAR versus open surgery was at the surgeon's discretion, and the criteria for determining patient suitability for TEVAR versus open surgery were not explicitly declared in many studies. This analysis does not enable the determination of optimal patient characteristics for selecting TEVAR versus open surgery.

Conclusions

In patients requiring intervention for descending thoracic aortic disease, nonrandomized evidence shows that TEVAR may reduce early mortality and paraplegia compared with conventional open surgical management. TEVAR may also reduce length of hospital stay and overall complications including neurologic, cardiac, respiratory, renal, and bleeding complications, without a significant increase in the need for reintervention during mid-term follow-up. Although it remains an important caveat that these conclusions are based on observational comparative studies, the consistency of results across aortic pathologies, baseline age groups, and time periods of patient recruitment increases confidence that the findings are robust. Nonetheless, randomized trials are required to confirm the results of this metaregression. Any future randomized trials should be encouraged to adhere to the guidelines for reporting studies of TEVAR (81) and will need to address clinically important gaps in the existing evidence base, including whether longer-term survival, stroke risk, need for reintervention, quality of life, and patient functionality are improved, and whether the cost-effectiveness warrants broader uptake of TEVAR in place of open surgery.

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