National Analysis of Short-Term Outcomes and Volume-Outcome Relationships for Transcatheter Aortic Valve Replacement in the Era of Commercialization

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Key Words

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Abstract

Objectives: We queried the 2012 National Inpatient Sample in order to (1) further describe the short-term outcomes for transcatheter aortic valve replacement (TAVR) and (2) characterize possible volume-outcome relationships and other prognostic factors for this procedure. **Methods:** Demographics and inhospital outcomes were tabulated for all patients, as were hospital characteristics and procedural-volume data for all centers at which patients underwent TAVR. Logistic regression analyses were performed to identify independent risk factors for mortality or morbidity. **Results:** 7,635 patients aged ≥ 18 years received TAVR during the study period; 84.5% ($n = 6,450$) underwent transfemoral TAVR and the rest were treated transapically. The median age was 83 years (IQR 77–88 years) and cardiovascular comorbidities were widespread. Overall inhospital mortality was 5.0% ($n = 380$), and 1.4% ($n = 105$) of the patients experienced a stroke. All-cause procedure-related morbidity was 24.7% ($n = 1,885$). Annual hospital TAVR volume did not predict inhospital mortality or morbidity (OR 1.00, 95% CI 0.99–

1.00, $p = 0.111$ and OR 1.00, 95% CI 0.99–1.00, $p = 0.947$, respectively). **Conclusions:** Our analysis helps to confirm the short-term safety profile of TAVR and further demonstrates that inhospital outcomes have remained acceptable as this procedure has become commercialized.

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Introduction

Transcatheter aortic valve replacement (TAVR) has become a viable treatment option for inoperable and high-risk patients with severe, symptomatic aortic stenosis [1–7]. The evidence base for the emergence of TAVR stems mainly from clinical trials with inclusion and exclusion criteria that may no longer be reflective of the ‘real-world’ experience with this technique now that it has been approved by the USA FDA for both the transfemoral (TF) and transapical (TA) approaches [8, 9]. To date, the largest postapproval studies on TAVR in the USA have come from the STS/ACC TVT (Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy) Registry, which has demonstrated inhospital and 30-day mortality rates for this procedure of 5.2–5.5% and 7.0–7.6%, respectively [5, 10].

Despite these early reports and in light of the rapid growth of TAVR, short-term safety and efficacy questions surrounding the mainstream use of this therapy remain incompletely answered. Moreover, as TAVR has moved beyond the confines of regimented clinical trials involving highly experienced centers, little has been done to examine the influence that hospital experience may have on the short-term outcomes of patients undergoing TAVR.

We therefore queried the National Inpatient Sample (NIS) in order to (1) further describe the short-term (i.e. in-hospital) outcomes for TAVR and (2) characterize possible volume-outcome relationships and other prognostic factors for this procedure during the era of its commercialization.

Methods

Data Source

The Healthcare Cost and Utilization Project (HCUP), with sponsoring from the Agency for Healthcare Research and Quality, has maintained the NIS since 1988. This database can be used to analyze national trends in health care utilization, access and outcomes, among other metrics [11–15]. The NIS contains data on more than 7 million hospital stays each year from approximately 1,000 nongovernmental institutions and, when weighted, it estimates roughly 40 million hospitalizations, making it the largest publicly available all-payer inpatient database in the USA [11]. Data contained within the NIS include patient and hospital demographics, admission and treating diagnoses, inpatient procedures, in-hospital mortality, length of stay and hospital charges as well as discharge status. The NIS dataset has numerous internal quality measures and is validated by the HCUP through comparisons to other similar databases [11]. This study was approved by the Institutional Review Board of Weill Cornell Medical College (protocol No. EXE 2011-040) and conforms to the data-use agreement for the NIS from the HCUP.

Study Cohort

The study cohort consisted of patients ≥ 18 years of age who underwent either TF or TA TAVR as their principal procedure upon admission to an NIS-participating hospital in 2012 – the only full year for which TAVR data are currently available from the NIS. These patients – and their corresponding data of interest – were identified within the NIS using ICD-9-CM diagnosis and procedure codes. A full listing of the codes used for query can be found in online supplementary appendix table 1 (for all online suppl. material, see www.karger.com/doi/10.1159/000440694).

Variables and Outcomes

Demographic data were obtained for each patient identified for inclusion: age at admission, gender, race and insurance status; relevant comorbidities were also collected. Hospital characteristics (i.e. size, setting and region) as well as procedural volume data were obtained for all of the centers at which cohort patients underwent TAVR. Operative details, i.e. cardiopulmonary bypass (CPB) and the use of intra-aortic balloon pump (IABP), were also recorded.

The outcomes of this study included short-term (i.e. in-hospital) mortality and morbidity (including procedure-related, cardiovascular, pulmonary, and infectious complications), length of stay and discharge status. Comorbidities and in-hospital complications were identified by means of the respective ICD-9-CM diagnosis or procedure codes for the patients (online suppl. appendix table 1); comorbidities were recorded using the NIS Comorbidity software v3.7 [16].

Study Objectives and Statistical Analyses

The primary objective of this study was to describe the short-term (i.e. in-hospital) mortality and morbidity for TAVR performed in the era during which they were commercialized. Secondly, we sought to determine the risk factors for these outcomes and, in so doing, investigated what effects the hospital experience, measured by annual procedural volumes, may have had on short-term mortality and morbidity.

Of note, in assessing for such possible volume-outcome relationships, hospitals were categorized into groups based on their 2012 TAVR experience. This grouping was defined using the Centers for Medicare and Medicaid Services' (CMS) recent National Coverage Determination for TAVR as a guide; in this document, the CMS states that in order for these operations to be reimbursed by the federal government, TAVRs are only to be performed by heart teams (i.e. centers) completing at least 20 such procedures annually [17]. We therefore defined the lowest-volume group as hospitals that performed <20 TAVRs in 2012, the next included hospitals performing the minimum CMS requirement up to double the CMS-mandated volume (i.e. 20–39 TAVRs), the third encompassed centers performing 2–3 times the CMS requirement (i.e. 40–59 TAVRs) and the highest-volume group was set as those hospitals performing at least triple the CMS-mandated number of procedures (i.e. ≥ 60 TAVRs).

SUDAAN v9.0.1 (Research Triangle Institute, Research Triangle Park, N.C., USA) was used to convert raw counts generated from the NIS database into weighted counts that were used to generate national estimates. All results presented here, including all statistical analyses, reflect these weighted data (i.e. the national estimates). For categorical data, the χ^2 test and analysis of variance for continuous data were used to test for statistical significance. All p values were 2-sided with statistical significance evaluated at the 0.05 alpha level. Logistic regression analysis was used to determine clinical characteristics that were independent risk factors for mortality or morbidity. Univariable predictors of mortality or morbidity with a p value ≤ 0.200 that were thought to be of clinical significance a priori were entered into multivariable models. Collinearity between independent variables was assessed using variance influence factors. No variables tested were found to be colinear. All statistical analyses were performed using SPSS v17.0 (SPSS Inc., Chicago, Ill., USA) and SUDAAN v9.0.1.

Results

Patient Demographics and Comorbidities

A total of 7,635 patients underwent TAVR during the 1-year study period; table 1 summarizes the demographics and comorbidities. Overall, the median age at the time of TAVR was 83 years (IQR 77–88 years) and 51.1% (n =

Table 1. Patient demographics and comorbidities

	Total (n = 7,635)	TF (n = 6,450)	TA (n = 1,185)	p value ^a
<i>Demographics</i>				
Median age, years (IQR)	83 (77–8)	84 (77–88)	81 (74–86)	<0.001
Gender				0.089
Male	3,900 (51.1)	3,355 (52.0)	545 (46.0)	
Female	3,735 (48.9)	3,095 (48.0)	640 (54.0)	
Race				0.116
White	6,040 (84.1)	5,170 (84.8)	870 (80.2)	
Non-White	1,145 (15.9)	930 (15.2)	215 (19.8)	
Insurance				0.019
Medicare	6,845 (89.7)	5,865 (90.9)	980 (82.7)	
Medicaid	80 (1.0)	60 (0.9)	20 (1.7)	
Commercial	580 (7.6)	435 (6.7)	145 (12.2)	
Other (uninsured)	130 (1.7)	90 (1.4)	40 (3.4)	
<i>Comorbidities</i>				
Stroke/TIA	965 (12.6)	810 (12.6)	155 (13.1)	0.826
Cardiovascular				
Hypertension	3,445 (45.1)	2,840 (44.0)	605 (51.1)	0.048
Hyperlipidemia	4,535 (59.4)	3,740 (58.0)	795 (67.1)	0.007
Angina	170 (2.2)	140 (2.2)	30 (2.5)	0.742
Coronary artery disease	5,090 (66.7)	4,370 (67.8)	720 (60.8)	0.043
Congestive heart failure	130 (1.7)	110 (1.7)	20 (1.7)	0.984
Cardiogenic shock	305 (4.0)	230 (3.6)	75 (6.3)	0.098
Endocarditis	1,320 (17.3)	1,165 (18.1)	155 (13.1)	0.042
Pacemaker	270 (3.5)	245 (3.8)	25 (2.1)	0.117
AICD	205 (2.7)	185 (2.9)	20 (1.7)	0.219
CABG	1,655 (21.7)	1,440 (22.3)	215 (18.1)	0.131
PCI	1,320 (17.3)	1,155 (17.9)	165 (13.9)	0.111
Chronic pulmonary disease	2,575 (33.7)	2,170 (33.6)	405 (34.2)	0.874
Peripheral vascular disease	2,385 (31.2)	1,925 (29.8)	460 (38.8)	0.009
Renal				
Chronic renal insufficiency/failure	2,645 (34.6)	2,300 (35.7)	345 (29.1)	0.044
Hemodialysis	100 (1.3)	100 (1.6)	0 (0.0)	<0.001
Chronic liver disease	145 (1.9)	>10 (–)	≤10 (–)	0.082
Diabetes	2,210 (28.9)	1,865 (28.9)	345 (29.1)	0.951
Hematologic				
Anemia	2,000 (26.2)	1,740 (27.0)	260 (21.9)	0.090
Coagulopathy	1,890 (24.8)	1,575 (24.4)	315 (26.6)	0.487
Constitutional				
Frailty	315 (4.1)	280 (4.3)	35 (3.0)	0.263
Overweight/obesity	1,040 (13.6)	895 (13.9)	145 (12.2)	0.483

Data are presented as n (%) unless otherwise noted. Frequencies ≤10 may not be disclosed as per the NIS data-use agreement. AICD = Automatic implantable cardioverter-defibrillator; PCI = percutaneous coronary intervention; TIA = transient ischemic attack. ^a TA vs. TF.

3,900) of the patients were male. The most common cardiovascular risk factors included coronary artery disease (66.7%, n = 5,090), hyperlipidemia (59.4%, n = 4,535) and hypertension (45.1%, n = 3,445). Rates of chronic pulmonary disease, peripheral vascular disease and chronic re-

nal insufficiency were each in excess of 30% (33.7%, n = 2,575; 31.2%, n = 2,385; 34.6%, n = 2,645). Almost 30% of the patients (n = 2,210) had diabetes, while anemia (n = 2,000) and coagulopathy (n = 1,890) were comorbid in approximately 25% of patients. Upwards of 20% (n =

Table 2. Hospital characteristics and procedural volumes

	Total (n = 7,635)	TF (n = 6,450)	TA (n = 1,185)	p value ^a
<i>Hospital characteristics</i>				
Bed size ^b				0.983
Small	340 (4.5)	285 (4.4)	55 (4.6)	
Medium	1,050 (13.8)	890 (13.8)	160 (13.5)	
Large	6,245 (81.8)	5,275 (81.8)	970 (81.9)	
Setting ^c				0.137
Urban (nonteaching) or rural	890 (11.7)	715 (11.1)	175 (14.8)	
Urban (teaching)	6,745 (88.3)	5,735 (88.9)	1,010 (85.2)	
Region				0.593
Northeast	1,725 (22.6)	1,495 (23.2)	230 (19.4)	
Midwest	1,680 (22.0)	1,415 (21.9)	265 (22.4)	
South	2,715 (35.6)	2,280 (35.3)	435 (36.7)	
West	1,515 (19.8)	1,260 (19.5)	255 (21.5)	
<i>TAVR volumes</i>				
Median annual TAVR cases/hospital (IQR)	50 (30–95)	50 (30–95)	50 (20–125)	0.088
Distribution of TAVRs across hospitals performing				<0.001
<20 TAVRs (123 centers)	875 (11.5)	615 (9.5)	260 (21.9)	
20–39 TAVRs (69 centers)	1,780 (23.3)	1,565 (24.3)	215 (18.1)	
40–59 TAVRs (32 centers)	1,460 (19.1)	1,300 (20.2)	160 (13.5)	
≥60 TAVRs (34 centers)	3,520 (46.1)	2,970 (46.0)	550 (46.5)	

Data presented as n (%) unless otherwise noted. ^a TA vs. TF. ^b See online suppl. appendix table 2 for bed size definitions. ^c See online suppl. appendix table 3 for hospital setting definitions.

1,655) of the patients had previously undergone coronary artery bypass grafting (CABG) and nearly 14% (n = 1,040) were overweight or obese.

Hospital Characteristics and Procedural Volumes

The majority (81.8%, n = 6,245) of patients underwent TAVR at large hospitals and almost 90% (n = 6,745) received their TAVRs at urban teaching centers [table 2; online suppl. appendix tables 2 (hospital bed size) and 3 (setting)]. Of the 258 hospitals that performed >7,600 TAVRs included in this study, the median number of annual TAVR cases per center was 50 (IQR 30–95). The plurality (46.1%, n = 3,520) of TAVRs were performed in the ‘highest-volume’ centers, i.e. in hospitals that performed at least triple the number of TAVRs mandated by CMS for reimbursement.

Operative Details and Short-Term Outcomes

Table 3 lists the operative details and short-term (i.e. in-hospital) outcomes of the entire study cohort. The majority of patients (84.5%, n = 6,450) underwent TF TAVR; the balance (15.5%, n = 1,185) was treated with the TA approach. Although 30.4% (n = 360) of TA cases were

performed on-pump, only 4.1% (n = 265) of the TF TAVRs required CPB (p < 0.001).

Short-term mortality for the total cohort was 5.0% (n = 380); in-hospital mortality did not differ significantly between patients receiving TF (4.7%, n = 305) and TA TAVR (6.3%, n = 75); p = 0.344. As further outlined in table 3, 72.0% (n = 5,495) of all patients experienced some type of morbidity. Procedure-related complications occurred in 24.7% (n = 1,885) of the TAVR patients. Even though the frequencies of overall procedural complications were equal for TF and TA TAVRs (24.6%, n = 1,585 vs. 25.3%, n = 300, respectively, p = 0.809), the rates of several individual procedure-related complications did differ. Accidental punctures or lacerations, hematomas and other peripheral vascular procedural complications affected significantly more TF than TA patients (3.4%, n = 220 vs. 1.3%, n = 15, p = 0.016; 6.4%, n = 410 vs. 3.0%, n = 35, p = 0.009; and n > 10 vs. n ≤ 10, p = 0.006). Aortic injuries and other nonspecified procedure-related cardiac complications were more common in the TA cases (5.9%, n = 70 vs. 2.4%, n = 155, p = 0.029 and 13.9%, n = 165 vs. 7.0%, n = 450, p = 0.004).

Table 3. Operative details and short-term (i.e. in-hospital) outcomes

	Total (n = 7,635)	TF (n = 6,450)	TA (n = 1,185)	p value ^a
<i>Operative details</i>				
CBP	625 (8.2)	265 (4.1)	360 (30.4)	<0.001
IABP	160 (2.1)	110 (1.7)	50 (4.2)	0.065
<i>Short-term outcomes</i>				
Mortality	380 (5.0)	305 (4.7)	75 (6.3)	0.344
Morbidity ^b				
Any complication	5,495 (72.0)	4,585 (71.1)	910 (76.8)	0.060
Procedural	1,885 (24.7)	1,585 (24.6)	300 (25.3)	0.809
Valve/device complication	280 (3.7)	245 (3.8)	35 (3.0)	0.490
Accidental puncture/laceration complicating surgery	235 (3.1)	220 (3.4)	15 (1.3)	0.016
Bleeding complicating procedure	295 (3.9)	230 (3.6)	65 (5.5)	0.222
Hematoma complicating procedure	445 (5.8)	410 (6.4)	35 (3.0)	0.009
Aortic dissection/injury	225 (2.9)	155 (2.4)	70 (5.9)	0.029
Other peripheral vascular complications from the procedure	200 (2.6)	>10 (–)	≤10 (–)	0.006
Other cardiac complications resulting from the procedure	615 (8.1)	450 (7.0)	165 (13.9)	0.004
Stroke	105 (1.4)	80 (1.2)	25 (2.1)	0.377
Cardiovascular	4,140 (54.2)	3,425 (53.1)	715 (60.3)	0.038
Supraventricular arrhythmia	3,505 (45.9)	2,890 (44.8)	615 (51.9)	0.046
Atrioventricular block	155 (2.0)	120 (1.9)	35 (3.0)	0.348
Pacemaker insertion	650 (8.5)	575 (8.9)	75 (6.3)	0.145
Postoperative shock	165 (2.2)	120 (1.9)	45 (3.8)	0.137
Myocardial infarction	295 (3.9)	235 (3.6)	60 (5.1)	0.350
Pulmonary embolism	15 (0.2)	≤10 (–)	≤10 (–)	0.540
Mural/ventricular aneurysm	≤10 (–)	≤10 (–)	0 (0.0)	0.318
Deep vein thrombosis	75 (1.0)	>10 (–)	≤10 (–)	0.803
Pulmonary	1,670 (21.9)	1,225 (19.0)	445 (37.6)	<0.001
Postoperative acute pneumothorax	60 (0.8)	>10 (–)	≤10 (–)	0.915
Postoperative pulmonary edema	65 (0.9)	50 (0.8)	15 (1.3)	0.522
Pulmonary collapse	770 (10.1)	555 (8.6)	215 (18.1)	<0.001
Pneumonia	345 (4.5)	235 (3.6)	110 (9.3)	0.004
Noninvasive ventilation	240 (3.1)	175 (2.7)	65 (5.5)	0.075
Mechanical ventilation	570 (7.5)	420 (6.5)	150 (12.7)	0.007
Tracheostomy	105 (1.4)	85 (1.3)	20 (1.7)	0.680
Infectious	905 (11.9)	750 (11.6)	155 (13.1)	0.540
Sepsis	145 (1.9)	105 (1.6)	40 (3.4)	0.155
Wound infection	50 (0.7)	>10 (–)	≤10 (–)	0.724
Urinary tract infection	760 (10.0)	650 (10.1)	110 (9.3)	0.700
Median length of stay, days (IQR)	6 (4–10)	6 (4–10)	7 (5–11)	<0.001
Discharge status				0.293
Routine	2,480 (32.5)	2,140 (33.2)	340 (28.7)	
Nonroutine	4,775 (62.5)	4,005 (62.1)	770 (65.0)	
Deceased	380 (5.0)	305 (4.7)	75 (6.3)	

Data are presented as n (%) unless otherwise noted. Frequencies ≤10 may not be disclosed as per the NIS data-use agreement.

^a TA vs. TF. ^b Some patients had >1 particular morbidity within the same grouping of complications.

Many patients experienced cardiovascular complications (54.2%, n = 4,140), with supraventricular arrhythmias occurring in 45.9% (n = 3,505) of patients overall; these were more common after TA TAVR than TF TAVR (51.9%, n = 615 vs. 44.8%, n = 2,890, p = 0.046). 3.9%

(n = 295) of TAVR patients had myocardial infarctions, 1.4% (n = 105) suffered a stroke and 8.5% (n = 650) required permanent pacemaker insertion; none of these rates differed significantly between the TF and TA TAVR recipients. Pulmonary complications were noted in 21.9%

Fig. 1. Unadjusted overall short-term (i.e. in-hospital) mortality (**a**) and morbidity (**b**) from TAVR, stratified by hospital experience.

($n = 1,670$) of all patients and were more frequent after TA TAVR than after TF TAVR (37.6%, $n = 445$ vs. 19.0%, $n = 1,225$, $p < 0.001$). 12.7% ($n = 150$) of the TA patients required mechanical ventilation compared to 6.5% ($n = 420$) of the TF recipients ($p = 0.007$).

The overall median length of stay was 6 days (IQR 4–10 days); the median TA TAVR hospitalization was 1 day longer than that for TF TAVR (7 days, IQR 5–11 days vs. 6 days, IQR 4–10 days, respectively, $p < 0.001$). Routine discharge (i.e. home, not against-medical-advice and not to any other facility) was achieved for 32.5% ($n = 2,480$) of all patients.

Volume-Outcome Relationships

In order to assess for possible relationships between hospital TAVR experience and outcomes, we stratified the overall rates of unadjusted short-term mortality and morbidity by the TAVR volumes of the different centers (fig. 1). Mortality following TAVR at hospitals performing at least the minimum but no more than double the number of procedures required by CMS (i.e. 20–39 TAVRs) was nearly twice the mortality observed for the highest-volume centers (7.0 vs. 3.6%, respectively, $p = 0.023$). There were no significant differences among the stratified hospitals with respect to overall morbidity.

Table 4. Univariable and multivariable predictors of short-term (i.e. in-hospital) mortality

	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
<i>Demographics</i>				
Age (continuous)	1.02 (0.99–1.06)	0.129	1.05 (1.01–1.09)	0.006
Gender				
Male	Reference			
Female	1.11 (0.70–1.76)	0.668		
Race				
White	Reference			
Non-White	0.97 (0.50–1.87)	0.917		
<i>Comorbidities</i>				
Stroke/TIA	0.92 (0.45–1.89)	0.830		
Hypertension	0.48 (0.29–0.80)	0.004	0.50 (0.25–0.98)	0.044
Hyperlipidemia	0.63 (0.40–1.01)	0.053	0.73 (0.44–1.20)	0.217
Coronary artery disease	1.02 (0.62–1.67)	0.934		
Endocarditis	1.90 (1.13–3.20)	0.016	1.54 (0.83–2.87)	0.174
CABG	0.60 (0.31–1.15)	0.122	0.63 (0.33–1.19)	0.158
PCI	0.63 (0.31–1.28)	0.202	0.82 (0.41–1.65)	0.581
Chronic pulmonary disease	0.96 (0.59–1.57)	0.875		
Peripheral vascular disease	1.30 (0.81–2.10)	0.281		
Chronic renal insufficiency/failure	1.48 (0.93–2.36)	0.101	1.00 (0.53–1.88)	0.996
Chronic liver disease	0.68 (0.09–5.06)	0.704		
Diabetes	0.64 (0.37–1.13)	0.123	0.81 (0.46–1.43)	0.468
Anemia	1.32 (0.80–2.17)	0.275		
Coagulopathy	1.84 (1.13–2.97)	0.014	1.55 (0.90–2.67)	0.116
Overweight/obesity	0.43 (0.17–1.09)	0.074	0.64 (0.26–1.61)	0.344
<i>Hospital characteristics and volumes</i>				
Setting ^a				
Teaching	Reference			
Nonteaching	0.89 (0.42–1.88)	0.753		
Annual TAVR cases (continuous)	0.99 (1.00–1.00)	0.028	1.00 (0.99–1.00)	0.111
Annual SAVR cases (continuous)	1.00 (0.99–1.00)	0.122	1.00 (0.99–1.00)	0.882
<i>Procedural</i>				
Approach				
TF	Reference			
TA	1.36 (0.76–2.44)	0.299		
CBP	3.58 (2.02–6.37)	<0.001	3.83 (1.84–7.98)	<0.001
IABP	15.55 (7.35–32.93)	<0.001	19.52 (6.97–54.70)	<0.001

PCI = Percutaneous coronary intervention; SAVR = surgical aortic valve replacement; TIA = transient ischemic attack. ^a See online suppl. appendix table 3 for hospital setting definitions.

Predictors of Mortality and Morbidity

Univariable and multivariable logistic regression analyses were then performed to evaluate whether hospital experience or other demographic, comorbidity and procedural variables were predictive of short-term (i.e. in-hospital) mortality or morbidity.

Although comorbid hypertension, endocarditis and coagulopathy were found to be univariable predictors of

mortality [odds ratio (OR) 0.48, 95% confidence interval (CI) 0.29–0.80, $p = 0.004$; OR 1.90, 95% CI 1.13–3.20, $p = 0.016$ and OR 1.84, 95% CI 1.13–2.97, $p = 0.014$], only hypertension was significantly predictive of death on multivariable analysis (OR 0.50, 95% CI 0.25–0.98, $p = 0.044$; table 4). Annual hospital TAVR volume was slightly protective against mortality when treated as a continuous variable in univariable regression (OR 0.99,

Table 5. Univariable and multivariable predictors of short-term (i.e. in-hospital) morbidity

	Univariable		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
<i>Demographics</i>				
Age (continuous)	1.01 (0.99–1.02)	0.351		
Gender				
Male	Reference			
Female	1.12 (0.89–1.39)	0.340		
Race				
White	Reference			
Non-White	0.98 (0.72–1.34)	0.916		
<i>Comorbidities</i>				
Stroke/TIA	1.20 (0.85–1.70)	0.297		
Hypertension	0.72 (0.58–0.90)	0.004	0.74 (0.54–1.01)	0.060
Hyperlipidemia	0.78 (0.62–0.99)	0.039	0.83 (0.65–1.05)	0.114
Coronary artery disease	1.08 (0.85–1.37)	0.519		
Endocarditis	1.36 (1.00–1.86)	0.051	1.35 (0.99–1.86)	0.062
CABG	0.91 (0.69–1.18)	0.470		
PCI	0.96 (0.71–1.28)	0.763		
Chronic pulmonary disease	1.18 (0.93–1.50)	0.172	1.22 (0.95–1.55)	0.113
Peripheral vascular disease	1.18 (0.92–1.51)	0.189	1.13 (0.88–1.45)	0.350
Chronic renal insufficiency/failure	1.18 (0.93–1.49)	0.178	0.89 (0.64–1.24)	0.502
Chronic liver disease	1.02 (0.45–2.33)	0.957		
Diabetes	0.85 (0.67–1.09)	0.204	0.88 (0.69–1.13)	0.315
Anemia	1.28 (0.98–1.66)	0.068	1.23 (0.94–1.61)	0.124
Coagulopathy	1.56 (1.18–2.05)	0.002	1.50 (1.14–1.99)	0.004
Overweight/obesity	0.93 (0.67–1.28)	0.654		
<i>Hospital characteristics and volumes</i>				
Setting ^a				
Teaching	Reference			
Nonteaching	0.85 (0.61–1.20)	0.365		
Annual TAVR cases (continuous)	1.00 (0.99–1.00)	0.947		
Annual SAVR cases (continuous)	1.00 (0.99–1.00)	0.914		
<i>Procedural</i>				
Approach				
TF	Reference			
TA	1.35 (0.97–1.86)	0.073	1.29 (0.92–1.81)	0.147
CBP	1.45 (0.93–2.26)	0.097	1.32 (0.84–2.08)	0.227
IABP	5.98 (1.42–25.16)	0.015	5.30 (1.27–22.17)	0.022

PCI = Percutaneous coronary intervention; SAVR = surgical aortic valve replacement; TIA = transient ischemic attack. ^a See online suppl. appendix table 3 for hospital setting definitions.

95% CI 1.00–1.00, $p = 0.028$) but was not predictive upon multivariable analysis. There were no significant predictive associations between centers' annual surgical aortic valve replacement caseloads and short-term mortality following TAVR (table 4). Similarly, TAVR approach (i.e. TF vs. TA) was not predictive of mortality. Utilization of either CPB or an IABP was highly predictive of post-TAVR mortality (OR 3.83, 95% CI 1.84–

7.98, $p < 0.001$ and OR 19.52, 95% CI 6.97–54.70, $p < 0.001$).

Preoperative hypertension and hyperlipidemia were protective against overall morbidity in the univariable analysis (OR 0.72, 95% CI 0.58–0.90, $p = 0.004$ and OR 0.78, 95% CI 0.62–0.99, $p = 0.039$) but not in multivariable analyses (table 5). Comorbid coagulopathy, however, was found to be a significant multivariable predictor of

Table 6. Comparisons of short-term (i.e. in-hospital) outcomes from the NIS to findings from previous studies

	NIS			STS/ACC TVT [5]			GARY [7]		
	Total (n = 7,635)	TF (n = 6,450)	TA (n = 1,185)	Total (n = 7,710)	TF (n = 4,972)	TA (n = 2,738)	Total (n = 3,875)	TF (n = 2,694)	TA (n = 1,181)
Mortality	380 (5.0)	305 (4.7)	75 (6.3)	427 (5.5)	207 (4.2)	220 (8.0)	229 (5.9)	138 (5.1)	91 (7.7)
Stroke	105 (1.4)	80 (1.2)	25 (2.1)	156 (2.0)	106 (2.1)	50 (1.8)	68 (1.8)	43 (1.6)	25 (2.1)

Data are presented as n (%). GARY = German Aortic Valve Registry.

short-term morbidity after TAVR (OR 1.50, 95% CI 1.14–1.99, $p = 0.004$) as was requiring an IABP (OR 5.30, 95% CI 1.27–22.17, $p = 0.022$).

Discussion

Principal Findings

To date, this study represents the largest examination of short-term TAVR outcomes using non-self-reported data, i.e. data that were independent from other institutional or society registries and clinical trials. In leveraging the NIS, we demonstrated a nationwide, in-hospital mortality rate of 5.0% for patients undergoing TAVR. Stroke was observed in 1.4% of patients, but overall procedure-related morbidity occurred in almost 25% of cases. While unadjusted data suggested a possible association between hospital TAVR volumes and short-term mortality, no such volume-outcome relationships emerged upon more rigorous multivariable regression analyses.

Results in Context

The short-term results we describe above largely mirror those reported in several other large-scale, postapproval TAVR studies (table 6). The most recent analysis of the STS/ACC TVT Registry, for example, documented rates for in-hospital mortality and stroke of 5.2 and 1.9%, respectively [10]. In its report immediately prior to that one, it stratified these short-term outcomes on the basis of TAVR approach [5]; here too, our findings closely match those of the Registry. The German Aortic Valve Registry identified in-hospital mortality and stroke in 5.9 and 1.8% of its 3,875 TAVR patients, respectively [7]; our short-term TF and TA outcomes are in line with those from this registry. In this light, the results provided by the NIS (1) help to affirm the short-term safety of TAVR during the era of its commercialization and rapid expansion

and (2) validate the findings of these TAVR-specific databases.

Prognostic Factors: Patient- and Hospital-Level Variables

Although the primary objective of our study was to describe the contemporary, short-term outcomes for patients undergoing TAVR, we also sought to identify risk factors for mortality and/or morbidity following this procedure. In so doing, we found that requiring CPB or an IABP were each significantly predictive of in-hospital mortality after TAVR (table 4). Neither of these modes of support is routinely needed during TAVR, so it is not surprising that both emerged as markers of mortality, given that they were likely utilized in the emergency of intraoperative cardiovascular collapse. Interestingly, despite the fact that we assessed many of the same variables, the TVT Registry group identified increasing age, male gender, severe chronic obstructive pulmonary disease, renal failure, atrial fibrillation and non-TF access as additional predictors of mortality following TAVR, but it must be noted that their analysis was at the 1-year time point [10].

An important distinction of our study is that we further considered whether hospital experience with TAVR played any role in determining the short-term outcomes of patients undergoing this type of valve surgery. Perhaps counterintuitively, the results of our multivariable analyses demonstrated that, when treated as a continuous variable, annual hospital TAVR volume was not predictive of in-hospital mortality or morbidity, following TAVR (table 4, 5). One can speculate that, in 2012, despite commercialization, many TAVRs were still being performed at centers with considerable transcatheter experience given the participation by these hospitals in the original TAVR trials. It will therefore be intriguing to see the results of similar analyses when data for the subse-

quent years become available from the NIS, as these will include more hospitals with new or evolving TAVR programs.

Limitations

There are several limitations to this study, most notably with respect to the type of data that are not collected by the NIS. The NIS is a powerful tool in that it provides us with reliable, independent, cross-sectional outcome statistics for very large numbers of patients; it does not, however, capture certain patient-level data of particular interest in TAVR. Data like valve brand/model, STS risk scores, frailty or functional-status measures (e.g. the Kansas City Cardiomyopathy Questionnaire or the 6-min walk test), New York Heart Association class, the presence of preoperative atrial fibrillation or postoperative new-onset arrhythmias, echocardiographic findings, operative times and transfusion requirements are all absent from the NIS. Not only would such information provide us with more detailed descriptions of our study cohort, inclusion of these data would be helpful in constructing more comprehensive predictive models of mortality and morbidity following TAVR.

Another limitation involves the data that are captured by the NIS; since the database relies on ICD-9-CM codes to describe the characteristics of patients and procedural outcomes, how these codes are defined (and interpreted by those feeding in the data) can hypothetically skew results. Most ICD-9-CM codes are not rigorously defined, so, for example, the exact complication constituting ‘Hematoma Complicating Procedure’ (code 998.12) for 1 patient in the NIS might differ from what was actually experienced by the next patient with that code. This may explain why we observed relatively high rates of proce-

dural complications, and it ultimately underscores the utility of standardized definitions for clinical end points, like those set forth by the Valve Academic Research Consortium [18].

Even when certain outcomes of interest are represented by series of ICD-9-CM codes, these codes do not often provide the level of detail requisite for meaningful analyses. For instance, although we were able to describe rates of postoperative supraventricular arrhythmias, current ICD-9-CM codes do not distinguish between preexisting and new-onset rhythm disturbances. Hence, the overall 45.9% prevalence of supraventricular arrhythmias in our cohort (table 3) was likely inflated by the inclusion of patients who had these disturbances preoperatively as well.

Conclusions

Our analysis further documents the short-term safety of TAVR during an era notable for the commercialization of this technique, thereby independently corroborating the results of several contemporary TAVR registries. While inhospital mortality remains acceptably low, this study highlights an opportunity for additional improvements with regard to procedure-related complications. As updated datasets become available, investigations into hospital and provider experience may provide insights into heretofore unrecognized prognostic factors in TAVR.

Conflict of Interest

Dr. Salemi is a site co-PI for Edwards Lifesciences and he has served as a proctor and consultant for the company. The remaining authors have no disclosures.

References

- 1 Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al: Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med* 2010;363:1597–1607.
- 2 Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al: Transcatheter versus surgical aortic-valve replacement in high-risk patients. *N Engl J Med* 2011;364:2187–2198.
- 3 Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, et al: 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. *J Am Coll Cardiol* 2012;59:1200–1254.
- 4 Généreux P, Head SJ, Van Mieghem NM, Kodali S, Kirtane AJ, Xu K, et al: Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. *J Am Coll Cardiol* 2012;59:2317–2326.
- 5 Mack MJ, Brennan JM, Brindis R, Carroll J, Edwards F, Grover F, et al: Outcomes following transcatheter aortic valve replacement in the United States. *JAMA* 2013;310:2069–2077.
- 6 Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al: Transcatheter aortic-valve replacement with a self-expanding prosthesis. *N Engl J Med* 2014;370:1790–1798.
- 7 Hamm CW, Möllmann H, Holzhey D, Beckmann A, Veit C, Figulla HR, et al: The German Aortic Valve Registry (GARY): in-hospital outcome. *Eur Heart J* 2014;35:1588–1598.

- 8 Department of Health and Human Services: Correspondence regarding premarket approval application for Edwards Sapien transcatheter heart valve. November 2, 2011. http://www.accessdata.fda.gov/cdrh_docs/pdf10/p100041a.pdf (accessed March 16, 2015).
- 9 Department of Health and Human Services: Correspondence regarding premarket approval application for Edwards Sapien transcatheter heart valve and transapical and transfemoral accessories. October 19, 2012. http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110021a.pdf (accessed March 16, 2015).
- 10 Holmes DR Jr, Brennan JM, Rumsfeld JS, Dai D, O'Brien SM, Vemulapalli S, et al: Clinical outcomes at 1 year following transcatheter aortic valve replacement. *JAMA* 2015;313:1019–1028.
- 11 Overview of the National (Nationwide) Inpatient Sample (NIS). <http://www.hcup-us.ahrq.gov/nisoverview.jsp> (accessed March 5, 2015).
- 12 Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, et al: Hospital volume and surgical mortality in the United States. *N Engl J Med* 2002;346:1128–1137.
- 13 Trivedi AN, Sequist TD, Ayanian JZ: Impact of hospital volume on racial disparities in cardiovascular procedure mortality. *J Am Coll Cardiol* 2006;47:417–424.
- 14 Fugate JE, Brinjikji W, Mandrekar JN, Cloft HJ, White RD, Wijdicks EF, et al: Post-cardiac arrest mortality is declining: a study of the US National Inpatient Sample 2001 to 2009. *Circulation* 2012;126:546–550.
- 15 Paul S, Jalbert J, Isaacs AJ, Altorki NK, Isom OW, Sedrakyan A: Comparative effectiveness of robotic-assisted vs. thoracoscopic lobectomy. *Chest* 2014;146:1505–1512.
- 16 Comorbidity software v3.7. <http://www.hcup-us.ahrq.gov/toolssoftware/comorbidity/comorbidity.jsp> (accessed January 24, 2015).
- 17 Centers for Medicare and Medicaid Services: National Coverage Determination (NCD) for Transcatheter Aortic Valve Replacement (TAVR) (20.32). <http://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=355> (accessed April 7, 2015).
- 18 Kappetein AP, Head SJ, Gnreux P, Piazza N, van Mieghem NM, Blackstone EH, et al: Updated standardized end point definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *J Thorac Cardiovasc Surg* 2013;145:6–23.