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ORIGINAL RESEARCH

VALVULAR HEART DISEASE

Outcomes After Transcatheter Aortic Valve Implantation in Patients Excluded From Clinical Trials

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ABSTRACT

BACKGROUND The use of transcatheter aortic valve implantation (TAVI) in patients with aortic valve disease excluded from clinical trials has increased with no large-scale data on its safety.

OBJECTIVES The purpose of this study was to assess the trend of utilization and adjusted outcomes of TAVI in clinical trials excluded (CTE) vs clinical trials included TAVI (CTI-TAVI) patients.

METHODS We used the National Readmission Database (2015-2019) to identify 15 CTE-TAVI conditions. A propensity score-matched analysis was used to calculate the adjusted odds ratio (aOR) of net adverse clinical events (composite of mortality, stroke, and major bleeding) in patients undergoing CTE-TAVI vs CTI-TAVI.

RESULTS Among the 223,238 patients undergoing TAVI, CTE-TAVI was used in 41,408 patients (18.5%). The yearly trend showed a steep increase in CTE-TAVI utilization ($P = 0.026$). At index admission, the adjusted odds of net adverse clinical events (aOR: 1.83, 95% CI: 1.73-1.95) and its components, including mortality (aOR: 2.94, 95% CI: 2.66-3.24), stroke (aOR: 1.20, 95% CI: 1.07-1.34), and major bleeding (aOR: 1.49, 95% CI: 1.36-1.63) were significantly higher in CTE-TAVI compared with CTI-TAVI. Among the individual contraindications to clinical trial enrollment in the CTE-TAVI, patients with bicuspid aortic valve, leukopenia, and peptic ulcer disease appeared to have similar outcomes compared with CTI-TAVI, while patients with end-stage renal disease, bioprosthetic aortic valves, and coagulopathy had a higher readmission rate at 30 and 180 days.

CONCLUSIONS CTE-TAVI utilization has increased significantly over the 4-year study period. Patients undergoing CTE-TAVI have a higher likelihood of mortality, stroke, and bleeding than those undergoing CTI-TAVI.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AI = aortic insufficiency
BMI = body mass index
BPV = bioprosthetic valve
CAD = central arterial disease
CTE = clinical trials excluded
CTI = clinical trials included
ESLD = end-stage liver disease
ESRD = end-stage renal disease
HCM = hypertrophic cardiomyopathy
ICD = International Classification of Diseases
IE = infective endocarditis
MCS = mechanical circulatory support
MVD = mitral valve disease
NACE = net adverse clinical events
PPM = permanent pacemaker
PUD = peptic ulcer disease
SMD = standardized mean difference
TAVI = transcatheter aortic valve implantation
ViV = valve-in-valve

With the recent update in guidelines that have expanded eligible transcatheter aortic valve implantation (TAVI) candidates to include younger patients and those at lower surgical risk, the number of TAVI procedures has risen exponentially.[1-3] This has resulted in increased utilization of TAVI in certain cardiac, hematologic, and systemic conditions that were excluded from the landmark TAVI trials (clinical trials excluded [CTE]-TAVI).[3-9] As a result, guidelines have identified most of these conditions as relative or absolute contraindications to TAVI.[1] These conditions include patients with bicuspid aortic valve (BAV), aortic insufficiency (AI), mitral valve disease (MVD), hypertrophic obstructive cardiomyopathy (HCM), bioprosthetic aortic valve (BPV), cardiac masses, infective endocarditis (IE), recent use of mechanical circulatory support (MCS), end-stage renal disease (ESRD), end-stage liver disease (ESLD), active peptic ulcer disease (PUD), central arterial disease, morbid obesity, leukopenia, and coagulopathy. TAVI use in some of these conditions is considered off-label.

CTE-TAVI does not necessarily suggest that therapy is ineffective or inappropriate in these conditions. Therapy might be appropriate based on operator discretion and limited alternative options; however, it does imply that more evidence for safety is required. Current literature on CTE-TAVI use was limited to earlier generations of TAVI and had a small sample size.[10,11] Therefore, we aimed to understand the patterns of CTE-TAVI indications and their association with cardiovascular and noncardiovascular outcomes. Accordingly, we studied the annual trends, subgroup variation, predictors, and in-hospital, 30- and 180-day adverse outcomes associated with CTE-TAVI compared with all other patients undergoing TAVI (collectively termed as clinical trial included TAVI [CTI-TAVI]).

METHODS

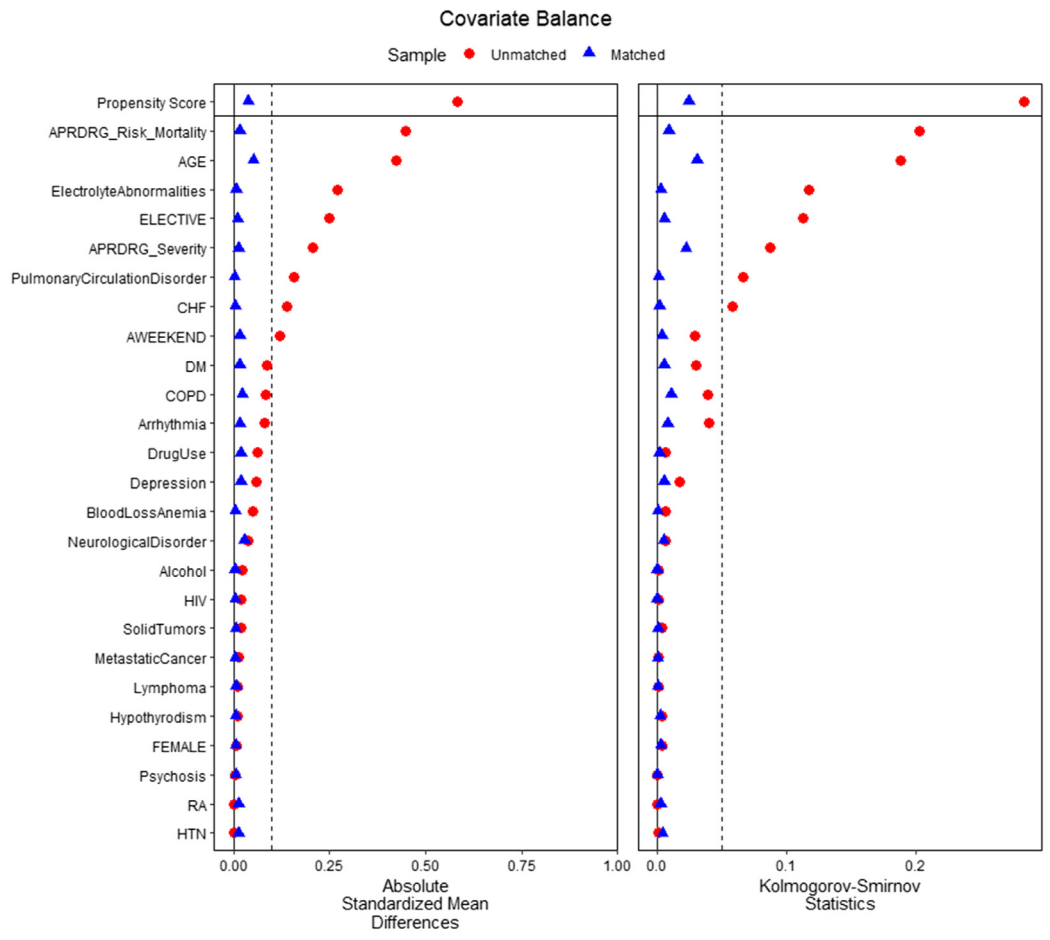
DATA SOURCE. The National Readmission Database (NRD) was utilized from September 1, 2015, to November 30, 2019, to identify all cases of TAVI, using the International Classification of Diseases-10th edition (ICD-10) codes [Supplemental Table 1]. The NRD consists of all-payer data, closely monitored by the Healthcare Cost and Utilization Project, established by the Agency for Healthcare Research and Quality. It is a nationally representative administrative database of the United States comprising discharge and readmission records of 58.2% of all hospitalizations. NRD contains more than 35 million weighted discharges annually from 28 states, which are deidentified and exempted from institutional review board approval.

SELECTION OF CASES. All cases were divided into 2 main groups, CTE-TAVI and the clinical trial included TAVI (CTI-TAVI). Patients with tricuspid or pulmonary valve disease or those undergoing concomitant mitral valve procedures were excluded from the analysis. The included study cohorts were studied at 3 intervals: index-hospitalization, 30-day readmission, and 180-day readmission. Individual cases were identified using the unique identifier code. The hospital NRD ("HOSP-NRD") and discharge weight ("DISCWTS") variables were used for clustering, stratification, and weighting of data, respectively. The number of days to procedure and length of stay variables were used to calculate the readmission day of the same population. Data were used in its totality for analysis at index admission. As NRD is annualized, and only patients admitted within the same calendar year could be identified, we sequentially included the first 11-month and 6-month data from each year to ensure all patients have 30- and 180-day follow-ups, respectively. Observations with a cell count <11 were not reported.

COMPARISON GROUPS. The CTE-TAVI cohort was a consolidated intervention group comprising the aforementioned 15 contraindications to enrollment in the pivotal randomized TAVI trials and/or in whom TAVI was an absolute or relative contraindication in the American College of Cardiology and American Heart Association 2020 guidelines[1] (Supplemental Table 2). These are discussed under 3 major categories: systemic CTE-TAVI, which includes patients with morbid obesity grade III with a body mass index (BMI) >50 kg/m^2, ESRD, ESLD, central arterial disease, and PUD; cardiac CTE-TAVI conditions, such as patients with AI, BAV, BPV, cardiac or valvular masses, HCM, IE, MVD, and recent use of MCS devices (within the last 30 days before TAVI); and measurable hematological CTE-TAVI uses which included coagulopathy and leukopenia. The central arterial disease included patients with carotid, iliac, and thoracoabdominal aortic diseases (Supplemental Table 2).

STUDY OUTCOMES. The primary outcome was a composite of all-cause mortality, major bleeding, and stroke termed net adverse clinical events (NACE) at the index admission. Secondary outcomes

FIGURE 1 **Propensity Matched Analysis Shows the Standardized Mean Differences of Major Comorbidities Showing No Deviation Beyond the Allowable Threshold (Standardized Mean Difference: 0.1 and Kolmogorov-Smirnov Statistics: 0.05)**



APRDRG = all patient refined diagnosis related groups; AWEEKEND = admitted over the weekend; CHF = congestive heart Failure; COPD = chronic obstructive pulmonary disease; DM = diabetes mellitus; ELECTIVE = elective procedure; HIV = human immunodeficiency virus; HTN = hypertension; RA = rheumatoid arthritis.

included components of NACE, paravalvular leak, valve migration, device thrombosis, cardiac tamponade, cardiogenic shock, and the need for a permanent pacemaker at index admission and follow-up. The 30- and 180-day readmission rates and outcomes were also calculated. Continuous outcomes included length of stay and adjusted cost of hospitalization.

STATISTICAL ANALYSIS. Categorical data were reported in percentages for each comparison group and were compared using the Pearson chi-squared test. Continuous data were presented as mean ± SD and median with interquartile ranges. After assessing for distribution of data, continuous variables were compared using the independent *t*-test analysis (for normally distributed) or the Mann-Whitney *U* test for non-normally distributed data. Unadjusted odds ratios for in-hospital outcomes on index admission of the pooled cohort (CTE-TAVI vs CTI-TAVI) were calculated using the Cochrane Mantel Hanzel test. The proportion and pattern of missing values were identified using Little's MCAR (missing completely at random) test; a significant value indicated systematically missing data, while nonsignificant values represented missing at random. Data were complete in all variables except the "mode of admission" and "primary expected payer," which have <0.35% of randomly missing data. As the overall missing data were minimal, we recorded them as "missing" and excluded them from the analysis. After handling

TABLE 1 Unadjusted and Propensity-Matched Demographic and Baseline Characteristics of Study Population Undergoing TAVI

	Crude		Propensity		
	CTE-TAVI (41,408)	CTI-TAVI (181,830)	CTE-TAVI (41,408)	CTI-TAVI (42,296)	SMD
Age, y	75.96 ± 10.1	80.29 ± 7.8	75.96 ± 10.1	76.32 ± 9.7	0.08
Sex					
Male	22,664 (54.70%)	99,349 (54.60%)	22,664 (54.70%)	23,059 (54.50%)	0.03
Female	18,744 (45.30%)	82,481 (45.40%)	18,744 (45.30%)	19,237 (45.50%)	
Admission day					
Weekday	38,922 (94.00%)	176,227 (96.90%)	38,922 (94.00%)	40,419 (95.60%)	0.04
Weekend	2,486 (6.00%)	5,603 (3.10%)	2,486 (6.00%)	1,877 (4.40%)	
Admission type					
Nonelective	11,179 (27.10%)	29,081 (16.00%)	11,179 (27.10%)	9,302 (22.10%)	0.04
Elective	30,144 (72.70%)	152,294 (83.80%)	30,144 (72.90%)	32,849 (77.56%)	
Missing	85 (0.20%)	455 (0.20%)	85 (0.20%)	145 (0.34%)	
Hospital bed size					
Small	1,860 (4.50%)	8,565 (4.70%)	1,860 (4.50%)	1,837 (4.30%)	
Medium	8,591 (20.70%)	39,002 (21.40%)	8,591 (20.70%)	8,624 (20.40%)	
Large	30,957 (74.80%)	134,263 (73.80%)	30,957 (74.80%)	31,835 (75.30%)	
Teaching status					
Metropolitan nonteaching	4,193 (10.10%)	19,296 (10.60%)	4,193 (10.10%)	4,426 (10.50%)	
Metropolitan teaching	36,806 (88.90%)	160,822 (88.40%)	36,806 (88.90%)	37,504 (88.70%)	
Nonmetropolitan hospital	409 (1.00%)	1,712 (0.90%)	409 (1.00%)	366 (0.90%)	
Primary payer					
Medicare	36,001 (87.00%)	165,763 (91.30%)	36,001 (87.00%)	36,201 (85.70%)	
Medicaid	951 (2.30%)	1,649 (0.90%)	951 (2.30%)	925 (2.20%)	
Private insurance	3,381 (8.20%)	10,433 (5.70%)	3,381 (8.20%)	4,136 (9.80%)	
Self-Pay	188 (0.50%)	559 (0.30%)	188 (0.50%)	206 (0.50%)	
No charge	22 (0.10%)	28 (0.00%)	22 (0.10%)	13 (0.00%)	
Other	827 (2.00%)	3,201 (1.80%)	827 (2.00%)	773 (1.80%)	
Missing	38 (0.09%)	197 (0.10%)	38 (0.09%)	42 (0.09%)	
Location					
"Central" counties of metro areas of ≥1 million population	9,145 (22.10%)	36,239 (20.00%)	9,145 (22.10%)	8,565 (20.30%)	
"Fringe" counties of metro areas of ≥1 million population	11,141 (26.90%)	50,811 (28.00%)	11,141 (26.90%)	11,878 (28.10%)	
Counties in metro areas of 250,000-999,999 population	9,595 (23.20%)	42,488 (23.40%)	9,595 (23.20%)	9,787 (23.20%)	
Counties in metro areas of 50,000-249,999 population	4,127 (10.00%)	19,194 (10.60%)	4,127 (10.00%)	4,435 (10.50%)	
Micropolitan counties	4,101 (9.90%)	17,685 (9.70%)	4,101 (9.90%)	4,113 (9.70%)	
Not metropolitan or micropolitan counties	3,233 (7.80%)	15,203 (8.40%)	3,233 (7.80%)	3,467 (8.20%)	
Hospital designation					
Large metropolitan area	25,689 (62.00%)	108,932 (59.90%)	25,689 (62.00%)	25,717 (60.80%)	
Small metropolitan area	15,310 (37.00%)	71,186 (39.10%)	15,310 (37.00%)	16,213 (38.30%)	
Micropolitan areas	368 (0.90%)	1702 (0.90%)	368 (0.90%)	361 (0.90%)	
Nonurban residual	41 (0.10%)	<11	41 (0.10%)	<11	
Severity of illness					
Minor loss of function (LOF)	1,233 (3.00%)	13,223 (7.30%)	1,233 (3.00%)	1,300 (3.10%)	0.04
Moderate LOF	5,390 (13.00%)	31,008 (17.10%)	5,390 (13.00%)	4,412 (10.40%)	
Major LOF	7,146 (17.30%)	22,964 (12.60%)	7,146 (17.30%)	5,122 (12.10%)	
Extreme LOF	27,639 (66.70%)	114,630 (63.00%)	27,639 (66.70%)	31,462 (74.40%)	

Continued on the next page

missing data, propensity score-matched (PSM) analyses models were created using a 1:many nearest neighbor strategy without replacement and keeping the allowable threshold for standardized mean difference of 0.1 and Kolmogorov-Smirnov Statistics of 0.05. Demographics, disease severity, mortality risk, and 18 different baseline comorbidities were used as potential confounders to obtain a balanced

TABLE 1 Continued

	Crude		Propensity		
	CTE-TAVI (41,408)	CTI-TAVI (181,830)	CTE-TAVI (41,408)	CTI-TAVI (42,296)	SMD
Risk of mortality					
Minor likelihood of dying	2,080 (5.00%)	18,273 (10.00%)	2,080 (5.00%)	2,910 (6.90%)	0.06
Moderate likelihood of dying	13,342 (32.20%)	85,698 (47.10%)	13,342 (32.20%)	16,906 (40.00%)	
Major likelihood of dying	18,643 (45.00%)	64,337 (35.40%)	18,643 (45.00%)	17,115 (40.50%)	
Extreme likelihood of dying	7,342 (17.70%)	13,518 (7.40%)	7,342 (17.70%)	5,364 (12.70%)	
Comorbidities					
Hypertension	37,082 (89.60%)	162,366 (89.30%)	37,082 (89.60%)	38,070 (90.00%)	0.03
Diabetes mellitus	5,919 (14.30%)	31,076 (17.10%)	5,919 (14.30%)	5,835 (13.80%)	0.04
Coronary artery disease	28,308 (68.4%)	127,152 (69.9%)	28,143 (68.9%)	29,610 (69.0%)	
Acute coronary syndrome	199 (0.5%)	255 (0.1%)	198 (0.5%)	99 (0.2%)	
Stable angina	130 (0.3%)	468 (0.3%)	124 (0.3%)	99 (0.2%)	
Atrial fibrillation	16,892 (40.8%)	69,337 (38.1%)	16,803 (41.0%)	17,913 (42.0%)	0.04
Atrial flutter	1,986 (4.8%)	6,472 (3.6%)	1,965 (4.7%)	1,965 (4.7%)	0.04
Other arrhythmias[a]	24,579 (59.40%)	100,758 (55.40%)	24,579 (59.40%)	25,369 (60.00%)	0.04
Alcohol use	61 (0.10%)	100 (0.10%)	61 (0.10%)	42 (0.10%)	0.03
Blood loss anemia	666 (1.60%)	1,718 (0.90%)	666 (1.60%)	707 (1.70%)	0.03
Heart failure	32,239 (77.90%)	131,464 (72.30%)	32,239 (77.90%)	33,218 (78.50%)	0.03
Chronic obstructive pulmonary disease	13,073 (31.60%)	49,882 (27.40%)	13,073 (31.60%)	13,658 (32.30%)	0.05
Depression	3,960 (9.60%)	14,108 (7.80%)	3,960 (9.60%)	3,839 (9.10%)	0.04
Drug use	405 (1.00%)	710 (0.40%)	405 (1.00%)	377 (0.90%)	0.04
Electrolyte abnormalities	10,622 (25.70%)	25,170 (13.80%)	10,622 (25.70%)	10,834 (25.60%)	0.04
Human immunodeficiency virus	38 (0.10%)	63 (0.00%)	38 (0.10%)	31 (0.10%)	0.03
Hypothyroidism	8,126 (19.60%)	36,154 (19.90%)	8,126 (19.60%)	8,195 (19.40%)	0.03
Lymphoma	269 (0.60%)	1,295 (0.70%)	269 (0.60%)	250 (0.60%)	0.03
Metastatic cancer	295 (0.70%)	1,154 (0.60%)	295 (0.70%)	232 (0.50%)	0.03
Neurological disorder	1,444 (3.50%)	5,162 (2.80%)	1,444 (3.50%)	1,270 (3.00%)	0.05
Paralysis	626 (1.50%)	1,435 (0.80%)	626 (1.50%)	619 (1.50%)	
Psychosis	97 (0.20%)	412 (0.20%)	97 (0.20%)	77 (0.20%)	0.03
Pulmonary circulation disorder	9,816 (23.70%)	30,799 (16.90%)	9816 (23.70%)	9,817 (23.20%)	0.03
Rheumatoid arthritis	1,863 (4.50%)	8,255 (4.50%)	1,863 (4.50%)	1,728 (4.10%)	0.03
Solid tumors	1,164 (2.80%)	4,510 (2.50%)	1,164 (2.80%)	1,103 (2.60%)	0.03
Long-term anticoagulant	8,659 (20.9%)	8,802 (4.84%)	8,659 (20.9%)	8,547 (20.2%)	

Values are mean ± SD or n (%) unless otherwise indicated. [a]Other arrhythmias include supraventricular arrhythmias, atrial tachycardia, and premature atrial complexes.
CTE-TAVI = clinical trials excluded-transcatheter aortic valve implantation; CTI-TAVI = clinical trials included-transcatheter aortic valve implantation; SMD = standardized mean difference.

population for comparison, as shown in **Figure 1** and Supplemental Table 1. A total of 45 PSM multivariable regression models were created, one for each component of CTE-TAVI (total of 15 CTE-TAVI conditions) in comparison with the corresponding CTI-TAVI at each level of assessment (index-admission, 30- and 180-day readmissions). Using logistic regression analysis, adjusted odds for each primary CTE-TAVI component (vs CTI-TAVI) were calculated by including all other secondary CTE-TAVI conditions in the covariates. Only the first readmission outcome was recorded to avoid overestimation of adverse events. A linear regression model was used for the yearly trend analysis. The Kaplan-Meier curves were constructed for a visual illustration of cumulative incidences of major outcomes. The predictors of mortality for the CTE-TAVI group were calculated using an "entry method" on a logistic regression model. A 2-way P value of <0.05 for outcomes was chosen as a cutoff for statistical significance. All analyses were performed on weighted samples of patients using SPSS v27 (IBM Corp) and R 3.2.

RESULTS

SELECTION OF CASES. A weighted sample of 223,238 patients was identified from September 2015 to November 2019. Of these, 41,408 patients had CTE-TAVI and 181,830 patients had CTI-TAVI. Using propensity-matched analysis, a balanced cohort of 41,408 CTE-TAVI was compared with 42,296

TABLE 2 Proportion of Major Outcomes on Index Admission, 30-Day and 180-Day Readmissions in Patients Who Underwent CTI-TAVI vs CTE-TAVI Using Propensity Matched Population

	Index Admission			30-Day Readmission			180-Day Readmission		
	CTE-TAVI	CTI-TAVI	OR (95% CI)	CTE-TAVI	CTI-TAVI	OR (95% CI)	CTE-TAVI	CTI-TAVI	OR (95% CI)
NACE	3,081 (7.40%)	1,778 (4.20%)	1.83 (1.73-1.95)	565 (8.70%)	444 (6.90%)	1.30 (1.14-1.48)	513 (8.50%)	390 (6.40%)	1.37 (1.19-1.57)
Mortality	1,532 (3.70%)	546 (1.30%)	2.94 (2.66-3.24)	286 (4.40%)	242 (3.70%)	1.19 (1.01-1.42)	278 (4.60%)	201 (3.30%)	1.42 (1.18-1.71)
Stroke	673 (1.60%)	577 (1.40%)	1.20 (1.07-1.34)	93 (1.40%)	87 (1.30%)	1.07 (0.80-1.44)	90 (1.50%)	80 (1.30%)	1.14 (0.84-1.55)
Major bleeding	1,152 (2.80%)	799 (1.90%)	1.49 (1.36-1.63)	205 (3.20%)	135 (2.10%)	1.54 (1.23-1.92)	161 (2.70%)	126 (2.10%)	1.30 (1.03-1.65)
Paravalvular leak	297 (0.7%)	181 (0.4%)	1.68 (1.39-2.02)	39 (0.6%)	32 (0.5%)	1.22 (0.76-1.95)	42 (0.7%)	35 (0.6%)	1.21 (0.77-1.91)
Valve migration	270 (0.7%)	99 (0.2%)	2.79 (2.22-3.52)	<11	12 (0.2%)	0.9 (0.71-1.92)	<11	<11	1.01 (0.14-7.2)
Device thrombosis	66 (0.2%)	27 (0.1%)	2.49 (1.59-3.91)	<11	18 (0.3%)	0.78 (0.10-1.48)	22 (0.4%)	22 (0.4%)	1.01 (0.56-1.83)
Cardiac tamponade	456 (1.10%)	304 (0.70%)	1.54 (1.33-1.78)	75 (1.20%)	49 (0.80%)	1.54 (1.07-2.21)	49 (0.80%)	22 (0.40%)	2.27 (1.37-3.76)
Need for PPM	3,619 (8.70%)	3,798 (9.00%)	0.97 (0.93-1.02)	633 (9.80%)	692 (10.7%)	0.91 (0.81-1.02)	617 (10.20%)	595 (9.70%)	1.06 (0.94-1.19)

Values are n (%) unless otherwise indicated.

CTE-TAVI = clinical trials excluded transcatheter aortic valve implantation; CTI-TAVI = clinical trials included-transcatheter aortic valve implantation; NACE = net adverse clinical events; OR = odds ratio; PPM = permanent Pacemaker.

CTI-TAVI. The CTE-TAVI was further subdivided into 15 different contraindications to clinical trial enrollment for TAVI, such as AI (6.98%), BAV (5.43%), BPV (11.63%), CM (2.85%), HCM (1.76%), IE (0.92%), MCS (0.83%), MVD (0.28%), ESRD (30.6%), ESLD (12.62%), CAD (13.31%), PUD (1.20%), BMI >50 (4.27%), leukopenia (0.79%), and coagulopathy (6.54%) (Supplemental Figure 1).

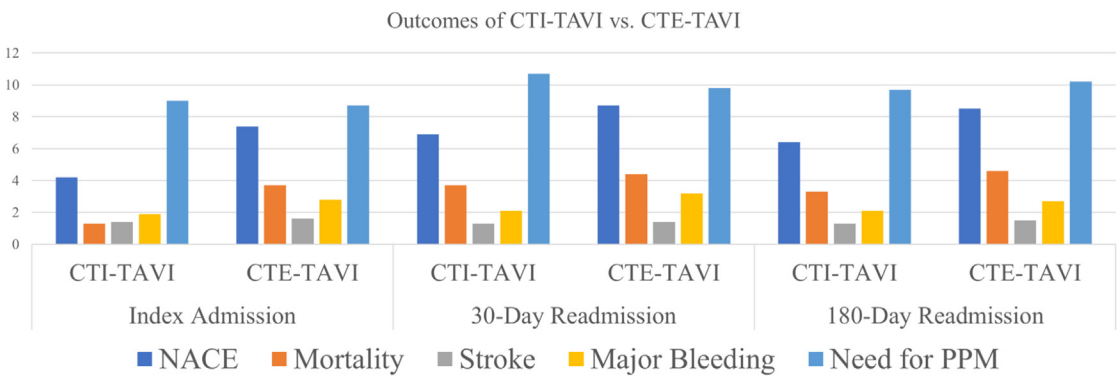
BASELINE CHARACTERISTICS. On unadjusted analysis, there were significant differences in demographics and baseline comorbidities of patients receiving CTE-TAVI compared with CTI-TAVI (**Figure 1**). Patients undergoing CTE-TAVI were younger (75 years vs 80 years), while the prevalence of heart failure (77.9% vs 72.3%) and pulmonary circulation disorder (23.7% vs 16.9%) were higher in CTE-TAVI compared with CTI-TAVI, respectively. Approximately 89% of CTE-TAVI procedures were performed at large metropolitan teaching hospitals, and 87% were paid for by Medicare. Micropolitan counties contributed <10% to the total TAVI procedures. A balanced matched group of CTE-TAVI compared to CTI-TAVI was obtained on PSM analysis, as shown in **Table 1**. Similarly, a PSM population was obtained for each component of CTE-TAVI in comparison with its corresponding CTI-TAVI (Supplemental Tables 3 and 4).

UNADJUSTED IN-HOSPITAL OUTCOMES OF OVERALL POPULATION AT INDEX ADMISSION. On unadjusted analysis, CTE-TAVI had statistically higher unadjusted odds of NACE, mortality, stroke, major bleed, valve complication, and need for PPM implantation compared with CTI-TAVI. A complete list of all complications and their estimates are presented in Supplemental Table 5.

PROPENSITY MATCHED IN-HOSPITAL OUTCOMES AT INDEX ADMISSION. On PSM of 83,704 patients (41,408 CTE-TAVI and 42,296 CTI-TAVI), there were significantly higher adjusted odds of NACE (adjusted odds ratio [aOR]: 1.83, 95% CI: 1.73-1.95), mortality (aOR: 2.94, 95% CI: 2.66-3.24), stroke (aOR: 1.20, 95% CI: 1.07-1.34), valve leak (aOR: 1.68, 95% CI: 1.39-2.02), valve migration (aOR: 2.79, 95% CI: 2.22-3.52), device thrombosis (aOR: 2.49, 95% CI: 1.59-2.49), and major bleeding (aOR: 1.49, 95% CI: 1.36-1.63) in CTE-TAVI compared with patients who underwent CTI-TAVI. In contrast to the unadjusted analysis, there was no significant difference in the adjusted odds of PPM implantation between the 2 groups (**Table 2**). The mean length of stay (7.1 ± 9.80 days) and adjusted mean hospital cost ($103,881 ± 18,538) were also significantly higher in CTE-TAVI, compared with CTI-TAVI (5.25 ± 6.79 and $88,864 ± 12,577), respectively (Supplemental Figure 2). The proportions of outcomes in CTE-TAVI and CTI-TAVI are presented in **Figure 2**, Supplemental Figure 3, Supplemental Tables 6 and 7.

TEMPORAL TRENDS ANALYSIS. The annual percentage of CTE-TAVI procedures remained around 18.1% to 19.5% per total TAVI procedures in the calendar year during 2015 to 2019. The yearly trend showed a significant increase in the utilization of cumulative CTE-TAVI per total CTE-TAVI procedures from 2016 (19.5%) to 2019 (30.7%; $P = 0.012$). Overall, there was a decline in the yearly frequency of NACE, mortality, major bleeding, and stroke in both groups. However, the annual relative risk remained significantly higher in CTE-TAVI at all-time points. Conversely, the yearly trend of PPM implantation with CTE-TAVI closely followed the CTI-TAVI

FIGURE 2 Major Outcomes in Patients Who Underwent CTI-TAVI vs CTE-TAVI



The y axis shows percentages. CTE-TAVI = clinical trials excluded-transcatheter aortic valve implantation; CTI-TAVI = clinical trials included-transcatheter aortic valve implantation; NACE = net adverse clinical events; PPM = permanent pacemaker.

(P = 0.20) (**Figure 3**). These trends were reflected among all the individual components of CTE-TAVI (Supplemental Figure 4). Overall, there was a gradual increase in major comorbidities burden from 2015 to 2019 (Supplemental Figure 5).

30- AND 180-DAY READMISSION RATES AND ADJUSTED OUTCOMES. Compared with CTI-TAVI, the 30-day (adjusted odds ratio [aOR]: 1.36, 95% CI: 1.31-1.40) and 180-day (aOR: 1.23, 95% CI: 1.19-1.27) readmission rates were significantly higher in CTE-TAVI (**Figure 4**, Supplemental Table 8). CTE-TAVI also conferred a higher risk of NACE, mortality, and major bleeding, while there remained no significant difference in the incidence of stroke and need for PPM between the 2 groups at both 30 and 180 days. However, these outcomes might be underestimated as events occurring outside the in-patient settings that could not be captured (**Table 2**, Supplemental Tables 9 to 12). The Kaplan-Meier estimates show a significant difference in major bleeding and a nonsignificant difference in stroke rate between CTE-TAVI and CTI-TAVI (**Figure 5**).

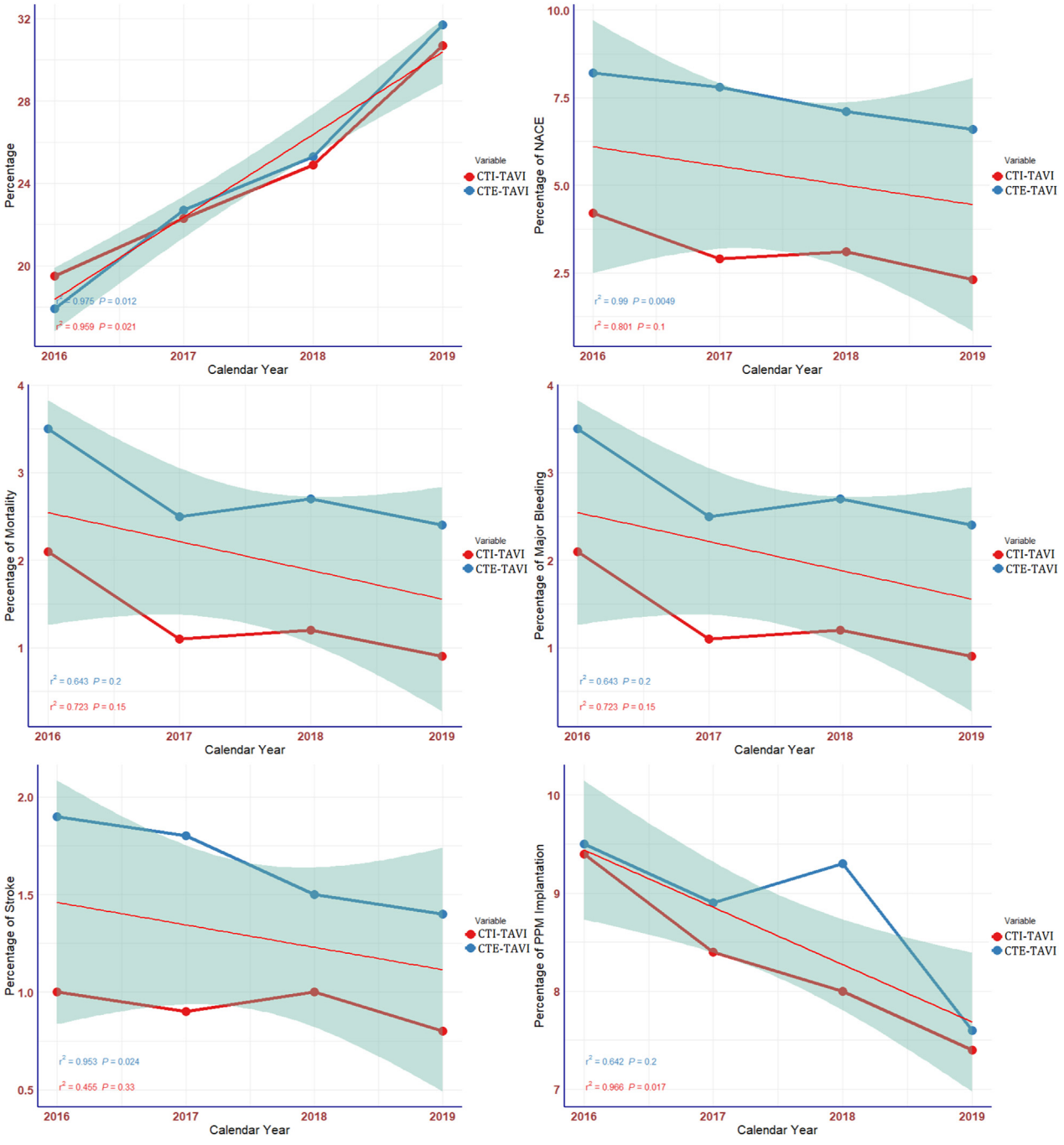
RELATIVE CONTRAINDICATIONS TO CLINICAL TRIAL ENROLLMENT IN THE CTE-TAVI POPULATION. The estimates of individual contraindications to clinical trial enrollment in the CTE-TAVI population vs CTI-TAVI at follow-up durations are given in Supplemental Tables 9 to 12. In concordance with net estimates, patients with AI, intracardiac mass, HCM, BPV, IE, MCS use, morbid obesity, ESRD, ESLD, central arterial disease, and coagulopathy had a significantly higher risk of NACE at index hospitalization. Contrary to pooled outcomes, the risk of NACE, in-hospital mortality, stroke, and major bleeding was not significantly different between patients undergoing TAVI in the setting of BAV, leukopenia, and PUD compared with CTI-TAVI. TAVI in BAV had a higher need for PPM (aOR: 1.38, 95% CI: 1.13-1.67), and those with BPV had a higher incidence of stroke (aOR: 1.87, 95% CI: 1.53-2.27) on index admission. There was no significant difference in the 30- and 180-day outcomes of CTI-TAVI in comparison with any individual component of TAVI, except that patients with coagulopathy, BPV, and ESRD remained to have a higher incidence of major bleeding and readmission rate at all follow-up durations (**Figure 4**, **Central Illustration**, Supplemental Tables 9 to 12).

PREDICTORS OF MORTALITY IN PATIENTS WITH CTE-TAVI: REGRESSION ANALYSIS. At index admission, acute kidney injury, cardiac tamponade, major bleeding, stroke, cardiac arrhythmias, postprocedural cardiogenic, and septic shock were associated with higher in-hospital mortality with CTE-TAVI. The variables and estimates of the regression analysis are presented in Supplemental Table 13.

DISCUSSION

The current study is the most extensive and contemporary evidence on the trends and safety of TAVI in patients who were excluded from the landmark TAVI trials.[1] Our study shows that 18.5% of all TAVI procedures recorded in the NRD from 2016 to 2019 were CTE-TAVI. Of these, 30.7% of TAVI procedures were performed during 2019, compared with 19.5% of cases in 2016. Large academic centers performed approximately 90% of all CTE-TAVI

FIGURE 3 The Yearly Trend of the Proportion of Utilization and Outcomes in Patients Undergoing CTI-TAVI vs CTE-TAVI From 2016 to 2019

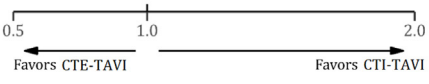


The **green shaded area** signifies the confidence interval. CTE-TAVI = clinical trials excluded-transcatheter aortic valve implantation; CTI-TAVI = clinical trials included-transcatheter aortic valve implantation; NACE = net adverse clinical events; PPM = permanent pacemaker.

procedures in metropolitan area hospitals with a population >249,000. This suggests that experienced centers are now expanding their use of TAVI to those who would not have been routinely considered candidates at the initial stages of TAVI technology. Overall, the adjusted odds of NACE, mortality, stroke, major bleeding, and valve-related complications (thrombosis, embolism) were 1.2- to 2.9- fold higher

FIGURE 4 Forest Plot Showing the Odds of 30 and 180-Day Readmission Rates of Cardiac CTE-TAVI

Subgroup	CTI-TAVI	CTE-TAVI	Estimate
All Patients			
30-Day Readmission	20897 (10.3%)	6467 (13.5%)	1.4 (1.3 to 1.4)
180-Day Readmission	21397 (22.2%)	6024 (25.9%)	1.2 (1.2 to 1.3)
AI			
30-Day Readmission	26933 (10.9%)	430 (10.0%)	0.9 (0.8 to 1.0)
180-Day Readmission	27009 (22.9%)	412 (20.0%)	0.8 (0.8 to 0.9)
BAV			
30-Day Readmission	27073 (10.9%)	290 (8.8%)	0.8 (0.7 to 0.9)
180-Day Readmission	27134 (22.9%)	288 (19.4%)	0.8 (0.7 to 0.9)
Cardiac Mass			
30-Day Readmission	27121 (10.9%)	242 (13.3%)	1.2 (1.0 to 1.4)
180-Day Readmission	27190 (22.9%)	231 (25.4%)	1.1 (1.0 to 1.3)
HCM			
30-Day Readmission	27249 (10.9%)	114 (10.4%)	0.9 (0.8 to 1.1)
180-Day Readmission	27300 (22.9%)	121 (21.0%)	0.9 (0.7 to 1.1)
BPV			
30-Day Readmission	26404 (10.9%)	959 (12.9%)	1.2 (1.1 to 1.3)
180-Day Readmission	26539 (22.8%)	882 (24.5%)	1.1 (1.0 to 1.3)
IE			
30-Day Readmission	27272 (10.9%)	91 (15.1%)	1.4 (1.0 to 1.8)
180-Day Readmission	27345 (22.9%)	76 (25.1%)	1.1 (0.9 to 1.5)
MCS			
30-Day Readmission	27126 (10.9%)	237 (11.6%)	1.1 (1.0 to 1.2)
180-Day Readmission	27212 (22.9%)	209 (20.7%)	0.9 (0.8 to 1.0)
MVD			
30-Day Readmission	27343 (10.9%)	20 (11.4%)	1.0 (0.6 to 1.7)
180-Day Readmission	27402 (22.9%)	19 (21.1%)	0.9 (0.5 to 1.5)

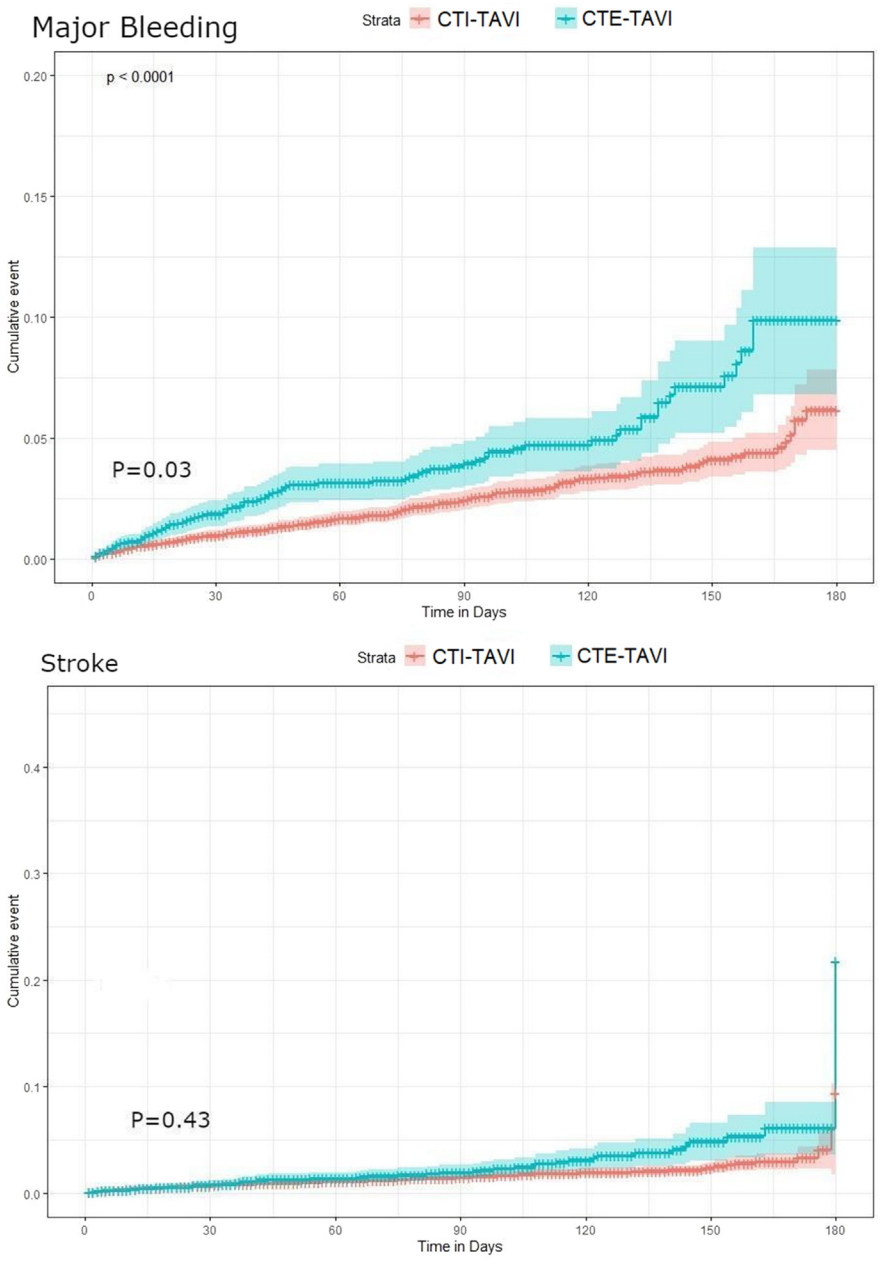


The **dotted line** presents the null line (OR: 1.00), the **horizontal black line** indicates the 95% confidence interval, and the **solid circle** indicates the point estimates. AI = aortic insufficiency; BAV = bicuspid aortic valve; BPV = bioprosthetic aortic valve; CTE-TAVI = clinical trials excluded-transcatheter aortic valve implantation; CTI-TAVI = clinical trials included-transcatheter aortic valve implantation; HCM = hypertrophic obstructive cardiomyopathy; IE = infective endocarditis; MCS = mechanical circulatory support; MVD = mitral valve disease.

in patients undergoing CTE-TAVI compared with CTI-TAVI at index hospitalization. Similarly, the 30- and 180-day readmission rates of CTE-TAVI were 1.23 to 1.36 times greater than CTI-TAVI. The annual outcomes trend from 2016 to 2019 showed a numerical decline in the proportion of major outcomes in both CTE-TAVI and CTI-TAVI. However, CTE-TAVI had a persistently higher relative rate of NACE, mortality, major bleeding, and stroke compared with CTI-TAVI in the corresponding year.

The higher in-hospital odds of mortality in patients undergoing CTE-TAVI were in agreement with the reports by Frerker et al and Hira et al.[10,11] The former was a single-center study that included only 156 patients undergoing off-label TAVI from 2008 to 2012. The latter compared 2,272 off-label TAVI procedures using the Transcatheter Valve Therapy Registry from 2011 to 2014. Both studies included only 5 off-label uses of TAVI and their conclusions were limited to the older generation device (SAPIEN, Edwards Lifesciences). Since then, there have been significant advancements in TAVI technology, operators' proficiency, procedure feasibility, and indications for TAVI. With the favorable outcomes of TAVI in recent

FIGURE 5 Kaplan-Meier Estimates of Cumulative Major Bleeding and Stroke Rate for Patients Undergoing CTI-TAVI vs CTE-TAVI

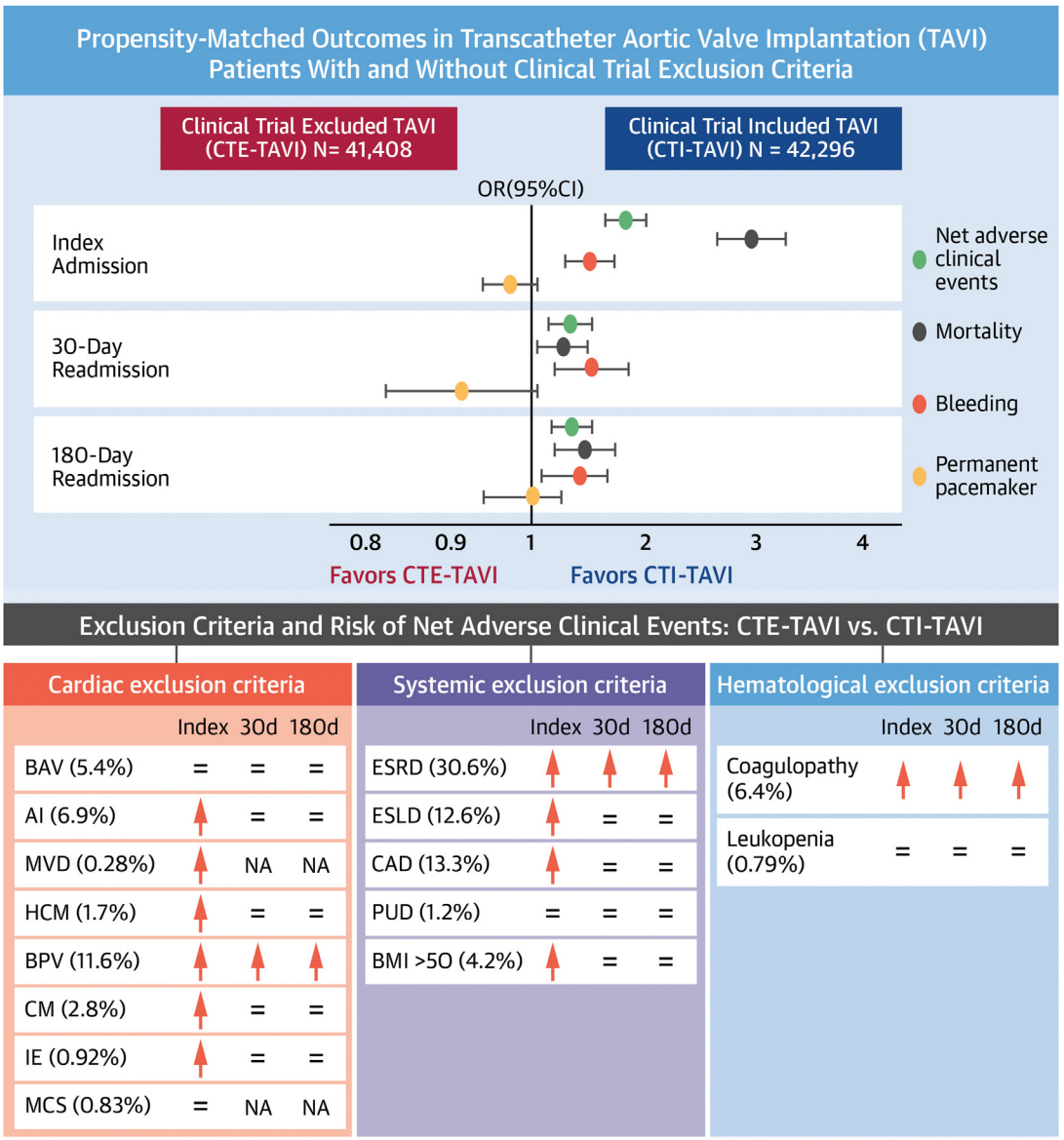


CTE-TAVI = clinical trials excluded-transcatheter aortic valve implantation; CTI-TAVI = clinical trials included-transcatheter aortic valve implantation.

randomized trials, approval has now been expanded to patients at low and intermediate risk of surgery.[6-9] Concurrently, the performance of CTE-TAVI has doubled in the last 4 years (18.5% in our study), compared with 9.5% reported in the Transcatheter Valve Therapy Registry. This highlights the importance of an updated and more comprehensive analysis.

In contrast to prior small-scale studies, we included 41,408 patients with 15 different

CENTRAL ILLUSTRATION **Propensity-Matched Outcomes in TAVI**



Ullah W, et al. JACC Adv. 2023;2(2):100271.

Within the exclusion criteria, **arrow** pointing up indicates significantly higher, = means no significant difference, and NA signifies that no estimates available. AI = aortic insufficiency; BAV = bicuspid aortic valve; BPV = bioprosthetic aortic valve; CTE-TAVI = clinical trials excluded-transcatheter aortic valve implantation; CTI-TAVI = clinical trials included-transcatheter aortic valve implantation; ESLD = end-stage liver disease; ESRD = end-stage renal disease; HCM = hypertrophic obstructive cardiomyopathy; IE = infective endocarditis; MCS = mechanical circulatory support; MVD = mitral valve disease; PUD = peptic ulcer disease.

contraindications to clinical trial enrollment (CTE-TAVI), using the most current data from 2015 to 2019. The cumulative in-hospital mortality in our CTE-TAVI cohort was 2.94 times higher than CTI-TAVI. This rate was greater than the 1.41-fold higher mortality reported for high-risk CTE-TAVI (vs CTI-TAVI) in prior studies.[11] This can be attributed to an increased risk of procedure-related complications, a higher burden of

unmeasured comorbidities, frailty, or a greater percentage of the "extreme likelihood of death" in the CTE-TAVI (17.7%) compared with CTI-TAVI (12.7%, despite PSM analysis). Although the utility of TAVI with that of medical therapy and surgical aortic valve (AV) replacement was not compared, our findings suggest that TAVI use in in-operable CTE-TAVI conditions should be approached cautiously.

The individual CTE-TAVI conditions reflected the findings of net analysis except that there was no significant difference in the in-hospital, 30- and 180-day incidence of stroke, and major bleeding between CTI-TAVI and TAVI in patients with BAV, leukopenia, and PUD. On-trend analysis, a steep increase in the utilization of TAVI and a decline in complications attest to its safety in BAV. This could suggest refinement in the patient selection process and advancement in transcatheter technology with improved repositioning and external sealing cuff capacity to prevent paravalvular leak and allow for better management of BAV-related challenges (asymmetric calcification, noncircular annulus, and aortopathy).[12,13] Regarding PUD, while GI bleed has been associated with high all-cause mortality, the mechanism reported was typical via angiodysplasia and acquired von Willebrand disease secondary to aortic stenosis rather than active PUD.[14] Data on TAVI in PUD are scarce, and our favorable findings in this cohort await further confirmation and elucidation in future studies.

The significantly higher odds of NACE and mortality in the overall CTE-TAVI group at the index admission were largely contributed by the off-label cardiac conditions, particularly patients with acute or subacute IE and those who had a recent use of MCS in the last 30 days before TAVI. Both MCS devices and TAVI require large-bore access, leading to a higher risk of arterial complications (dissection, perforation, pseudoaneurysm, and avulsion). This plausibly explains the higher incidence of major bleeding and mortality in these patients. In concordance with our results, prior studies also showed that MCS use with TAVI confers a 10-fold increase in mortality.[15,16]

In our study, ESLD, ESRD, BPV, and coagulopathy accounted for nearly 40% of CTE-TAVI and drove the higher frequency of readmission and major bleeding events in the net CTE-TAVI group at 30 and 180 days. In ESRD, severe AV calcification compounded by the higher prevalence of hypertension augments the risk of major bleeding, valve complications, and severe sepsis after TAVI.[17] Comparable to our results, prior studies also reported double the risk of short- and long-term adverse outcomes with TAVI in ESRD.[18,19] Similarly, preexisting coagulopathy and ESLD in patients undergoing TAVI had a higher incidence of major bleeding, presumably worsened by the mandated use of post-TAVI dual antiplatelet therapy in these patients.

Prior studies used the term "off-label" for TAVI use in conditions excluded from clinical trials.[10,11] However, the criterion for off-label indications is dynamic. For instance, a recent expansion of device labels included patients who underwent a valve-in-valve (ViV) procedure, possibly due to its success rates (compared with surgical AV replacement) in high-risk patients.[20,21] However, patients with BPV were excluded from the pivotal TAVI trials and its safety in low- and intermediate-risk patients remains unknown.[3-9] In our study, despite a similar risk of index mortality in ViV-TAVI (vs CTI-TAVI), the incidence of NACE, stroke, major bleeding, device thrombosis, and valve embolization were significantly higher with ViV-TAVI compared with CTI-TAVI. The higher in-hospital adverse events in the remaining contraindications to enrollment in the TAVI trials (ie, components of CTE-TAVI: AI, CAD, HCM, IE, CM, ESLD, and obesity) tended to attenuate with time, showing no significant difference in primary endpoint compared with CTI-TAVI at 30- and 180-day follow-ups.

STUDY LIMITATIONS. NRD is a retrospective database that lacks vital information on disease severity, procedure complexity, echocardiographic metrics, ViV TAVI, and prosthesis type, precluding our ability to account for these variables. Although multiple PSM analyses enabled to account for baseline variations, the possibility of unknown and unmeasurable covariates driving these outcomes could not be excluded. Similarly, given the inherent limitation of NRD, events occurring outside the hospital, such as deaths in the community or emergency department could not be captured, which would be a competing risk for readmission, particularly in the CTE-TAVI group where the competing risk of mortality is expected to be higher. This may result in under-reported rates of readmissions in the CTE-TAVI cohorts. Although there was no direct assessment of the covariates, such as operator skills and device type, the yearly trend in our analysis gave us an indirect measure of these estimates. ICD codes may vary in degree of detail and accuracy and are subject to inadvertent misclassification. Given the study design, residual confounding is possible, and the results are subject to selection bias. Despite this, our study is the first and largest study on the outcomes of CTE-TAVI, which can provide directions for future research that has a long-term follow-up.

CONCLUSIONS

Due to a steep increase in utilization, about 1 in 5 patients in the United States is receiving TAVI for conditions that were excluded from clinical trials. Compared with CTI-TAVI, CTE-TAVI has a significantly higher incidence of NACE, mortality, major bleeding, and stroke at index admission and a higher readmission rate and major bleeding up to 6 months on follow-up. TAVI in patients with BAV, leukopenia, and PUD appears to have favorable outcomes, while those with BPV, coagulopathy, and ESRD continued to have worse outcomes. In summary, our findings underscore the importance of informed decision-making with patients who were excluded from major TAVI trials. The higher utilization of TAVI in untested populations coupled with persistently worse outcomes calls for caution while selecting these patients. While specific individual contraindications to clinical trial enrollment in CTE-TAVI appear to have better results than others, prospective trials are needed to expand the approved indications for TAVI.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Shah is a proctor for Edwards has received educational grants from Edwards, Medtronic, and Abbott; and is on the Advisory Board for Xenter. Dr Michos has relationships with Amarin, AstraZeneca, Bayer, Boehringer Ingelheim, Esperion, Novartis, Novo Nordisk, and Pfizer. Dr Bhatt has stock in Bristol Myers Squibb; is on the Advisory Board for AngioWave, Bayer, Boehringer Ingelheim, Cardax, CellProthera, Cereno Scientific, Elsevier Practice Update Cardiology, Janssen, Level Ex, Medscape Cardiology, Merck, MyoKardia, NirvaMed, Novo Nordisk, PhaseBio, PLx Pharma, Regado Biosciences, and Stasys; is on the Board of Directors of AngioWave (stock options), Boston VA Research Institute, DRS.LINQ (stock options), Society of Cardiovascular Patient Care, and TobeSoft; Chair: Inaugural Chair, American Heart Association Quality Oversight Committee; Data Monitoring Committees: Acesion Pharma, Assistance Publique-Hôpitaux de Paris, Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute, for the PORTICO trial, funded by St. Jude Medical, now Abbott), Boston Scientific (Chair, PEITHO trial), Cleveland Clinic (including for the ExCEED trial, funded by Edwards), Contego Medical (Chair, PERFORMANCE 2), Duke Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine (for the ENVISAGE trial, funded by Daiichi Sankyo; for the ABILITY-DM trial, funded by Concept Medical), Novartis, Population Health Research Institute, and Rutgers University (for the NIH-funded MINT Trial); Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org; Chair, ACC Accreditation Oversight Committee), Arnold and Porter law firm (work related to Sanofi/Bristol-Myers Squibb clopidogrel litigation), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim; AEGIS-II executive committee funded by CSL Behring), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Canadian Medical and Surgical Knowledge Translation Research Group (clinical trial steering committees), Cowen and Company, Duke Clinical Research Institute (clinical trial steering committees, including for the PRONOUNCE trial, funded by Ferring Pharmaceuticals), HMP Global (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), K2P (Co-Chair, interdisciplinary curriculum), Level Ex, Medtelligence/ReachMD (CME steering committees), MJH Life Sciences, Oakstone CME (Course Director, Comprehensive Review of Interventional Cardiology), Piper Sandler, Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national co-leader, funded by Bayer), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees), and Wiley (steering committee); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Abbott, Acesion Pharma, Afimmune, Aker Biomarine, Amarin, Amgen, AstraZeneca, Bayer, Beren, Boehringer Ingelheim, Boston Scientific, Bristol-Myers Squibb, Cardax, CellProthera, Cereno Scientific, Chiesi, CSL Behring, Eisai, Ethicon, Faraday Pharmaceuticals, Ferring Pharmaceuticals, Forest Laboratories, Fractyl, Garmin, HLS Therapeutics, Idorsia, Ironwood, Ischemix, Janssen, Javelin, Lexicon, Lilly, Medtronic, Merck, Moderna, MyoKardia, NirvaMed, Novartis, Novo Nordisk, Owkin, Pfizer, PhaseBio, PLx Pharma, Recardio, Regeneron, Reid Hoffman Foundation, Roche, Sanofi, Stasys, Synaptic, The Medicines Company, 89Bio; Royalties: Elsevier (Editor, Braunwald's Heart Disease); Site Co-Investigator: Abbott, Biotronik, Boston Scientific, CSI, Endotronix, St. Jude Medical (now Abbott), Philips, and Svelte; Trustee: American College of Cardiology; and Unfunded Research: FlowCo, Takeda. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: TAVI in patients excluded from clinical trials is associated with increased mortality, major bleeding, stroke, and NACE compared with TAVI in patients included by the trials.

TRANSLATIONAL OUTLOOK: Further studies are needed to decide upon the expansion of indications of TAVI to populations that were excluded from the landmark TAVI trials.

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KEY WORDS CTE, clinical trials excluded, CTI, clinical trials included, TAVI, transcatheter aortic valve implantation

APPENDIX For supplemental tables and figures, please see the online version of this paper.