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TAVR FOCUS ISSUE

CLINICAL RESEARCH

Long-Term Outcomes After Transcatheter Aortic Valve Replacement in High-Risk Patients With Severe Aortic Stenosis

The U.K. Transcatheter Aortic Valve Implantation Registry

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ABSTRACT

OBJECTIVES The U.K. Transcatheter Aortic Valve Implantation Registry reported 30-day and 1-year mortality rates of 7.1% and 21.4%, respectively, for patients who underwent transcatheter aortic valve replacement (TAVR) in the United Kingdom between 2007 and 2009. The study aim was to report long-term outcomes in this same cohort of patients.

BACKGROUND There are few data on outcomes beyond 3 years after TAVR in any notable number of patients.

METHODS Data from all TAVR procedures performed in the United Kingdom between January 2007 and December 2009 were prospectively collected. All-cause mortality status was reported in March 2014. Mortality tracking was achieved in 97.7% patients.

RESULTS The minimal time from replacement to census was 4.1 years, and the maximal time was 7.0 years. The 3- and 5-year survival rates were 61.2% and 45.5%, respectively. Independent predictors of 3-year mortality were renal dysfunction (hazard ratio [HR]: 1.65), atrial fibrillation (HR: 1.36), logistic European System for Cardiac Operative Risk Evaluation (EuroSCORE) ≥18.5 (HR: 1.33), respiratory dysfunction (HR: 1.28), and ventricular dysfunction (left ventricular ejection fraction <30%) (HR: 1.53). Coronary artery disease (HR: 1.28) and age (HR: 1.03) were additional independent predictors of mortality at 5 years. Stroke within 30 days of TAVR was the only independent procedural predictor of mortality at 3 and 5 years (HR: 2.17 at 3 years). Device type, access route, and paravalvular leak did not independently predict long-term outcome.

CONCLUSIONS In the large U.K. Transcatheter Aortic Valve Implantation Registry, long-term outcomes after TAVR are favorable with 3- and 5-year survival rates of 61.2% and 45.5%, respectively. Long-term survival after TAVR is largely determined by intrinsic patient factors. Other than stroke, procedural variables, including paravalvular aortic leak, did not appear to be independent predictors of long-term survival. (J Am Coll Cardiol Intv 2015;8:645–53)

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ABBREVIATIONS AND ACRONYMS

EuroSCORE = European System for Cardiac Operative Risk Evaluation

HR = hazard ratio

LVEF = left ventricular ejection fraction

TAVR = transcatheter aortic valve replacement

Symptomatic severe aortic stenosis carries a poor prognosis (1,2). In the past decade, transcatheter aortic valve replacement (TAVR) has become an alternative treatment strategy to surgical aortic valve replacement in high-risk patients and is superior to conservative management in inoperable patients (3). Randomized, controlled trials and registry data have established the safety and efficacy of TAVR, and procedural, 30-day, and 1-year outcomes after TAVR have been well documented (4–7). The outcomes up to 2 or 3 years have been reported (8–17). However, longer term clinical outcomes beyond 3 years in any notable number of patients are less frequently described (18–20). The U.K. Transcatheter Aortic Valve Implantation (U.K.-TAVI) Registry was set up in 2007 as a national program to coordinate and monitor the practice and dissemination of TAVR in the United Kingdom and has captured every TAVR performed in the United Kingdom since the beginning of 2007. Initial data from the U.K.-TAVI Registry reported 30-day, 1-year, and 2-year survival rates after TAVR as 92.9%, 78.6%, and 73.7%, respectively, in 870 patients who underwent TAVR between January 1, 2007 and December 31, 2009 (21). The aim of the current study was to report late clinical outcomes and assess predictors of late mortality using data from the U.K.-TAVI registry in this same initial cohort of patients.

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METHODS

The process of patient selection for TAVR was previously described in detail (19). Demographic data, risk factors, and outcome measures of all patients who underwent TAVR at a total of 25 centers in England and Wales between January 1, 2007 and December 31, 2009 were collected and submitted to the National Institute for Cardiovascular Outcomes Research (22), a web-based system for data entry, encryption, and transfer. This database formed the basis of the U.K.-TAVI Registry (21). All fields were examined for missing data or extreme values, and invalid data or values indicating "unknown" were excluded from analysis. Post-TAVR, aortic regurgitation (AR) was assessed visually according to standard angiographic criteria at the termination of the TAVR procedure (21). Mortality tracking was undertaken by the National Health Service Central Register using unique patient identifiers. Survival status for the whole cohort was determined as of March 1, 2014. The study was performed in compliance with current U.K. Data Protection and Information Governance legislation. All patients provided signed, informed consent.

STATISTICS. Categorical data were presented as percents, and comparison between groups done using the chi-square or Fisher exact test. Numerical data were presented as mean ± SD, and comparisons were performed with the 2-sample Student *t* test or the 2-sample Wilcoxon rank sum (Mann-Whitney) test. Time-to-event data analysis was performed using the Cox proportional hazards model. Kaplan-Meier survival curves were drawn to assess differences between groups for the time to an event data. For the Cox model, univariate analysis of each of the possible predictors of the outcome were tested, and only those variables that were significant at $p < 0.05$ were included in a multivariate model to determine the independent predictors of the outcome variables. The hazard ratio was presented as mean and 95% confidence interval. The analysis was performed using Stata statistical software version 10.1 (StataCorp, College Station, Texas).

RESULTS

Data for 877 valve implantations in 870 patients were submitted to National Institute for Cardiovascular Outcomes Research. A second TAVR was performed as a valve-in-valve procedure after the original TAVR in 7 patients. The second procedure was censored, so that the registry contained 870 patients. Completeness of valid data was 99.6% for demographic data, 96.4% for risk factors, 97.4% for procedural variables, and 98.5% for in-hospital outcomes. All-cause mortality tracking was performed on March 1, 2014 and was achieved in 850 patients (97.7%); an update of mortality tracking in Scotland was not available. Thus, 850 patients provide the basis of the survival analysis for this study. The minimal time from TAVR to census was 4.1 years, and the maximal follow-up was 7.0 years.

BASELINE CHARACTERISTICS. Baseline demographic data and risk factors are shown in **Table 1**. Significant concomitant coronary artery disease was defined as ≥50% stenosis affecting more than 1 major epicardial coronary artery, and significant renal impairment was defined as serum creatinine greater than 200 μg/mmol. The median EuroSCORE (European System for Cardiac Operative Risk Evaluation) was 18.5. A Medtronic CoreValve (Medtronic, Minneapolis, Minnesota) was deployed in 52.5% patients; the remainder received an Edwards SAPIEN valve (Edwards Lifesciences Corp., Irvine, California). The access route was transfemoral in 68.4%.

PERIPROCEDURAL AND POST-PROCEDURAL OUTCOMES. Peri- and post-procedural outcomes in this cohort

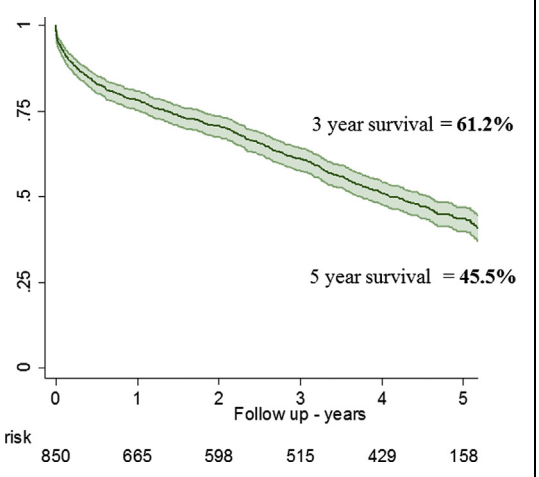
TABLE 1 Baseline Demographics and TAVR Procedure (N = 850)

Age, yrs	82 ± 7
Male	442/850 (52.0)
Coronary artery disease	381/808 (47.2)
Previous cardiac surgery	248/833 (30.4)
Peripheral vascular disease	238/812 (29.8)
COPD	232/814 (28.5)
Atrial fibrillation	202/846 (23.9)
Diabetes	193/841 (22.9)
Creatinine >200 μg/mmol	54/833 (6.5)
NYHA functional class I/II	197/846 (23.3)
NYHA functional class III/IV	649/846 (76.7)
LVEF ≥50%	549/845 (65.0)
LVEF 30%–49%	223/845 (26.4)
LVEF <30%	73/845 (8.6)
Aortic valve peak gradient, mm Hg	81 ± 27
CoreValve*	442/843 (52.5)
SAPIEN valve†	401/846 (47.5)
Transfemoral route	581/850 (68.4)
Nontransfemoral route	269/850 (31.6)

Values are mean ± SD or n (%). *Medtronic, Minneapolis, Minnesota. †Edwards Lifesciences, Irvine, California.

COPD = chronic obstructive pulmonary disease; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; TAVR = transcatheter aortic valve replacement.

FIGURE 1 Kaplan-Meier Survival Curve for the U.K. Transcatheter Aortic Valve Implantation Registry Cohort Undergoing TAVR Between January 1, 2007 and December 31, 2009, Censored January 3, 2014



A total of 550 patients were alive and at risk more than 3 years after TAVR and 158 patients were alive and at risk more than 5 years after TAVR. The 3- and 5-year actuarial survival rates were was 61.2% and 45.5%, respectively. TAVR = transcatheter aortic valve replacement.

have been described in detail (21). In brief, procedural success was achieved in 97.2% cases; the incidence of stroke within 30 days, myocardial infarction, need for new permanent pacing, and major vascular complications was 4.1%, 1.3%, 16.3%, and 8.4%, respectively. Some degree of aortic paravalvular leak (angiographic grade 1 or higher) occurred in 61% of patients, with moderate to severe paravalvular leak reported in 13.6%.

LONG-TERM MORTALITY. The Kaplan-Meier survival curve for the whole population is shown in Figure 1. A total of 515 patients were alive and at risk more than 3 years after TAVR, and 158 patients were alive and at risk more than 5 years after TAVR. The 3- and 5-year actuarial survival rates were 61.2% and 45.5%, respectively.

PREDICTORS OF LONG-TERM MORTALITY. Baseline demographics. Demographic predictors of mortality are presented in Tables 2 and 3. Independent predictors of mortality at 3 years were renal dysfunction, atrial fibrillation, chronic obstructive pulmonary disease, and logistic EuroSCORE ≥18.5. The baseline left ventricular ejection fraction (LVEF) (<49%) was an independent predictor of mortality at 3 years and a predictor of mortality at 5 years when the LVEF was <30%. At 5 years, renal dysfunction, atrial fibrillation, chronic obstructive pulmonary disease, and logistic EuroSCORE ≥18.5 again were independent predictors of mortality, with the addition of coronary artery disease and age (Figure 2). Sex, diabetes, previous cardiac surgery, peripheral vascular disease, New York Heart Association functional class, and peak aortic gradient were not independent predictors of long-term mortality at either 3 or 5 years.

TAVR procedural predictors. The only independent predictor of mortality at 3 and 5 years was periprocedural stroke (Tables 4 and 5, Figure 3). There was no significant difference in mortality between device type or access route, and neither was an independent predictor of survival at either 3 or 5 years. The presence of moderate to severe paravalvular leak (Figure 3), vascular complications, and the need for permanent pacing were also not independent predictors of long-term outcome.

DISCUSSION

Recent studies investigating long-term outcome up to 3 years after TAVR have reported survival rates of between 62% and 74% at 2 years and between 56% and 61% at 3 years (8-10,12,13,15,16,23). Most of these studies, however, come from single centers, with either limited patient numbers or a bias toward a particular access route or device. In contrast, the U.K.-TAVI Registry represents a 'real-world' experience. In the current study, we report the long-term

TABLE 2 Baseline Demographics: Predictors of Mortality at 3-Year Follow-Up

	Alive (n = 520)	Dead (n = 330)	Univariate Model, HR (95% CI)	p Value	Multivariate Model, HR (95% CI)	p Value
Age, yrs	81 ± 7	83 ± 7	1.02 (1.00–1.03)	0.056	1.02 (1.00–1.04)	0.016
Male	259/520 (49.8)	183/330 (55.5)	1.18 (0.95–1.47)	0.130		
Creatinine >200 μg/mmol	21/507 (4.1)	33/326 (10.1)	1.92 (1.34–2.76)	<0.0001	1.86 (1.26–2.75)	0.002
Atrial fibrillation	108/517 (20.9)	94/329 (28.6)	1.35 (1.07–1.72)	0.012	1.36 (1.05–1.76)	0.018
EuroSCORE ≥18.5	234/520 (45.0)	190/330 (57.8)	1.49 (1.19–1.85)	<0.0001	1.24 (0.96–1.60)	0.099
COPD	126/499 (25.2)	106/315 (33.7)	1.37 (1.08–1.73)	0.009	1.34 (1.04–1.72)	0.024
LVEF						
>50%	364/517 (70.4)	185/328 (56.4)	1.00		1.00	
30%–49%	115/517 (22.2)	108/328 (32.9)	1.65 (1.30–2.09)	<0.001	1.35 (1.02–1.77)	0.036
<30%	38/517 (7.4)	35/328 (10.7)	1.66 (1.15–2.38)	0.006	1.72 (1.16–2.54)	0.007
Diabetes	105/511 (20.6)	88/330 (26.7)	1.27 (0.99–1.62)	0.056		
Coronary artery disease	225/498 (45.2)	156/310 (50.3)	1.19 (0.95–1.49)	0.123		
Previous cardiac surgery	156/507 (30.8)	92/326 (28.2)	0.92 (0.72–1.17)	0.49		
Peripheral vascular disease	137/493 (27.8)	101/319 (31.7)	1.17 (0.93–1.49)	0.18		
NYHA functional class						
I/II	129/517 (24.9)	68/329 (20.7)	1.00			
III/IV	388/517 (75.1)	261/329 (79.3)	1.21 (0.93–1.58)	0.16		
Aortic peak gradient, mm Hg	81 ± 27	80 ± 28	0.999 (0.995–1.003)	0.57		

Values are mean ± SD or n (%), unless otherwise indicated.
CI = confidence interval; HR = hazard ratio; EuroSCORE = European System for Cardiac Operative Risk Evaluation; other abbreviations as in Table 1.

outcome of patients with severe symptomatic aortic stenosis who underwent TAVR in the United Kingdom between January 2007 and December 2009, regardless of access route or device. These data from the U.K.-TAVI Registry reflect the largest series of consecutive cases reported to date of long-term outcome after TAVR, with a minimal follow-up period of more than 4 years and a maximal follow-up of just more than 7 years.

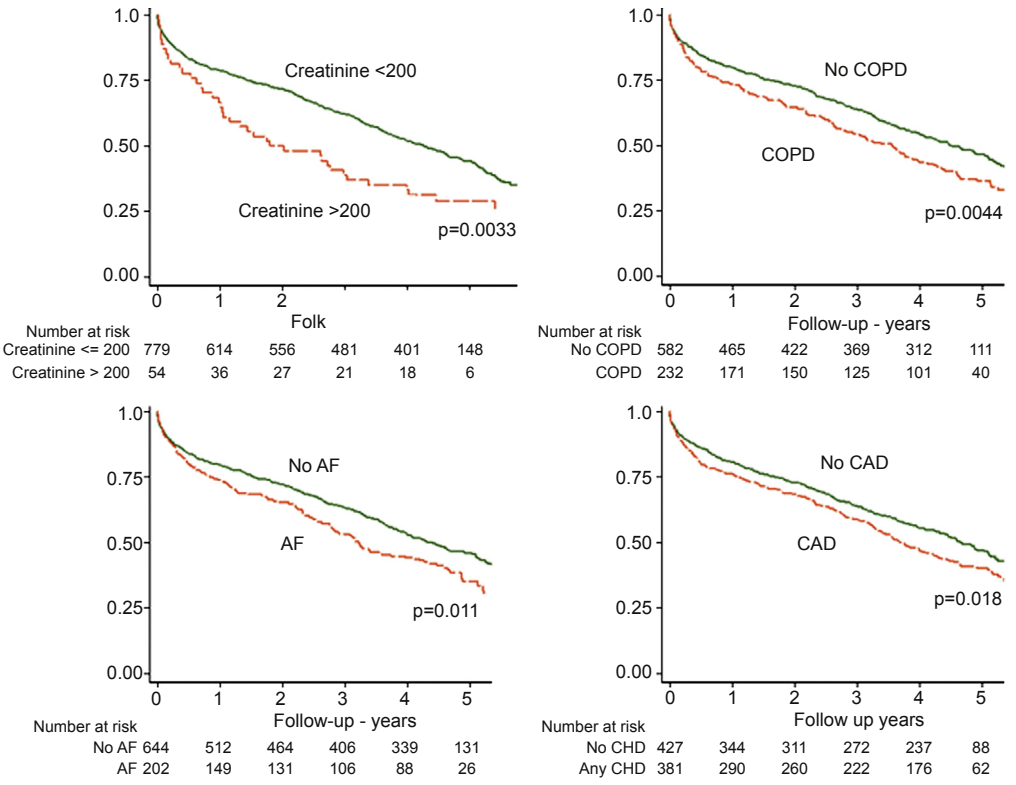
Principal findings. The U.K.-TAVI Registry study demonstrated favorable long-term outcomes after TAVR. From a cohort of 850 patients with a mean age of 82 years at the time of the TAVR procedure, a large number of patients (n = 515) were alive and at risk

TABLE 3 Baseline Demographics: Predictors of Mortality at 5-Year Follow-Up

	Alive (n = 387)	Dead (n = 463)	Univariate Model, HR (95% CI)	p Value	Multivariate Model, HR (95% CI)	p Value
Age, yrs	81 ± 8	83 ± 6	1.02 (1.01–1.04)	0.001	1.03 (1.01–1.05)	<0.001
Male	192/387 (49.4)	251/463 (54.2)	1.15 (0.96–1.38)	0.132		
Creatinine >200 μg/mmol	16/377 (4.2)	39/442 (8.8)	1.67 (1.19–2.32)	0.003	1.60 (1.11–2.32)	0.013
COPD	89/373 (23.9)	143/441 (32.4)	1.33 (1.09–1.63)	0.005	1.40 (1.12–1.74)	0.003
Atrial fibrillation	79/385 (20.5)	123/461 (26.7)	1.30 (1.06–1.60)	0.013	1.30 (1.04–1.63)	0.020
Coronary artery disease	160/372 (43.0)	221/436 (50.1)	1.25 (1.03–1.50)	0.021	1.35 (1.10–1.65)	0.004
EuroSCORE ≥18.5	164/387 (42.4%)	260/463 (56.2)	1.47 (1.23–1.77)	<0.0001	1.32 (1.07–1.62)	0.009
LVEF						
>50%	267/386 (69.2)	282/459 (61.4)	1.00		1.00	
30%–49%	88/386 (22.8)	135/459 (29.4)	1.38 (1.13–1.70)	0.002	1.17 (0.93–1.49)	0.182
<30%	31/386 (8.0)	42/445 (9.2)	1.36 (0.98–1.88)	0.062	1.36 (0.97–1.92)	0.073
Diabetes	77/381 (20.2)	116/460 (25.2)	1.22 (0.99–1.51)	0.063	1.22 (0.97–1.54)	0.096
Peripheral vascular disease	101/368 (27.5)	137/444 (30.9)	1.15 (0.94–1.40)	0.181		
Previous cardiac surgery	119/379 (31.4)	129/454 (28.4)	0.92 (0.75–1.13)	0.409		
NYHA functional class						
I/II	97/385 (25.2)	100/461 (21.7)				
III/IV	298/385 (74.8)	361/461 (78.3)	1.18 (0.94–1.47)	0.149		
Aortic peak gradient, mm Hg	81 ± 27	81 ± 28	0.999 (0.996–1.002)	0.715		

Values are mean ± SD or n (%), unless otherwise indicated.
Abbreviations as in Tables 1 and 2.

FIGURE 2 **Demographic Predictors of 5-Year Survival After TAVR**



Renal impairment, respiratory disease (chronic obstructive pulmonary disease), ventricular dysfunction, and atrial fibrillation were independent predictors of mortality at 3 years. All remained independent predictors of mortality at 5 years. Age and coronary artery disease emerged as independent predictors of mortality for the first time. AF = atrial fibrillation; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease.

more than 3 years after TAVR, and the 3-year survival rate was 61.2%. This is similar to results from several recent single-center studies (10,15,16,23) and is comparable to the 66.1% 2-year survival rate in the PARTNER A (Placement of Aortic Transcatheter Valves) trial (11) and better than the 3-year survival rate in the PARTNER B trial (45.9%) (18), although we note that the cohort of patients reported in the

TABLE 4 **Device/Access/Procedural Complications as Predictors of Mortality at 3-Year Follow-up**

	Alive (n = 520)	Dead (n = 330)	Univariate Model, HR (95% CI)	p Value	Multivariate Model, HR (95% CI)	p Value
Device type						
CoreValve*	283/519 (54.5)	159/324 (49.1)	0.84 (0.67–1.04)	0.11		
SAPIEN†	236/519 (45.5)	165/324 (50.9)	1.00			
Route						
Transfemoral	369/520 (70.9)	212/330 (64.2)	0.76 (0.61–0.95)	0.018	0.81 (0.64–1.02)	0.077
Nontransfemoral	151/520 (29.1)	118/330 (35.8)	1.00		1.00	
Procedural complications						
Stroke	13/520 (2.5)	21/324 (6.5)	2.33 (1.50–3.63)	<0.0001	2.32 (1.47–3.65)	<0.001
Major vascular complication	28/520 (5.4)	26/329 (7.9)	1.47 (0.98–2.19)	0.059		
Moderate/severe paravalvular leak	63/512 (12.3)	47/319 (14.7)	1.22 (0.90–1.67)	0.20		
Permanent pacemaker	85/519 (16.4)	53/328 (16.2)	0.97 (0.73–1.31)	0.86		

Values are n (%) unless otherwise indicated. *Medtronic, Minneapolis, Minnesota. †Edwards Lifesciences, Irvine, California.
Abbreviations as in Table 2.

TABLE 5 Device/Access/Procedural Complications as Predictors of Mortality at 5-Year Follow-up

	Alive (n = 387)	Dead (n = 463)	Univariate Model HR (95% CI)	p Value	Multivariate Model HR (95% CI)	p Value
Device type						
CoreValve*	212/386 (54.9)	230/467 (50.33)	0.86 (0.71–1.03)	0.103		
SAPIEN valve†	174/386 (45.1)	227/457 (49.7)	1.00			
Route						
Transfemoral	281/387 (72.6)	300/463 (64.8)	0.76 (0.62–0.91)	0.004	0.88 (0.71–1.09)	0.241
Nontransfemoral	106/387 (27.4)	163/463 (35.2)	1.00		1.00	
Procedural complications						
Cerebrovascular accident	10/387 (2.6)	24/457 (5.3)	1.93 (1.28–2.91)	0.002	1.84 (1.19–2.82)	0.006
Moderate/severe paravalvular leak	45/383 (11.8)	65/448 (14.5)	1.22 (0.92–1.58)	0.145	1.25 (0.95–1.66)	0.115
Major vascular complications	24/387 (6.2)	30/462 (6.5)	1.21 (0.83–1.75)	0.319		
Permanent pacemaker	62/387 (16.0)	76/460 (16.5)	0.99 (0.77–1.26)	0.924		

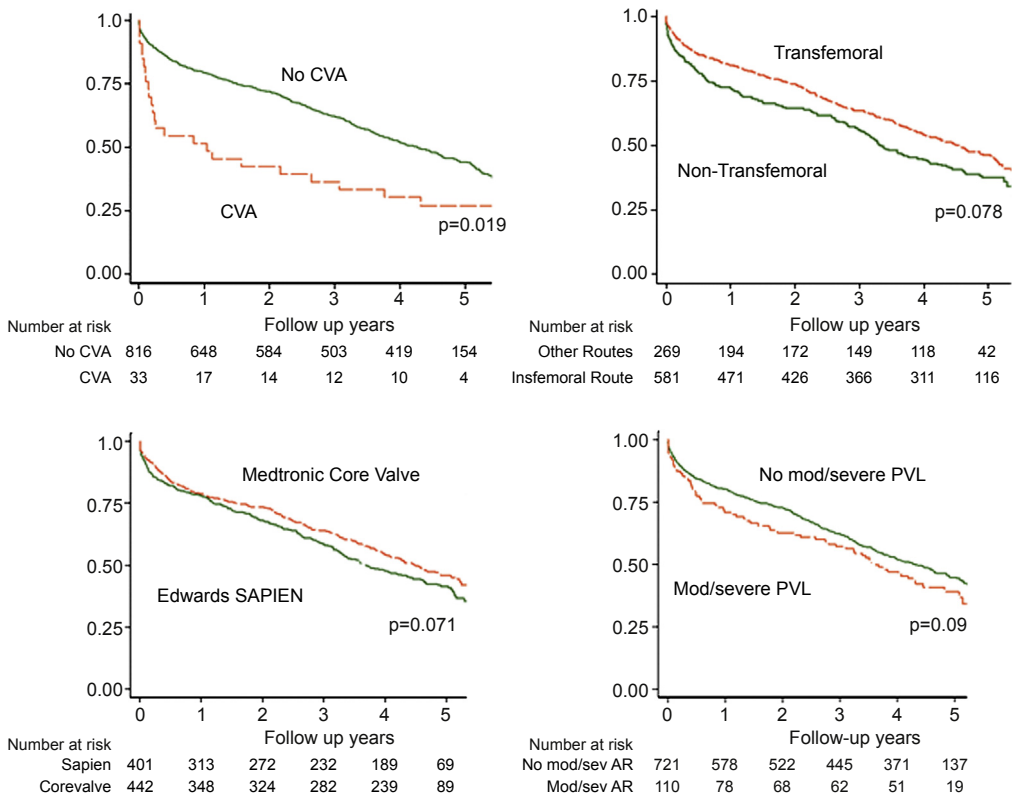
Values are n (%) unless otherwise indicated. *Medtronic, St. Paul, Minnesota. †Edwards Lifesciences, Irvine, California.
CI = confidence interval; HR = hazard ratio.

U.K.-TAVI Registry is likely to be a composite of PARTNER A- and PARTNER B-type patients (i.e., encompassing both high and extreme risk). Very few studies have reported 5-year survival rate after TAVR, and those that have report many fewer patients alive and at risk at 5 years compared with this study (18–20). In the U.K.-TAVI Registry, a sizable number of patients (n = 158) were still alive and at risk more than 5 years after TAVR. The actuarial survival rate was 45.5%. Previous studies report 5-year survival rates between 35% and 41% (18–20).

In the initial U.K.-TAVI Registry report (21), 1-year predictors of mortality were left ventricular impairment (LVEF ≤30%), chronic obstructive pulmonary disease, and the presence of moderate to severe paravalvular aortic regurgitation (22). In essentially the same cohort of patients in the current study, long-term mortality was dominated by intrinsic patient factors (significant renal dysfunction, atrial fibrillation, respiratory disease, impaired left ventricular function, and logistic EuroSCORE) (18,19,23–29). The only procedural variable that was an independent predictor of long-term mortality was post-procedural stroke, which was associated with a more than 2-fold risk of death at 3 years with a similar finding at 5 years. At 5 years, advancing age emerged as an additional independent predictor of mortality, as did coronary artery disease. Because coronary artery disease has not previously been shown to be a predictor of early and mid-term outcome after TAVR (21,30,31), we speculate that the progression of coronary artery disease with longer follow-up after TAVR may be clinically important. Sex (32) and previous cardiac surgery (33) did not predict long-term survival. Left ventricular function (LVEF 30% to 49% and <30%) were both independent predictors of mortality at 3 and 5 years, but only LVEF predicted mortality at 5 years when <30%. This result is difficult to explain; we postulate that it may have been as a result of a relatively small but statistically important number of missing data in patients with an LVEF of 30% to 49% who died after 5 years compared with other groups.

As reported, stroke within 30 days of TAVR was the only independent predictor of long-term mortality. There was no statistically significant difference in mortality rates at either 3 or 5 years between patients treated with the SAPIEN or CoreValve devices. We acknowledge that in the cohort studied, more than one-half of the SAPIEN procedures were performed via the transapical approach, whereas more than 90% of CoreValve procedures were performed transfemorally (21), and so the access route may have been a confounding factor in this analysis. However, we found no difference in mortality rates when transfemoral access was compared with nontransfemoral access. Similar findings were reported recently in the PRAGMATIC (Pooled Rotterdam-Milan-Toulouse In Collaboration) and CHOICE (A Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: Medtronic CoreValve Versus Edwards Sapien XT) studies, which found no significant between-group differences in procedural, 30-day, and 1-year mortality rates or in symptom improvement between device types (34,35). Perhaps the most controversial was the finding that more than moderate paravalvular leak was not an independent predictor of long-term outcome in the U.K.-TAVI Registry (36). Moderate to severe paravalvular aortic regurgitation has previously been consistently shown to be associated with reduced early survival after TAVR (11,13,37–39), and indeed, the U.K.-TAVI Registry report in 2011 was one of the first to demonstrate that paravalvular aortic regurgitation was associated with increased mortality at 1 year (21). However, in

FIGURE 3 Procedural Predictors of 5-Year Survival After TAVR



Stroke-associated with TAVR had a highly significant effect on long-term survival. There was a trend toward reduced mortality with a Medtronic CoreValve compared with an Edwards SAPIEN device via a transfemoral approach compared with a nontransfemoral approach and with the absence of moderate to severe paravalvular leak, but these did not reach statistical significance. AR = aortic regurgitation; CVA = cerebrovascular accident; mod/sev = moderate to severe; PVL = paravalvular leak; TAVR = transcatheter aortic valve replacement.

the same cohort of patients in the current study, there was only a nonsignificant trend toward reduced survival in patients with moderate to severe paravalvular leak 5 years after TAVR. Potential explanations include our use of all-cause mortality rather than cardiovascular mortality as an endpoint. Several studies have shown limited predictive power of paravalvular leak with all-cause mortality, and in the recent PARTNER B trial 5-year follow-up report, only cardiovascular mortality (not all-cause mortality) was influenced by moderate to severe paravalvular leak (17). Moreover, in the U.K.-TAVI Registry, angiographic paravalvular leak severity was self-reported without core lab adjudication; thus, interobserver variability in the estimation of regurgitation severity might explain the lack of independent predictive value of paravalvular leak on long-term mortality. However, the methodology described was robust enough to show a difference at 1 year. Because moderate to severe paravalvular leak proved to be a significant predictor of mortality at 1 year in the U.K.-TAVI Registry (19), the reduced predictive trends at 3 and 5 years in the same cohort of patients might be related to the high incidence of overall mortality (55%) for nonrelated causes. Alternatively, intrinsic patient comorbidities may actually overwhelm the deleterious effects of paravalvular leak in the long term, or the presence of paravalvular leak may be itself a surrogate for patients with significant comorbidities (40). Continued advances in imaging to size the aortic annulus with greater accuracy, along with improvements in device function, should in any case reduce the incidence of paravalvular leak after TAVR, and the uncertainty over the long-term effect of paravalvular leak may become less important than reported after TAVR when the procedure was in its relative infancy.

STUDY LIMITATIONS. Like all registries, ours is only as credible as the quality of the data within it. Data

completeness in this registry was good, but although data on the numbers of procedures and survival outcome is believed to be extremely robust, data concerning morbidity and complications are likely less so. Although internal consistency checks were applied, these data are self-reported and have not been systematically validated or independently adjudicated. Through the Office of National Statistics, the U.K.-TAVI Registry reports the date of death, not cause of death, and therefore our study was only able to report all-cause mortality, not cardiovascular mortality. Determining predictors of late mortality in a highly comorbid group of patients in whom noncardiac death may have been frequent and in whom even cardiac death may have been unrelated to valve-related complications is thus a limitation of the study, and many "true" predictors of mortality may have been overshadowed by the overall high rates of mortality due to other causes. Our results may thus have favored baseline patient demographics (such as age and coronary and renal disease) as positive predictors of mortality because these are generally associated with late mortality. Procedural factors (which would not normally be associated with late mortality) may have therefore been less discriminant, remaining only as trends without statistical significance. Moreover, we were unable to provide risk adjustments or propensity-matched cohorts to support our results. Specifically with respect to paravalvular leak, although the numbers of patients at risk are larger than in other studies, the actual numbers are still relatively small, and, thus, there may be a chance of a type II error in the finding that paravalvular aortic regurgitation did not influence long-term mortality. We will be able to address this concern in future follow-up studies from the Registry.

CONCLUSIONS

Although procedural factors are important predictors of early mortality, this study suggests that the dominant predictors of long-term mortality after TAVR are intrinsic patient factors. At 5 years, age and the presence of concomitant coronary artery disease emerge for the first time as independent predictors of mortality. The only procedural variable that was an independent predictor of long-term mortality was post-procedural stroke.

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PERSPECTIVES

The U.K.-Transcatheter Aortic Valve Implantation (TAVI) Registry previously reported a 30-day mortality rate of 7.1% and a 1-year mortality rate of 21.4% in patients undergoing transcatheter aortic valve replacement between January 2007 and December 2009. In the same cohort, we report 3- and 5-year mortality of survival rates of 38.8% and 54.5%, respectively. Long-term survival after transcatheter aortic valve replacement was determined by intrinsic patient factors (age, baseline renal dysfunction, respiratory dysfunction, ventricular dysfunction, coronary artery disease, and atrial fibrillation). Periprocedural stroke was the only independent procedural predictor of mortality. Device type, access route, and paravalvular leak did not independently predict long-term outcome.

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