Propensity-matched cohort validates findings of the VALOR trial

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Introduction: **The Evaluation of the Medtronic Vascular Talent Thoracic Stent Graft System for the Treatment of Thoracic Aortic Aneurysms (VALOR) trial findings noted superior 30-day and 1-year outcomes of the Talent thoracic endograft (Medtronic Vascular, Santa Rosa, Calif) compared with surgical repair of descending thoracic aneurysms (DTAs). Data from 195 prospective thoracic endovascular aneurysm repair (TEVAR) patients treated with the Talent device and 189 retrospective controls undergoing open surgical repair (OSR) from three centers of excellence were included in the trial after completion of TEVAR enrollment and compared. Such comparisons are biased by baseline differences among TEVAR vs OSR, however, propensity score (PS) analysis can reduce bias and validate such comparisons.**

Methods: **Logistic regression was used to generate a PS (range, 0-1) to identify baseline characteristics more likely in TEVAR. The PS estimated the probability that any patient would undergo TEVAR (eg, a PS of 0.99 represents a 99% chance a patient belongs to TEVAR). PSs were then generated for all patients, and TEVAR and OSR patients were divided into tertiles based on the PS to reduce up to 80% of inherent bias. Outcomes from the middle tertile (T2), patients equally likely (midrange PS) to be in TEVAR or OSR and therefore best matched, were compared using regression analysis and were also compared with the outcomes in the overall trial group.**

Results: **Correlates of membership in TEVAR were smaller aneurysm ($P < .001$), anticoagulants ($P < .01$), no previous abdominal aortic aneurysm (AAA) repair ($P < .01$), no peripheral vascular disease ($P = .001$), statin use ($P = .002$), aspirin use ($P = .002$), older age ($P = .028$), race ($P = .007$), male gender ($P = .02$), and heart failure ($P = .035$). T2 included 68 TEVAR (PS, 0.58 ± 0.2) and 67 OSR patients (PS, 0.46 ± 0.2). VALOR overall reported differences in aneurysm size (56 mm TEVAR vs 69 mm open) and prior AAA repair (19% TEVAR vs 37% open), and this adjusted to no differences in T2 patients. In the well-matched T2 cohort, TEVAR patients had similar 30-day mortality (0% vs 3% OSR; $P = .2$) and improved 1-year aneurysm-related mortality rates (0% TEVAR vs 8% OSR; $P = .05$) compared with the OSR patients. This finding was in concurrence with the VALOR trial reporting similar benefit in TEVAR patients. The all-cause 1-year mortality showed a favorable trend for TEVAR in the VALOR trial; however, in T2 patients, 1-year all-cause mortality was similar in both groups of patients (17% TEVAR vs 15% OSR; $P = .8$). Age ($P = .01$), history of cerebrovascular accident ($P < .05$), antiarrhythmia medication ($P = .04$), and renal disease ($P < .03$) independently predicted all-cause and aneurysm-related mortality by regression analysis.**

Conclusions: **PS analysis is an important tool for elimination of bias inherent when retrospective controls are used. Its application to VALOR validates the long-term benefit in aneurysm-related mortality conferred by TEVAR in patients undergoing endovascular DTA repair. (J Vasc Surg 2011;54:22-9.)**

The Evaluation of the Medtronic Vascular Talent Thoracic Stent Graft System for the Treatment of Thoracic Aortic Aneurysms (VALOR) trial recently reported the safety and efficacy of the Medtronic Vascular (Medtronic Vascular, Santa Rosa, Calif) Talent thoracic stent graft (TEVAR) system for the treatment of descending thoracic aortic aneurysms (DTAs).[1] A fourfold reduction in 30-day mortality, a twofold reduction in major adverse events, and improved 1-year aneurysm-related mortality (ARM) for patients undergoing DTA treatment with TEVAR compared with open surgical repair (OSR) was noted.[1] The VALOR trial, however, was compromised in design because it was originally approved by the U.S. Food and Drug Administration (FDA) as a single-arm trial wherein patients treated with TEVAR were prospectively enrolled according to predetermined inclusion and exclusion criteria. After accrual of prospective TEVAR patient data and upon presentation of the safety and efficacy data to the FDA for device approval, a mandate for open surgical controls was issued. Patients undergoing OSR were then included, after enrollment of TEVAR patients, from the prospectively maintained databases of three centers of excellence in the treatment of DTA. The OSR control group therefore included retrospectively derived patient outcomes data that were subjected to the inclusion and exclusion criteria applied to the originally designed single-arm TEVAR group. Comparisons thus made between the TEVAR and OSR groups and the conclusions derived from such unmatched and temporally disparate groups of patients may be invalid as a

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Competition of interest: none.

Presented at the Thirty-sixth Annual Meeting of the New England Society of Vascular Surgery, Boston, Mass, Oct 2-4 2009.

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a competition of interest.

0741-5214/$36.00

doi:10.1016/j.jvs.2010.12.052

result of inherent biases in the data and unforeseen differences in the patient groups.

In light of the recent single-center[2-8] and multicenter data[9,10] espousing the benefit of TEVAR for the treatment of DTA and overall surgeon and public perceptions about the benefits of "less invasive surgery," completion of a prospective randomized trial to generate level I data for the treatment of DTA is nearly impossible. As such, a number of recent pivotal device trials have resorted to the use of a large proportion (>50%) of retrospective patients as open surgical controls in trial design and conclusions.[11,12] Such trials may be inherently biased by design and necessity; however, statistical methods may be applied to such potentially biased data to achieve meaningful conclusions.

Propensity score (PS) analysis has been applied to large sets of nonrandomized data to model the selection process of randomization and adjust for differences in background characteristics leading to bias reduction.[13] The goal of this study was to evaluate the validity of the VALOR trial outcomes by using PS analysis to define a well-matched cohort of TEVAR and OSR patients for comparison of outcomes.

METHODS

The VALOR trial was a prospective multicenter, nonrandomized study evaluating the safety and efficacy of TEVAR in the treatment of DTA. The study reported the 30-day and 12-month outcomes of 195 TEVAR patients and 189 OSR controls.[1] TEVAR patients were prospectively recruited from December 2003 until June 2005 from 38 institutions. TEVAR group inclusion criteria included Society of Vascular Surgery (SVS) class 0, 1, or 2, thoracic aortic aneurysm size ≥5 cm or greater than two times the diameter of nonaneurysmal aorta, proximal and distal aortic diameters of 18 to 42 mm, and a minimal 20-mm proximal and distal seal zones. Numerous anatomic and medical exclusion criteria were reported by Fairman et al.[1]

The OSR controls were retrospectively included into the trial and were derived from prospectively maintained databases of patients undergoing open repair of DTA from the Cleveland Clinic Foundation (CCF), the Hospital of the University of Pennsylvania (UniversityPenn), and Massachusetts General Hospital (MGH). Patients treated for localized aneurysms of the DTA between 1990 and 2005, meeting inclusion and exclusion criteria applied to the TEVAR group and with 1-year follow-up data, were included in the OSR group. Anatomic inclusion criteria included all fusiform DTA >5 cm in size with a proximal and distal aortic neck such that the proximal anastomosis would be distal to the left subclavian artery and the distal anastomosis would be placed cephalad to the celiac artery. A total of 73 patients were included from CCF, 50 from UniversityPenn, and 66 from MGH. Data provided from institutional registries were internally validated and audited by institution-specific protocols.

PS analysis was performed as previously described using baseline clinical features and patient demographics (covariates; Table I) reported in the VALOR trial.[13,14] Nonparsimonious logistic regression analysis was performed in which being a member of the TEVAR group was the dependent variable and the covariates listed in Table I were independent variables. A PS ranging in value from 0 to 1 was generated for every patient, whether a TEVAR or OSR patient, defining the probability that that individual patient would be part of the TEVAR group rather than in the OSR group given baseline clinical features of that individual. A patient with a PS close to 1 would therefore be highly likely to be a member of the TEVAR group, and a patient with a PS close to 0 would be highly likely to be a member of the OSR group. A patient with a PS close to 0.5 would be equally likely to be a TEVAR or OSR patient. All patients were stratified into tertiles based on PS with the tertiles and respective PS score ranges as follows: tertile 1 (T1), with PS values of 0.0 to 0.33; tertile 2 (T2), with PS values of 0.34 to 0.66; and tertile 3 (T3), with PS values of 0.67 to 1.0.

Table I. Baseline clinical features of VALOR trial patients

Variable[a]	*TEVAR (n = 195)*	*OSR (n = 189)*
Age, years	70 ± 11	70 ± 9
Male gender	115 (59)	99 (52)
TAA size, mm	56 ± 11[b]	69 ± 12[b]
Nonwhite race	33 (17)	12 (6)
Blood pressure, mm Hg		
Systolic	132 ± 21	136 ± 19
Diastolic	74 ± 12	79 ± 12
Stroke (CVA)	19 (10)	25 (13)
Renal insufficiency	34 (17)	30 (16)
Myocardial infarction	27 (14)	39 (21)
Congestive heart failure	17 (9)	21 (11)
Hypertension	170 (87)	168 (89)
CABG	20 (10)	25 (13)
COPD	72 (37)	80 (42)
Tobacco use	150 (77)	144 (76)
Diabetes	31 (16)	16 (8)
PVD	32 (16)	70 (37)
Medications		
Acetylsalicylic acid	101 (52)[b]	49 (26)[b]
Anticoagulants	32 (16)	12 (6)
ACE inhibitors	78 (40)[b]	52 (28)[b]
β-blockers	128 (66)	122 (65)
Calcium antagonists	63 (32)	63 (33)
Antiarrhythmics		
Class I	1 (0.5)	5 (3)
Class III	12 (6)	1 (0.5)
Digitalis	12 (6)	15 (8)
Vasodilators	27 (14)[b]	10 (5)[b]
Statins	101 (52)[b]	42 (22)[b]
AAA		
Prior AAA	37 (19)	70 (37)
Prior AAA repair	4 (2)	52 (28)

AAA, Abdominal aortic aneurysm; *ACE,* angiotensin-converting enzyme; *CABG,* coronary artery bypass grafting; *COPD,* chronic obstructive pulmonary disease; *CVA,* cerebrovascular accident; *OSR,* open surgical repair; *PVD,* peripheral vascular disease; *TAA,* thoracic aortic aneurysm; *TEVAR,* thoracic endovascular aneurysm repair.

[a]Continuous data are mean ± standard deviation; categoric data are number (%).

[b]Values represent statistical differences ($P < .05$) between the TEVAR and OSR groups.

Such stratification into three groups can theoretically reduce bias by up to 80%.[15] Further stratification into groups of four or five would theoretically reduce bias further; however, this was not feasible due to patient imbalances in T1 (12 TEVAR vs 115 OSR) and T3 (119 TEVAR vs 7 OSR) patients.

The clinical features of OSR and TEVAR patients within each tertile were compared. Given the disparate OSR and TEVAR patient numbers in T1 and T3, further outcomes analysis of 30-day mortality, 1-year ARM, and 1-year all-cause mortality (ACM) was performed using patients from T2, which includes 64 TEVAR and 67 OSR patients.

All clinical features and demographic data are presented as the number in each category and the percentage this number represents. All mean data are presented with the standard deviation. Kaplan-Meier analysis was used to evaluate freedom from ARM or ACM over time. The log-rank test for the equality of the survival distribution curves was used to evaluate for differences in ACM and ARM between TEVAR and OPEN. Nonparsimonious logistic regression analysis was used to generate the PS for each patient. Multivariate regression analysis was performed after adjustment for PS alone and with PS and covariates to identify independent predictors of ARM or ACM. Odds ratios (ORs) and 95% confidence intervals (CIs) are presented. An independent statistician used SAS 9.1 software (SAS Institute, Cary, NC) to perform the statistical analysis. A two-sided $P < .05$ was considered statistically significant.

Table II. Coefficients of the propensity score equation

Variable	*Score*
Age in years	0.0493[a]
Male gender	0.7550[a]
TAA size	–0.1351[a]
Nonwhite race	1.4472[a]
Blood pressure	
Systolic	–0.00257
Diastolic	–0.0134
Stroke (CVA), Y/N	–0.2359
Renal insufficiency, Y/N	0.7870
Miocardial infarction, Y/N	0.1814
Congestive heart failure, Y/N	–1.5157[a]
Hypertension, Y/N	–0.0251
CABG, Y/N	–0.2263
COPD, Y/N	0.0301
Tobacco use, Y/N	0.3374
Diabetes, Y/N	0.2223
PVD, Y/N	–1.3620[a]
Medications, Y/N	
Acetylsalicylic acid	1.1113[a]
Anticoagulants	2.0690[a]
ACE inhibitors	0.1765
β-blockers	–0.3831
Ca^{++} antagonists	–0.5586
Antiarrhythmics	
Class I	–1.8652
Class III	1.3574
Digitalis	–0.3255
Vasodilators	0.4167
Statins	1.1168[a]
Concurrent AAA	–0.5579
Prior AAA repair	–2.6293[a]

AAA, Abdominal aortic aneurysm; *ACE,* angiotensin-converting enzyme; *CABG,* coronary artery bypass grafting; *COPD,* chronic obstructive pulmonary disease; *CVA,* cerebrovascular accident; *PVD,* peripheral vascular disease;
[a]Coefficients are most likely to predict inclusion into the TEVAR group ($P < .05$).

RESULTS

The baseline clinical features and patient demographics for the VALOR trial are presented in Table I. TEVAR patients were more likely to have a smaller TAA size, less likely to have a prior AAA or previous AAA repair, and were more likely to be taking aspirin, angiotensin-converting enzyme inhibitors, vasodilators, and statins, as previously reported.[1] We used logistic regression with inclusion into TEVAR as the dependent variable and the covariates as independent variables, to generate coefficients for the propensity equation (Table II). The covariates most likely to predict membership in TEVAR (by χ^2 analysis) were lower TAA size ($P < .0001$), use of anticoagulants (warfarin; $P = .0005$), no history of AAA repair ($P = .0008$), no history of peripheral vascular disease (PVD; $P = .0010$), use of statins ($P = .0017$), use of aspirin ($P = .0022$), older age ($P = .028$), race ($P = .0066$), gender ($P = .0207$), and congestive heart failure ($P = .0352$). The coefficient and the presence of the noted covariate were used to generate a PS for every patient in the study.

As previously noted, patients were stratified into tertiles based on PS, and TEVAR and OSR patients in each tertile were compared. The distribution of TEVAR and OSR patients in each tertile and their mean PS are presented in Table III. The distribution of patients in T1 and T3 was uneven, and clinical features were disparate, making meaningful comparisons unlikely. T2 patients were evenly distributed in number and were well matched, with no differences in demographics and clinical features (Table IV).

The 30-day mortality and 1-year ARM rates in T2 TEVAR patients were lower than for T2 OSR patients, similar to the VALOR trial results (Table V). The VALOR trial reported no significant difference in 1-year ACM, with a trend favoring TEVAR ($P = .1$); however, in well-matched T2 patients, TEVAR and OSR patients had similar rates of ACM (Table V). The ARM and ACM survival curves for T2 patients are presented in Figs 1 and 2, respectively. The unadjusted OR for ARM favored patients treated with TEVAR (0.24; 95% CI, 0.01-0.61; $P = .002$). The propensity-adjusted OR for ARM trended in favor of TEVAR (0.48; 95% CI, 0.14-1.7; $P = .13$). The unadjusted (OR, 0.73; 95% CI, 0.43-1.2; $P = .23$) and propensity-adjusted (OR, 1.4; 95% CI, 0.63-2.9; $P = .43$) ORs for ACM revealed no differences between TEVAR and OSR. After adjustment for PS, independent predictors of ARM included previous cerebrovascular accident (CVA; $P = .01$), use of an antiarrhythmia medication ($P = .04$), and renal disease ($P = .03$). Independent predictors of ACM included age ($P = .01$), previous CVA ($P = .002$), use of an antiarrhythmia medication ($P = .04$), and renal disease ($P = .02$).

Table III. Distribution of thoracic endovascular aneurysm repair (*TEVAR*) and open surgical repair (*OSR*) patients by tertile

	Tertile 1		*Tertile 2*		*Tertile 3*	
Variable	*TEVAR*	*OSR*	*TEVAR*	*OSR*	*TEVAR*	*OSR*
Patients, No.	12	115	64	67	119	7
Mean PS	0.17 ± 0.08	0.06 ± 0.06	0.58 ± 0.17	0.46 ± 0.16	0.94 ± 0.06	0.89 ± 0.04

PS, Propensity score.

Table IV. Baseline clinical features of tertile 2 patients

Variable[a]	*TEVAR (n = 64)*	*OSR (n = 67)*
Age	68 ± 12	69 ± 9
Male gender	37 (58)	35 (52)
TAA size	61 ± 9	63 ± 6
Nonwhite race	4 (6)	5 (7)
Blood pressure		
Systolic	140 ± 20	140 ± 17
Diastolic	75 ± 13	78 ± 11
Stroke (CVA)	9 (14)	9 (13)
Renal insufficiency	8 (13)	6 (9)
Myocardial infarction	9 (14)	10 (15)
Congestive heart failure	4 (6)	3 (4)
Hypertension	53 (83)	57 (85)
CABG	8 (13)	6 (9)
COPD	27 (42)	29 (43)
Tobacco use	47 (73)	46 (69)
Diabetes	6 (9)	11 (16)
PVD	11 (17)	13 (19)
Medications		
Acetylsalicylic acid	23 (36)	16 (24)
Anticoagulants	6 (9)	5 (7)
ACE inhibitors	25 (39)[b]	16 (24)[b]
β-blockers	39 (61)	38 (57)
Calcium antagonists	18 (28)	13 (19)
Antiarrhythmics		
Class I	0	0
Class III	2 (3)	0
Digitalis	6 (9)	5 (7)
Vasodilators	6 (9)[b]	1 (1)[b]
Statins	22 (34)	20 (30)
Concurrent AAA	15 (23)	10 (15)
Prior AAA repair	1 (2)	2 (3)

AAA, Abdominal aortic aneurysm; *ACE,* angiotensin-converting enzyme; *CABG,* coronary artery bypass grafting; *COPD,* chronic obstructive pulmonary disease; *CVA,* cerebrovascular accident; *OSR,* open surgical repair; *PVD,* peripheral vascular disease; *TAA,* thoracic aortic aneurysm; *TEVAR,* thoracic endovascular aneurysm repair.

[a]Continuous data are mean ± standard deviation; categoric data are number (%).

[b]Values represent statistical differences ($P < .05$) between the TEVAR and OSR groups.

DISCUSSION

The VALOR trial was initially designed and executed as a single-armed prospective trial of TEVAR with a historical OSR control group. The FDA considered the historical controls specified as the comparator to the single-arm trial inadequate. Medtronic therefore proposed and obtained an OSR control group from three centers of excellence of approximately the same size as the study cohort. The surgical control arm was subjected to the same inclusion and exclusion criteria as the VALOR trial patients. Comparative analyses of such nonrandomized groups may be affected by selection and observational biases as well as baseline differences in the populations being studied. The statistical methodology of PS analysis has been validated and successfully applied to a variety of clinical data sets to facilitate bias reduction and strengthen study conclusions.[13-17] PS analysis was therefore agreed to between Medtronic and the FDA after the VALOR trial, and part of this analysis was included in the initial postmarket analysis submission.

PS analysis depends on adjustment for all potentially prognostic characteristics and is therefore limited by the availability of such data for both groups. Unlike a randomized trial, bias reduction using PS analysis can thus be compromised by missing data or unmeasured characteristics in one or both groups. The availability of measured data was close to complete for all characteristics in the VALOR study. Other characteristics that have been reported to affect clinical outcomes (eg, such as surgeon or hospital volume), clinical presentation, operative characteristics (eg, clamp times or use of surgical adjuncts), type of anesthetic, and preoperative functional status were not evaluated in the VALOR trial and pose the major limitation to our propensity analysis.

Propensity matching can be performed in numerous ways, such as direct matching of patients based on PS value in very large data sets or, as in our study, by stratifying the two patient cohorts using ranges of PS values. The stratification may result in small numbers of patients in one treatment group or the other in the highest and lowest strata. When the latter occurs, it is necessary to reduce the number of strata to get the number into an acceptable range. Reducing the number of strata reduces the amount of bias reduction, which was necessary in our analysis and poses another limitation of our study.

The goal of our study was to evaluate the results of the VALOR trial using patients whose clinical, demographic, and anatomic features were well matched by the PS. Our propensity-matched TEVAR and OSR patients were similar with respect to age, sex, and baseline demographics, with the exception of differences in use of angiotensin-converting enzyme inhibitors and vasodilators. The previously noted differences in aneurysm size, aspirin use, statin use, and concurrent AAA or previous AAA repair were all corrected for by propensity matching. Propensity analysis therefore

Table V. Mortality rates in VALOR (all patients) and tertile 2 patients

	VALOR trial patients			*Tertile 2 (PS-matched) patients*		
Mortality	*TEVAR, No. (%) (n = 195)*	*OSR, No. (%) (n = 189)*	P	*TEVAR, No. (%) (n = 68)*	*OSR, No. (%) (n = 67)*	P
30-day	4 (2)[a]	12 (8%)[a]	<.01	0 (0%)	2 (3%)	.2
ARM	6 (3)[a]	22 (12%)[a]	<.01	0 (0%)[a]	5 (8%)[a]	.05[a]
ACM	31 (16)	39 (21%)	.17	11 (17%)	10 (15%)	.8

ACM, All-cause mortality; *ARM*, aneurysm-related mortality; *OSR*, open surgical repair; *PS*, propensity score; *TEVAR*, thoracic endovascular aneurysm repair.
[a]Statistical differences ($P \leq .05$) between the TEVAR and OSR groups.

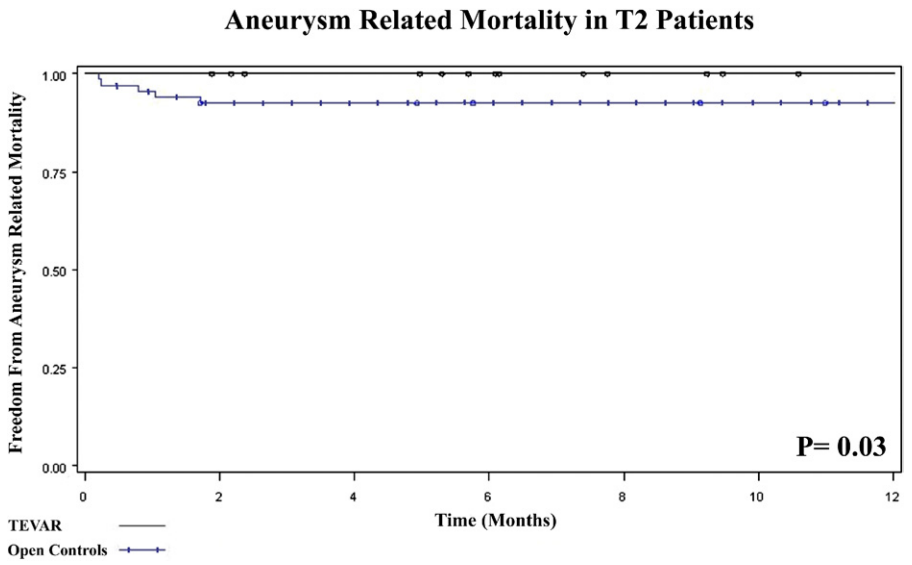

Fig 1. Kaplan-Meier curves plot freedom from aneurysm-related mortality for the fraction of the tertile 2 thoracic endovascular aneurysm repair (*TEVAR*) and open group surgical repair patients alive over time. The *solid line* represents survival in patients treated with TEVAR, and the *cross-hatched* line represents the survival of the open surgical controls.

Month	*0*	*2*	*4*	*6*	*8*	*10*	*12*
Open surgical repair							
Patients at risk	67	61	61	59	59	58	57
Proportion surviving	1	.93	.93	.93	.93	.93	.93
95% confidence interval	—	0.86-0.99	0.86-0.99	0.86-0.99	0.86-0.99	0.86-0.99	0.86-0.99
TEVAR							
Patients at risk	64	63	61	58	54	52	51
Proportion surviving	1	1	1	1	1	1	1
95% confidence interval	—	—	—	—	—	—	—

resulted in a well-matched albeit smaller subset of VALOR trial patients for which 30-day mortality and 1-year ARM and ACM were evaluated.

Our matched patient cohort (T2 TEVAR vs OSR) showed no statistically significant difference in (procedural) mortality for TEVAR for DTA over that of patients undergoing open surgical repair. The low event rate for 30-day mortality (0 for TEVAR and 2 for OSR) in this matched cohort resulted in an absence of a statistical difference; however, a difference might have been noted had the T2 patient cohort been larger in size. Similarly, our own single-center comparative study of concurrently treated stent graft vs open surgical controls showed only a trend in favor of improved procedural mortality for TEVAR.[6] The lack of a significant benefit with respect to 30-day mortality in our previous study may be have been related to the early (1996-2005) experience with TEVAR represented by that report, the inclusion of aneurysms requiring urgent repair (15%), and most importantly, patient selection, because up to 30% of TEVAR patients in that study were deemed unfit for

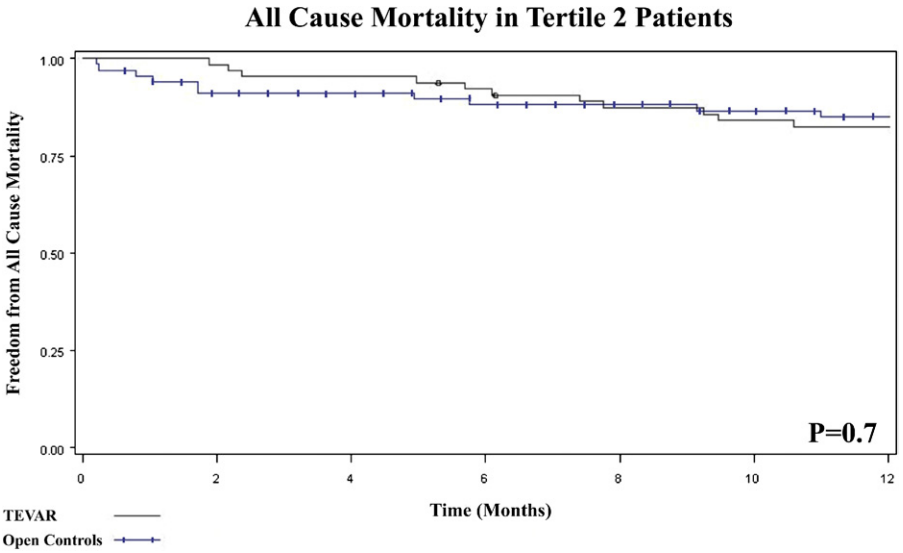

Fig 2. Kaplan-Meier curves plot freedom from all-cause mortality in the fraction of the tertile 2 thoracic endovascular aneurysm repair (*TEVAR*) and open surgical repair patients alive over time. The *solid line* represents survival in patients treated with TEVAR, and the *cross-hatched* line represents the survival of the open surgical controls.

Month	*0*	*2*	*4*	*6*	*8*	*10*	*12*
Open surgical repair							
Patients at risk	67	61	61	59	59	58	57
Proportion surviving	1	.91	.91	.88	.88	.86	.85
95% confidence interval	—	0.84-0.98	0.84-0.98	0.80-0.96	0.80-0.96	0.78-0.95	0.77-0.94
TEVAR							
Patients at risk	64	63	61	58	54	52	51
Proportion surviving	1	0.98	.95	.92	.87	.84	0.83
95% confidence interval	—	0.95-1.0	0.90-1.0	0.86-0.98	0.79-0.96	0.75-0.93	0.73-0.92

OSR, with Society of Vascular Surgery risk scores ≥3. Although this study did not validate it, most publications, including more contemporary single-center comparative reports, a recent meta-analysis, and recent multicenter comparative trials are in agreement with VALOR that TEVAR is associated with reduced procedural mortality compared with OSR.[11,12,18,19]

The 1-year ARM in our matched patient cohort yielded conflicting results. The Kaplan-Meier analysis of TEVAR and OSR patients in T2 validated the VALOR findings showing a statistically significant benefit of TEVAR in reducing ARM. A statistically significant benefit in OR for ARM was noted for TEVAR patients when using all (VALOR) patients. However, the propensity-adjusted OR for ARM only showed a trend in favor of TEVAR for aneurysm-related 1-year survival. This discrepancy may be explained by the small sample size resulting in a larger 95% CI for the propensity-adjusted OR and loss of statistical significance. One may argue that the adjusted OR may be more reflective of the truth because adjustments were made for baseline differences in the patient groups. The same argument can be made in favor of survival differences because the T2 patients were propensity matched; therefore, differences seen in the survival curves were already adjusted for by propensity matching.

The exclusion of patients with prior AAA repair from entry into the trial in the VALOR test group while a significant number of OSR controls had undergone prior AAA repair was a major criticism of the VALOR report. The inclusion of more complicated open surgical cases may have increased ARM in the OSR group, thereby favoring TEVAR; however, after exclusion of patients with prior AAA repair, the 12-month ARM continues to favor TEVAR (97% ± 1% TEVAR vs 92 ± 2% OSR; $P = .49$; data not shown).

The benefit of TEVAR over OSR in reducing ARM has been similarly variable in the literature. Our single-center series reported similar ARM in OSR and TEVAR patients; however, TEVAR patients were a higher surgical risk group, as discussed above.[6] The TX2 (William Cook Europe, Bjaeverskov, Denmark) international multicenter pivotal trial reported no benefit of TEVAR with respect to ARM, whereas the TAG (W. L. Gore and Associates, Flagstaff, Ariz) multicenter pivotal trial showed a statistically significant benefit of TEVAR in reducing ARM.[11,12] The benefit of TEVAR in reducing ARM in the GORE

pivotal trial may be partly explained by the definition of ARM in that trial, which included procedural mortality associated with the index TEVAR procedure. Meanwhile, the VALOR and TX2 trials both included mortality associated with secondary procedures in the calculation of ARM. The benefit of TEVAR with respect to ARM is therefore unresolved at this time and warrants a more uniform definition and further study.

In our propensity-matched T2 patients, 1-year ACM was similar, with both TEVAR and OSR patients having similar mortality of 17% and 15%, respectively. No differences in ACM between TEVAR and OSR were reported by the TAG and TX2 pivotal trials.[11,12] In addition, single-center and multicenter registry studies reported similar long-term survival in medically high-risk patients.[6,10,18] The 5-year results of the TAG pivotal trial noted similar ACM rates (~40%) for TEVAR and OSR.[20] Despite improved periprocedural mortality and ARM in favor of TEVAR, the absence of benefit with respect to ACM reflects the long-term mortality of elderly patients with DTA and their associated comorbidities. The all-cause mortality (~15%/year) reported in our current study is similar to that in previously reported retrospective and natural history studies.[21-23] TEVAR is not likely to affect improvements in ACM of this patient population. In such patients, the extensive comorbidities and limited long-term survival argue in favor of TEVAR, the least morbid approach, as the primary modality for treatment of DTA when possible.

The VALOR trial data were used to identify independent predictors of ACM and ARM after adjustment for the PS. ACM was independently predicted by older age, previous history of CVA, use of antiarrhythmia medication, and renal disease. ARM was independently predicted by history of CVA, use of antiarrhythmia medication, and renal disease. These clinical features reflect a more medically unfit patient population with death a more likely eventual outcome in such patients. Dillavou et al[24] reviewed the TAG pivotal trial data, noting a higher mortality in men and in those with symptomatic aneurysms. Data on independent predictors of mortality associated with TEVAR are limited; however, renal insufficiency has been noted to predict 30-day and long-term mortality in patients treated with TEVAR.[25,26] Whether the presence of such risk factors, especially renal insufficiency, should be prohibitive in recommending treatment of DTA with TEVAR requires further investigation.

Our study is limited by its small size of 64 TEVAR and 67 OSR patients; hence, the observation of 0% 30-day mortality and 0% 1-year ARM in the TEVAR group likely represents a selection bias or sampling error. Despite the small size of the T2 group, the outcomes in our cohort mirror that of the VALOR trial and the true rates of procedural mortality and ARM likely lie somewhere in between 0% and those reported in VALOR (2.1% 30-day and 3.1% ARM). In support of our findings, the TAG and TX2 pivotal trials similarly reported very low mortality rates of 2.1% 30-day and 3% ARM and 1.9% 30-day and 5.8% ARM, respectively.[11,12] More recently, the 5-year TAG trial outcomes were reported by Makaroun et al[20] noting a significant benefit with very low rates of ARM in TEVAR patients (2.8% TEVAR vs 11.7% OSR; $P = .008$) with up to 66 months of follow-up.[20]

One may argue that both of the other pivotal trials included a large number of retrospective open surgical controls of up to 53% (TAG) and 73% (TX2) and may have been similarly affected by biases as the VALOR trial. Our current analysis validates the favorable findings of the VALOR report with respect to the role of TEVAR in management of DTA. Had the results of our analysis shown the contrary, that TEVAR was inferior to OSR, further study in the form of a prospective randomized controlled trial would be feasible. Such a finding would also support limitation of TEVAR use in patients at high-risk for open surgery or those with reduced long-term survival; however, this was not the case. Data from international registries[10] report low rates of procedural morbidity and rapid patient recovery, and because all currently available stent grafts for use in the United States have long been approved for human use in other parts of the world, there exists a very large international experience supporting these findings. Furthermore, the conclusions of all three pivotal U.S. trials concur with one another and with many single-center reports with respect to the clinical efficacy and relative safety of TEVAR for the treatment of DTA, making TEVAR widely applicable to appropriately selected patients.

CONCLUSIONS

Using PS analysis, we have validated the findings of the VALOR trial. All-cause mortality for patients with DTA is unaffected by the modality of treatment, whereas TEVAR for the treatment of DTA may reduce periprocedural and aneurysm-related mortality. TEVAR should therefore be the preferred modality for treatment of DTA in anatomically and medically suitable patients.

AUTHOR CONTRIBUTIONS

Conception and design: VP, KO, RF, RC
Analysis and interpretation: VP, MC, CK, RF, RC
Data collection: Not applicable
Writing the article: VP, RC
Critical revision of the article: VP, MC, CK, KO, RF, RC
Final approval of the article: VP, MC, CK, KO, RF, RC
Statistical analysis: Not applicable
Obtained funding: Not applicable
Overall responsibility: VP

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Submitted Nov 29, 2009; accepted Dec 14, 2010.