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ORIGINAL ARTICLE
Valvular heart disease

Autoimmune connective tissue diseases and aortic valve replacement outcomes: a population-based study

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Aims Patients with autoimmune connective tissue diseases (CTDs) have a high burden of valvular heart disease and are often thought of as high surgical risk patients.

Methods and results Patients undergoing aortic valve replacement (AVR) were identified in the Nationwide Readmissions Database between January 2012 and December 2018. Patients with a history of systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, mixed C, Sjögren syndrome, polymyositis, and dermatomyositis were included in the CTD cohort. Patients undergoing coronary artery bypass grafting concomitantly with AVR were excluded. A total of 569 600 hospitalizations were included, of which16 531 (2.9%) had CTD. CTD patients were more likely to be females, with higher rates of heart failure, pulmonary hypertension, and more likely to be insured by Medicare. CTD patients had lower mortality than non-CTD patients [odds ratio (OR) 0.66; 95% confidence interval (CI): 0.59–0.74] and stroke [OR 0.87; 95% (CI): 0.79–0.97]. CTD patients undergoing SAVR had lower mortality [OR 0.69; 95% (CI): 0.60–0.80] and stroke [OR 0.86; 95% (CI): 0.75–0.98). CTD patients undergoing TAVR had lower mortality outcomes [OR 0.67; 95% (CI): 0.56–0.80]; however, they had comparable stroke outcomes [OR 0.97; 95% (CI): 0.83–1.13, $P = 0.69$].

Conclusions Outcomes for patients with CTD requiring AVR are not inferior to their non-CTD counterparts. A comprehensive heart team selection of patients undergoing AVR approaches should place CTD history under consideration; however, pre-existing CTD should not be prohibitive of AVR interventions.

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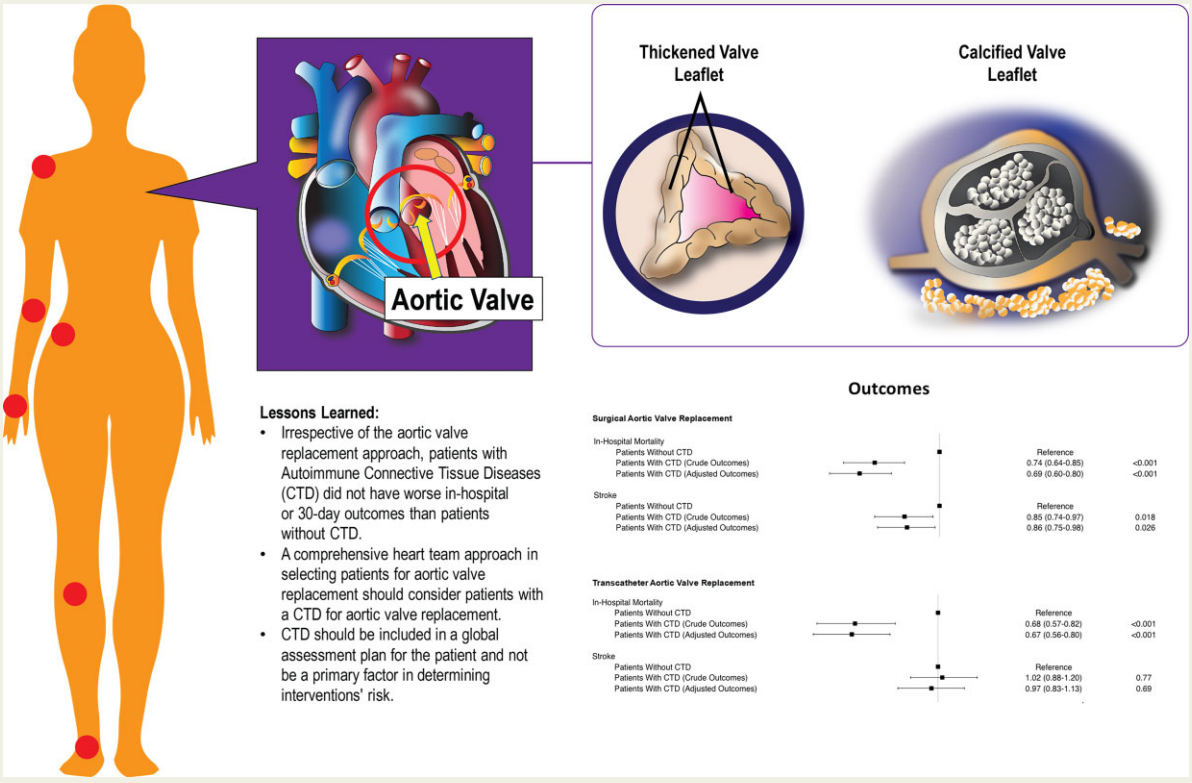
Graphical Abstract



Outcomes of patients with autoimmune connective tissue disorders undergoing aortic valve replacement and lessons learned from current study findings.

Keywords Autoimmune connective tissue diseases • Aortic valve replacement • Valvular heart disease

Introduction

Autoimmune connective tissue diseases (CTDs) comprise a broad spectrum of disorders, including systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), Sjogren's, and mixed connective tissue disorder that affect 1–5% of the general population.[1] The prevalence of aortic valve disease in patients suffering from CTD is as high as 35–40% in SLE[2] and 10–30% in RA.[3]

Several different underlying mechanisms can contribute to aortic valve pathology related to systemic inflammation and circulating inflammatory markers, which can destroy the valvular connective tissue, leading to regurgitation or valvular fibrosis and scarring, in turn, resulting in calcification and stenosis.[4,5] RA can result in rheumatoid granulomas within the valve leaflet, resulting in valve calcification.[6,7] On the other hand, SLE can present with inflammatory or thrombotic vegetations (Libman–Sacks endocarditis), traditionally found on the ventricular side of the aortic valve on the leaflets' closure line, resulting in valvular obstruction and stenosis.[2] SSc can also contribute to aortic valve stenosis; however, this is encountered less frequently.[8]

There is limited available data in patients with CTDs and aortic valve disease undergoing surgical or interventional procedures that characterize the patient characteristics and clinical outcomes, with prior studies focusing primarily on one subtype of CTD or a specific treatment strategy.[9,10] We sought to investigate this knowledge gap by comparing contemporary outcomes in CTD and non-CTD subjects undergoing isolated aortic valve replacement (AVR).

Methods

Data source

The Nationwide Readmissions Database (NRD) was queried for data detailing hospital admissions from January 2010 until December 2018. The NRD is a database by the Agency for Healthcare Research and Quality for the Healthcare Cost and Utilization Project (HCUP).[11] The need for an institutional review board (IRB) approval was waived for this study because of the anonymized and de-identified nature of the publicly available data in the NRD. The NRD embodies half of the US's total hospitalizations and is the most extensive database to study and analyse readmission outcomes. The NRD provides a weight-to-discharge variable for estimating national statistics. The NRD provides a linking variable to track patient hospitalizations in the same state across different health care facilities within a single year. This observational cohort study was conducted according to the guidelines of the Strengthening the Reporting of Observational Studies in Epidemiology Statement checklist.[12]

Table 1 Overall study cohort baseline characteristics, demographics, complications, in-hospital outcomes, and 30-day outcomes of patients included in the current study

Variables	No CTD	CTD	Total	*P*-value
N	*N* = 553 069	*N* = 16 531	*N* = 569 600	
Age, mean (SD)	71.47 (13.82)	72.09 (12.54)	71.49 (13.79)	0.034
Atrial fibrillation, %	35.0	32.1	34.9	<0.001
Carotid artery disease, %	4.6	5.0	4.7	0.063
Chronic kidney disease stage 3 or higher, %	15.9	17.5	15.9	<0.001
Concomitant mitral valve disease, %	4.2	4.7	4.2	<0.001
Coronary artery atherosclerosis, %	48.3	47.6	48.3	0.105
Diabetes mellitus—uncomplicated, %	18.5	15.9	18.4	<0.001
Diabetes mellitus—with chronic complications, %	11.0	9.9	11.0	<0.001
Dyslipidemia, %	60.3	58.2	60.2	<0.001
Female gender, %	40.4	68.7	41.2	<0.001
Heart failure, %	51.1	56.5	51.3	<0.001
Hypertension, %	78.4	80.5	78.4	<0.001
Length of hospital stay, median (IQR)	6 (4–10)	6 (3–10)	6 (4–10)	0.062
Obesity, %	19.7	18.1	19.6	<0.001
Prior history of any valve surgery, %	4.1	4.3	4.1	0.205
Prior history of CABG*, %	10.8	7.3	10.7	<0.001
Prior history of myocardial infarction, %	7.7	8.4	7.8	0.003
Prior history of stroke, %	4.1	4.4	4.1	0.046
Pulmonary hypertension, %	15.4	19.2	15.5	<0.001
Smoking, %	35.7	33.6	35.6	<0.001
Protein calorie malnutrition, %	3.4	4.1	3.4	<0.001
Demographics				
Primary expected payer, %				<0.001
Medicare	71.4	79.4	71.7	
Medicaid	4.3	3.2	4.3	
Private insurance	20.8	15.3	20.6	
Self-pay	1.3	0.6	1.3	
No charge	0.2	0.1	0.2	
Other	2.0	1.3	2.0	
Median household income, %				0.003
Quartile 1	21.4	22.6	21.4	
Quartile 2	26.5	26.4	26.5	
Quartile 3	26.9	26.1	26.9	
Quartile 4	24.8	24.5	24.8	
Bed size of hospital, %				0.846
Small	5.9	5.8	5.9	
Medium	19.1	19.2	19.1	
Large	75.1	75.0	75.1	
Control of hospital, %				0.003
Government controlled	7.9	7.7	7.9	
Non-for private	83.6	84.5	83.6	
For profit	8.5	7.8	8.5	
Hospital urban–rural designation, %				<0.001
Large metropolitan	60.7	62.4	60.8	
Small metropolitan	38.0	36.1	37.9	
Micropolitan	1.3	1.4	1.3	
Non-urban	0.0	0.0	0.0	
Teaching status of urban hospitals, %				<0.001
Metropolitan non-teaching	14.8	13.8	14.8	

Continued

Table 1 *Continued*

Variables	No CTD	CTD	Total	*P*-value
Metropolitan teaching	83.8	84.8	83.9	
Non-metropolitan hospital	1.3	1.4	1.3	0.001
Complications, %				
Ventilator	7.4	7.5	7.4	0.619
Transfusion	21.7	23.9	21.7	<0.001
Acute kidney injury	15.4	14.2	15.4	<0.001
Cardiac tamponade	1.1	1.1	1.1	0.599
Cardiac arrest	1.8	1.5	1.8	0.016
Cardiogenic shock	3.7	2.9	3.6	<0.001
Sepsis	3.6	3.2	3.6	0.008
Mechanical circulatory support devices	23.9	19.7	23.8	<0.001
Outcomes, %				
In-hospital mortality	2.7	1.9	2.6	<0.001
Stroke	2.7	2.4	2.7	<0.001
30-day readmission outcomes				
Readmission eligible cohort	492 425	14 719	507 144	
30-day readmission rate, %	13.6	16.4	13.7	<0.001
Mortality rate in readmission, %	3.4	4.0	3.5	0.059
Readmission for stroke, %	0.3	0.3	0.3	0.605

Study population

Patients who underwent AVR during the index hospitalization [either transcatheter AVR (TAVR) or surgical AVR (SAVR)] were identified and grouped into those who had a diagnosis of CTD, including SLE, RA, SSc, mixed CTD, Sjogren syndrome, polymyositis, and dermatomyositis, using the appropriate International Classification of Diseases-9th and 10th Edition-Clinical Modification (ICD-CM 9 and ICD-10) diagnosis and procedure codes in the NRD database (see Supplementary material online, *Table S1*).

To selectively study patients undergoing isolated AVR, patients who underwent concomitant coronary artery bypass grafting (CABG), patients undergoing other cardiac surgeries, or patients missing critical demographic information, i.e. age or gender, were excluded from the current study. The study focused on isolated AVR to avoid confounding indications for surgical AVR in patients with indications for other cardiac surgeries. Patients were excluded from readmission outcome analysis if: (i) they died during the index hospitalization or (ii) the discharge month was the last month of the year's dataset, as 30-day readmission outcomes would be non-feasible.

Patient and hospital characteristics

Baseline characteristics including demographics (age, sex), medical comorbidities present on the index admission (e.g. atrial fibrillation, carotid artery disease, chronic kidney disease stage 3 or higher, concomitant mitral valve disease, coronary artery atherosclerosis, diabetes mellitus, dyslipidemia, heart failure, hypertension, obesity, prior history of any valve surgery, previous history of CABG, previous history of acute myocardial infarction, previous history of stroke, pulmonary hypertension, and smoking), and complications during the index hospitalization were identified using the corresponding ICD-CM 9 and 10 codes (see Supplementary material online, *Table S1*).

Outcome measure

The primary outcome of this study was in-hospital mortality. Secondary outcomes included stroke and 30-day readmission outcomes. The patient was considered as readmitted if they were re-hospitalized to any hospital in the same state for any cause. In patients with multiple readmissions within 30 days, only the first readmission was included in the analysis. Length of stay in the primary/index hospitalization was used to determine the discharge date of the index admission, and time to readmission was calculated using the index discharge date and the subsequent admission date. Subgroup analyses for outcomes were reported based on the type of CTD and mechanism of aortic valve disease.

Statistical analysis

Patient baseline characteristics, comorbidities, and outcomes were compared between patients with CTD vs. patients without CTD. Categorical variables were compared using the Mantel–Haenszel chi-square test, and continuous variables were expressed as mean with standard deviation in case of a normal distribution, or by the median with the interquartile range (IQR) when not normally distributed using the Student's *t*-test or Mann–Whitney U-test, as appropriate. A backward stepwise multivariate logistic regression model was used to adjust for different baseline characteristics, and an alpha-to-remove value of 0.10 was used to eliminate variables included in the model. All statistical analyses were done using the weighted values of observations provided by the NRD to measure national estimates. Because of the significant differences in baseline patient characteristics between patients with CTD and those without CTD, a propensity score-matched model was used. Patients were matched in a 1:1 fashion to the nearest match, with a calliper of 0.1, and propensity scores were calculated using a multivariate logistic regression model (see Supplementary material online, *Figure S1*). Absolute mean differences were calculated for covariates before and after matching. Absolute mean differences <0.1 were used as an indicator of minimal match imbalances. Statistical analyses were conducted using RStudio® software (RStudio, Boston, MA) or SPSS software version 27 (IBM Corp. IBM SPSS Statistics, Armonk, NY).[13,14] A 2-sided value of $P < 0.05$ was set for statistical significance. Odds ratios (ORs) and the 95% confidence intervals (CIs) were used to report the regression analysis results.

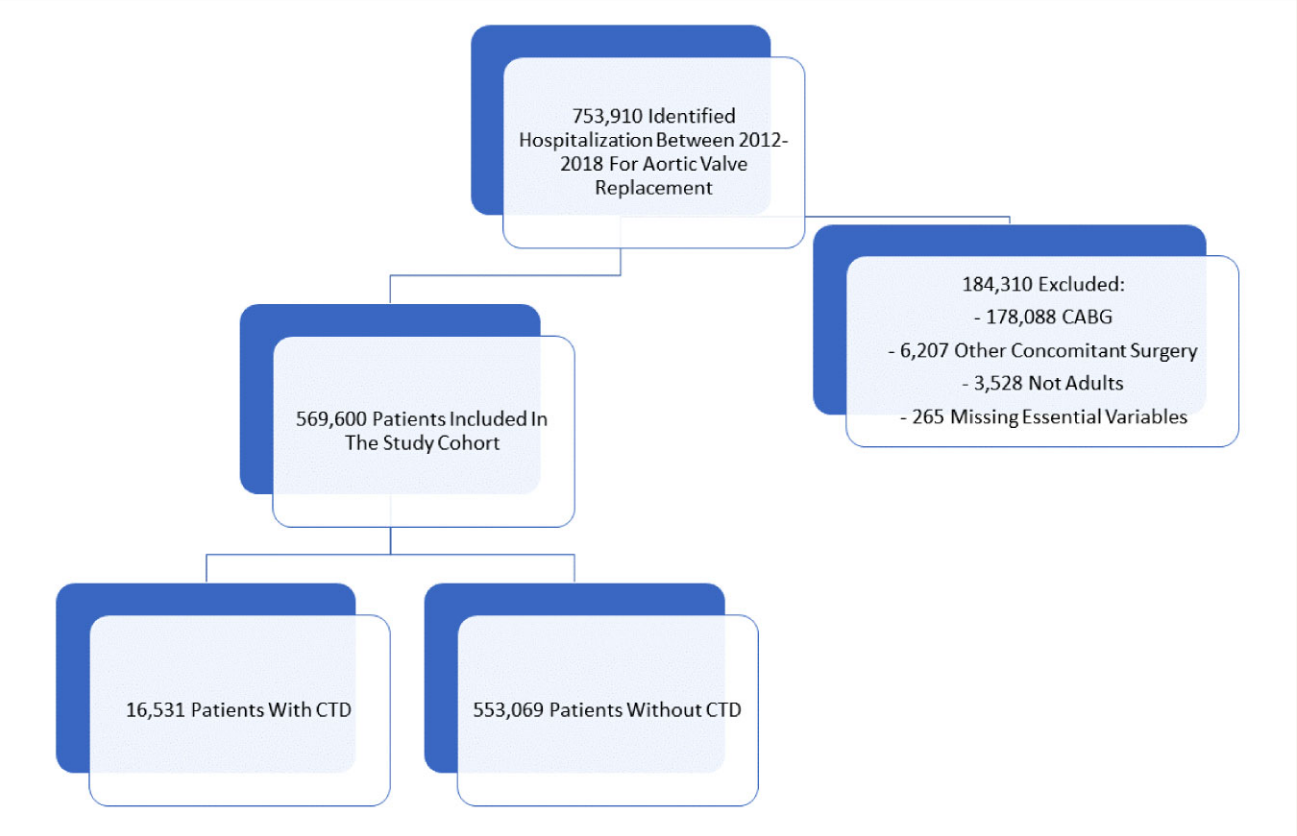


Figure 1 Patient selection. The number of the overall patients identified in the dataset for undergoing aortic valve replacement, the number of patients excluded for undergoing coronary artery bypass grafting, other concomitant surgery, being not adults, and missing essential variables.

Results

Population characteristics

A total of 569 600 patients were included in the final analysis, of which 16 531 hospitalizations (2.9%) were also identified with autoimmune CTDs, 3769 (22.8%) were SLE, and 12 088 (73.1%) were RA (*Figure 1*). In the total cohort, CTD patients were more likely to be females (68.7 vs. 40.4%, $P < 0.001$); have higher rates of heart failure (HF) (56.5 vs. 51.1%, $P < 0.001$) and pulmonary hypertension (19.2 vs. 15.4%, $P < 0.001$); and were more likely to be insured by Medicare (79.4 vs. 71.4%, $P < 0.001$) (*Table 1*).

When patients were stratified based on their undergoing SAVR or TAVR, those with CTD who underwent SAVR were more likely to be female (66.0 vs. 37.0%, $P < 0.001$); have stage 3 or higher chronic kidney disease (CKD) (13.3 vs. 9.5%, $P < 0.001$); and higher rates of HF (40.7 vs. 36.1%, $P < 0.001$) and pulmonary hypertension (16.7 vs. 12.8%, $P < 0.001$) than those without CTD. CTD patients undergoing SAVR were mostly insured by Medicare (67.8 vs. 58.1%, $P < 0.001$) (*Table 2*).

CTD patients undergoing TAVR were younger [mean age 78.42 (8.31) vs. 80.29 (8.46), $P < 0.001$], were females (71.6 vs. 45.4%, $P < 0.001$), and had a lower rate of atrial fibrillation, CKD, coronary artery disease, diabetes mellitus, obesity, and dyslipidemia than non-CTD patients undergoing TAVR (*Table 3*).

Outcomes

CTD patients had lower rates of in-hospital mortality (1.9 vs. 2.7%, *P*-value < 0.001) and stroke (2.4 vs. 2.7%, *P*-value < 0.001) than non-CTD patients in the overall cohort. These differences persisted when patients undergoing SAVR were examined: an in-hospital mortality rate of 2.2 vs. 3.0%, $P < 0.001$ and stroke rates of 2.7 vs. 3.1%, $P = 0.017$. CTD patients undergoing TAVR had a lower in-hospital mortality rate than non-CTD patients: 1.5 vs. 2.2%, $P < 0.001$; however, they had similar stroke rates: 2.1 vs. 2.1%, $P = 0.749$.

On propensity score-matched analysis, in patients undergoing SAVR, patients with CTD had lower in-hospital mortality (2.2 vs. 2.8%, $P = 0.009$) and stroke (2.7 vs. 3.3%, $P = 0.014$). In patients undergoing TAVR, CTD patients had similarly lower in-hospital mortality but higher stroke rates (see Supplementary material online, *Table S2*).

When in-hospital outcomes were adjusted for different baseline comorbidities, CTD patients undergoing AVR (combined SAVR and TAVR) had favourable mortality outcomes [OR of 0.66; 95% (CI): 0.59–0.74, $P < 0.001$] and stroke [OR of 0.87; 95% (CI): 0.79–0.97, $P = 0.008$]. CTD patients undergoing SAVR had favourable mortality outcomes [OR of 0.69; 95% (CI); 0.60–0.80, $P < 0.001$] and stroke [OR of 0.86; 95% (CI): 0.75–0.98, $P = 0.026$]. CTD patients undergoing TAVR had favourable mortality outcomes [OR of 0.67; 95% (CI): 0.56–0.80, $P < 0.001$]; however, they had

Table 2 Patients undergoing surgical aortic valve replacement baseline characteristics, demographics, complications, in-hospital outcomes, and 30-day outcomes of patients undergoing surgical aortic valve replacement

Variables	No CTD	CTD	Total	*P*-value
N	*N* = 329 598	*N* = 8512	*N* = 338 110	
Age, mean (SD)	65.45 (13.55)	66.12 (12.93)	65.5 (13.53)	<0.001
Atrial fibrillation, %	35.4	34.6	35.4	0.139
Carotid artery disease, %	3.4	4.0	3.4	0.002
Chronic kidney disease stage 3 or higher, %	9.5	13.3	9.6	<0.001
Concomitant mitral valve disease, %	3.2	4.0	3.2	<0.001
Coronary artery atherosclerosis, %	34.5	33.5	34.5	0.051
Diabetes mellitus—uncomplicated, %	17.8	15.9	17.8	<0.001
Diabetes mellitus—with chronic complications, %	7.7	7.4	7.7	0.462
Dyslipidemia, %	55.0	52.6	54.9	<0.001
Female gender, %	37.0	66.0	37.7	<0.001
Heart failure, %	36.1	40.7	36.2	<0.001
Hypertension, %	73.0	75.9	73.1	<0.001
Length of hospital stay, median (IQR)	7 (5–11)	7 (5–13)	7 (5–11)	<0.001
Obesity, %	22.0	21.4	22.0	0.214
Prior history of any valve surgery, %	4.5	5.4	4.5	<0.001
Prior history of CABG*, %	4.8	3.3	4.8	<0.001
Prior history of myocardial infarction, %	4.6	5.4	4.7	0.001
Prior history of stroke, %	4.3	5.3	4.3	<0.001
Pulmonary hypertension, %	12.8	16.7	12.9	<0.001
Smoking, %	35.7	34.1	35.6	0.002
Protein calorie malnutrition, %	3.6	4.3	3.6	0.001
Demographics				
Primary expected payer, %				<0.001
Medicare	58.1	67.8	58.3	
Medicaid	6.5	5.6	6.5	
Private insurance	30.9	23.9	30.8	
Self-pay	1.9	0.9	1.8	
No charge	0.2	0.1	0.2	
Other	2.3	1.7	2.2	
Median household income, %				<0.001
Quartile 1	22.1	24.5	22.1	
Quartile 2	26.4	26.7	26.4	
Quartile 3	26.6	25.2	26.6	
Quartile 4	24.4	23.1	24.4	
Bed size of hospital, %				0.968
Small	6.9	6.9	6.9	
Medium	19.3	19.3	19.3	
Large	73.9	73.8	73.9	
Control of hospital, %				0.001
Government controlled	7.8	7.7	7.8	
Non-for private	83.0	84.3	83.1	
For profit	9.2	8.0	9.1	
Hospital urban–rural designation, %				0.149
Large metropolitan	59.1	60.0	59.1	
Small metropolitan	39.2	38.2	39.2	
Micropolitan	1.6	1.8	1.6	
Non-urban	0.1	0.0	0.1	
Teaching status of urban hospitals, %				0.405
Metropolitan non-teaching	18.0	17.7	18.0	

Continued

Table 2 ***Continued***

Variables	No CTD	CTD	Total	*P*-value
Metropolitan teaching	80.3	80.5	80.3	
Non-metropolitan hospital	1.6	1.8	1.7	
Complications				
Ventilator, %	8.8	9.7	8.8	0.004
Transfusion, %	29.1	35.2	29.3	<0.001
Acute kidney injury, %	17.4	17.6	17.4	0.589
Cardiac tamponade, %	1.3	1.3	1.3	0.940
Cardiac arrest, %	1.9	1.5	1.9	0.011
Cardiogenic shock, %	4.7	3.9	4.7	0.001
Sepsis, %	5.1	4.9	5.1	0.318
Mechanical circulatory support devices, %	38.9	36.9	38.8	<0.001
Outcomes				
In-hospital mortality, %	3.0	2.2	2.9	<0.001
Stroke, %	3.1	2.7	3.1	0.017
30-day readmission outcomes				
Readmission eligible cohort	*N* = 293 682	*N* = 7627	*N* = 301 309	
30-day readmission rate, %	13.3	16.6	13.4	<0.001
Mortality rate in readmission, %	3.0	3.6	3.1	0.110
Readmission for stroke, %	0.3	0.3	0.3	0.309

comparable stroke outcomes [OR of 0.97; 95% (CI): 0.83–1.13, $P = 0.69$] (Central Illustration) (*Figure 2*).

CTD patients had a higher 30-day readmission rate (16.4 vs. 13.6%, $P < 0.001$); and the higher readmission rate was observed in CTD patients undergoing SAVR (16.6 vs. 13.3%, $P < 0.001$); as well as CTD patients undergoing TAVR (16.2 vs. 14.0%, $P < 0.001$) (*Tables 1–3*) (see Supplementary material online, *Figure S2*).

In-hospital complications

In the overall cohort, patients with CTD had similar complication rates with ventilator need (7.5 vs 7.4%, $P = 0.619$); cardiac tamponade (1.1 vs. 1.1%, $P = 0.599$); lower rates of acute kidney injury (14.2 vs. 15.4%, $P < 0.001$); and cardiogenic shock, (2.9 vs. 3.7%, $P < 0.001$) (*Table 1*).

CTD patients undergoing SAVR required more transfusions than non-CTD patients (36.2 vs. 29.1%, $P < 0.001$) and higher rates of ventilator use (9.7 vs. 8.8%, $P = 0.012$). However, CTD patients had lower rates of cardiac arrest (1.5 vs. 1.9%, $P = 0.011$) and cardiogenic shock (3.9 vs. 4.7%, $P = 0.001$) (*Table 2*).

CTD patients undergoing TAVR had similar rates of ventilator use, cardiac tamponade, cardiac arrest, cardiogenic shock, sepsis, and the need for mechanical circulatory support devices compared with non-CTD patients (*Table 3*).

Subgroup analyses

Patients with SLE undergoing SAVR had comparable in-hospital mortality compared with patients without CTD (3.1 vs. 3.0%, $P = 0.778$) and stroke (3.5 vs. 3.1%, $P = 0.270$), while SLE patients undergoing TAVR had similar in-hospital mortality compared with those without CTD (2.6 vs. 2.2%, $P = 0.360$) and similar stroke outcomes compared with patients without CTD (2.5 vs. 2.1%, $P = 0.268$). RA patients had better in-patient mortality outcomes than those without CTD, both in SAVR (1.8 vs. 3.0%, $P < 0.001$) and in TAVR (1.3 vs. 2.2%, $P = 0.002$) (*Table 4*).

When the patients were sub-grouped by the type of AVRs, CTD patients with aortic regurgitation had comparable mortality outcomes both in the SAVR (1.5 vs. 1.8%, $P = 0.446$) and TAVR groups (1.0 vs. 2.1%, $P = 0.311$) to non-CTD patients. Stroke outcomes were also similar between CTD and non-CTD patients in SAVR (2.3 vs. 3.1%, $P = 0.183$) and TAVR (3.1 vs. 1.8%, $P = 0.188$). CTD patients with aortic stenosis undergoing SAVR had lower mortality than non-CTD patients (0.9 vs. 1.8%, $P = 0.004$); however, those undergoing TAVR had comparable outcomes (1.2 vs. 1.4%, $P = 0.223$). Stroke outcomes between CTD and non-CTD groups were comparable regardless of the type of intervention (1.1 vs. 1.7%, $P = 0.084$) in SAVR and (2.1 vs. 1.9%, $P = 0.412$) in TAVR. Patients with CTD and mixed AS and AR had better chances of survival than non-CTD patients undergoing SAVR (2.7 vs. 3.8%, $P < 0.001$) and TAVR (1.9 vs. 3.3%, $P < 0.001$), but stroke outcomes were better in those undergoing SAVR (3.2 vs. 3.8%, $P = 0.02$) but not in those undergoing TAVR (2.0 vs. 2.2%, $P = 0.291$) (*Table 5*).

Temporal trends

Over the study duration, the rate of in-hospital mortality in CTD patients undergoing SAVR was stable from 1.5% in 2012 to 1.6% in 2018 (*P*-trend = 0.209) and the rates in CTD patients undergoing TAVR trended down from 3.3% in 2012 to 0.8% in 2018 (*P*-trend <0.001) (*Figure 3A and 3B*).

The rate of stroke in CTD patients undergoing SAVR was stable (*P*-trend= 0.455). In addition to this, in CTD patients undergoing TAVR, the stroke rate was stable (*P*-trend = 0.172) (*Figure 4A and 4B*).

Table 3 Patients undergoing transcutaneous aortic valve replacement baseline characteristics, demographics, complications, in-hospital outcomes, and 30-day outcomes of patients undergoing transcutaneous aortic valve replacement.

Variables	No CTD	CTD	Total	*P*-value
N	*N* = 223 471	*N* = 8019	*N* = 231 490	
Age, mean (SD)	80.29 (8.46)	78.42 (8.31)	80.23 (8.46)	<0.001
Atrial fibrillation, %	34.3	29.5	34.1	<0.001
Carotid artery disease, %	6.5	6.0	6.5	0.053
Chronic kidney disease stage 3 or higher, %	25.2	21.9	25.1	<0.001
Concomitant mitral valve disease, %	5.6	5.6	5.6	0.835
Coronary artery atherosclerosis, %	68.6	62.7	68.4	<0.001
Diabetes mellitus—uncomplicated, %	19.4	15.9	19.3	<0.001
Diabetes mellitus—with chronic complications, %	15.9	12.6	15.8	<0.001
Dyslipidemia, %	68.1	64.1	68.0	<0.001
Female gender, %	45.4	71.6	46.3	<0.001
Heart failure, %	73.2	73.3	73.2	0.770
Hypertension, %	86.3	85.4	86.2	0.026
Length of hospital stay, median (IQR)	3 (2–7)	3 (2–7)	3 (2–7)	0.532
Obesity, %	16.3	14.6	16.3	<0.001
Prior history of any valve surgery, %	3.5	3.0	3.4	0.044
Prior history of CABG*, %	19.7	11.5	19.4	<0.001
Prior history of myocardial infarction, %	12.3	11.5	12.3	0.038
Prior history of stroke, %	3.7	3.4	3.7	0.104
Pulmonary hypertension, %	19.3	21.9	19.4	<0.001
Smoking, %	35.7	33.0	35.6	<0.001
Protein calorie malnutrition, %	3.0	3.9	3.1	<0.001
Demographics				
Primary expected payer, %				<0.001
Medicare	91.1	91.7	91.1	
Medicaid	1.1	0.8	1.1	
Private insurance	5.8	6.2	5.8	
Self-pay	0.4	0.2	0.4	
No charge	0.0	0.0	0.0	
Other	1.6	1.0	1.6	
Median household income, %				0.415
Quartile 1	20.4	20.6	20.4	
Quartile 2	26.7	26.2	26.7	
Quartile 3	27.3	27.0	27.3	
Quartile 4	25.4	26.0	25.4	
Bed size of hospital, %				0.461
Small	4.4	4.6	4.4	
Medium	18.7	19.1	18.7	
Large	76.9	76.3	76.8	
Control of hospital, %				0.579
Government controlled	8.0	7.7	8.0	
Non-for private	84.4	84.7	84.4	
For profit	7.6	7.6	7.6	
Hospital urban–rural designation, %				<0.001
Large metropolitan	63.1	65.1	63.1	
Small metropolitan	36.1	33.9	36.0	
Micropolitan	0.8	1.0	0.8	
Non-urban	0.0	0.0	0.0	
Teaching status of urban hospitals, %				0.142
Metropolitan non-teaching	10.1	9.7	10.1	
Metropolitan teaching	89.0	89.3	89.0	

Continued

Table 3 ***Continued***

Variables	No CTD	CTD	Total	*P*-value
Non-metropolitan hospital	0.9	1.0	0.9	
Complications				
Ventilator, %	5.5	5.3	5.5	0.452
Transfusion, %	10.7	11.9	10.7	<0.001
Acute kidney injury, %	12.5	10.6	12.4	<0.001
Cardiac tamponade, %	0.8	0.8	0.8	0.799
Cardiac arrest, %	1.6	1.5	1.6	0.695
Cardiogenic shock, %	2.2	1.8	2.2	0.011
Sepsis, %	1.4	1.5	1.4	0.613
Mechanical circulatory support devices, %	1.9	1.5	1.8	0.011
Outcomes				
In-hospital mortality, %	2.2	1.5	2.2	<0.001
Stroke, %	2.1	2.1	2.1	0.749
30-day readmission outcomes				
Readmission eligible cohort	*N* = 198 743	*N* = 7092	*N* = 205 835	
30-day readmission rate, %	14.0	16.2	14.1	<0.001
Mortality rate in readmission, %	3.9	4.2	3.9	0.377
Readmission for stroke, %	0.4	0.3	0.4	0.100

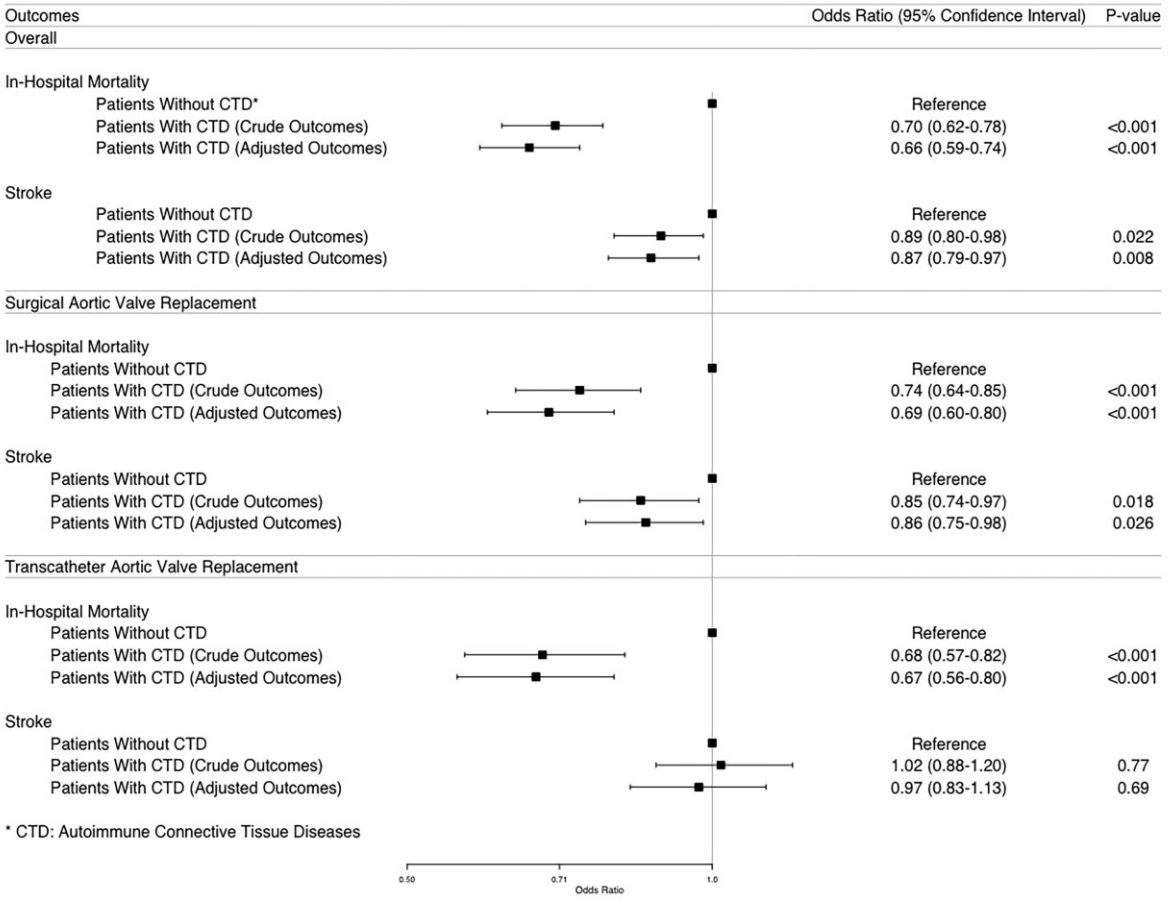


Figure 2 In-hospital outcomes. In-hospital mortality and stroke outcomes unadjusted and adjusted to different baseline characteristics.

Table 4 Outcomes by subtype of auto-immune connective tissue disorder outcomes including in-hospital mortality, and stroke in patients with systemic lupus erythematosus and rheumatoid arthritis compared with patients without autoimmune connective tissues disorders

Variables	Non-CTD	SLE	*P*-value
Mortality			
SAVR	3.0%	3.1%	0.778
TAVR	2.2%	2.6%	0.360
Stroke			
SAVR	3.1%	3.5%	0.270
TAVR	2.1%	2.5%	0.268
	Non-CTD	RA	
Mortality			
SAVR	3.0%	1.8%	<0.001
TAVR	2.2%	1.3%	0.002
Stroke			
SAVR	3.1%	2.5%	0.006
TAVR	2.1%	2.0%	0.828

Table 5 Outcomes by aortic valve pathology outcomes including in-hospital mortality, and stroke in patients with pure aortic regurgitation, pure aortic stenosis, combined aortic regurgitation and aortic stenosis, and bicuspid aortic valve in patients with autoimmune connective tissues disorders compared with patients without autoimmune connective tissues disorders

Variables	No-CTD	CTD	*P*-value
AR	*N* = 61 690	*N* = 1085	
Mortality			
SAVR	1.8%	1.5%	0.446
TAVR	2.1%	1.0%	0.311
Stroke			
SAVR	3.1%	2.3%	0.183
TAVR	1.8%	3.1%	0.188
AS	*N* = 201 060	*N* = 6446	
Mortality			
SAVR	1.8%	0.9%	0.004
TAVR	1.4%	1.2%	0.223
Stroke			
SAVR	1.7%	1.1%	0.084
TAVR	1.9%	2.1%	0.412
Mixed AS+AR	*N* = 284 289	*N* = 8802	
Mortality			
SAVR	3.8%	2.7%	<0.001
TAVR	3.3%	1.9%	<0.001
Stroke			
SAVR	3.8%	3.2%	0.02
TAVR	2.2%	2.0%	0.291
Bicuspid	*N* = 56 456	*N* = 946	
Mortality			
SAVR	1.1%	1.2%	0.728
TAVR	2.4%	1.9%	0.753
Stroke			
SAVR	1.9%	1.3%	0.235
TAVR	2.4%	6.8%	0.006

Discussion

Our study is the most extensive analysis evaluating AVR outcomes in patients with autoimmune CTDs. Our findings show that patients with a CTD did not have worse outcomes than patients without a CTD. Following adjustment for differences in baseline characteristics, subjects with CTD experienced superior overall in-hospital mortality and stroke outcomes regardless of the chosen procedure. However, the clinical relevance of such observed differences may be minimal and overall serve to stress that CTD patients are not at a higher risk compared with their non-CTD counterparts.

The female predominance of the CTD population in our study highlights the unique demographics of CTD patients. Female patients have thus far been under-represented in clinical trials studying AVR.[15] Patients with CTD are considered a higher surgical risk group due to increased background immunosuppression and consequently increased risk of infections and wound-healing complications. Pulmonary and renal involvement of the underlying CTD may also contribute to this observation. The Society of Thoracic Surgeons (STS) score considers immunosuppressive treatment as an independent risk factor in risk assessment.[16] In this real-world dataset of CTD patients, we observed a lower rate of in-hospital mortality and comparable rates of adverse in-hospital complications with AVR even after adjustment for differences in baseline variables. Published literature highlighted CTD as an independent risk factor for delayed healing as well as post-procedural infectious complications, with prior studies showing an increased rate of 30-day re-admission due to infectious complications.[9,17,18]

The dominant aortic lesion in subjects with CTD ranges from isolated aortic stenosis to pure aortic regurgitation, to a mixed disease picture.[19–22] CTD patients suffering from aortic valve disease often suffer from concomitant mitral valve disease, with mitral regurgitation being the most common concomitant valvular lesion in SLE and mitral valve prolapse being common in SSc patients.[23,24]

Although CTD patients have traditionally been noted to be younger than non-CTD patients,[25] we found that the age at the time of the procedure was comparable between the two groups. This suggests that the dominant aortic valve pathological process in CTD patients is similar to that in their non-CTD counterparts. These findings suggest that in the vast majority of patients with CTD, valve choice and the nature of aortic intervention should mirror the population at large.

We observed a significantly lower risk of stroke in CTD patients undergoing TAVR during the index hospitalization and within 30 days. The different rates of stroke in the TAVR group before and after adjustment highlight that patients selected for TAVR had higher rates of confounding comorbidities and shed more light on the conflicting evidence available currently.[9,26–28] The clotting and

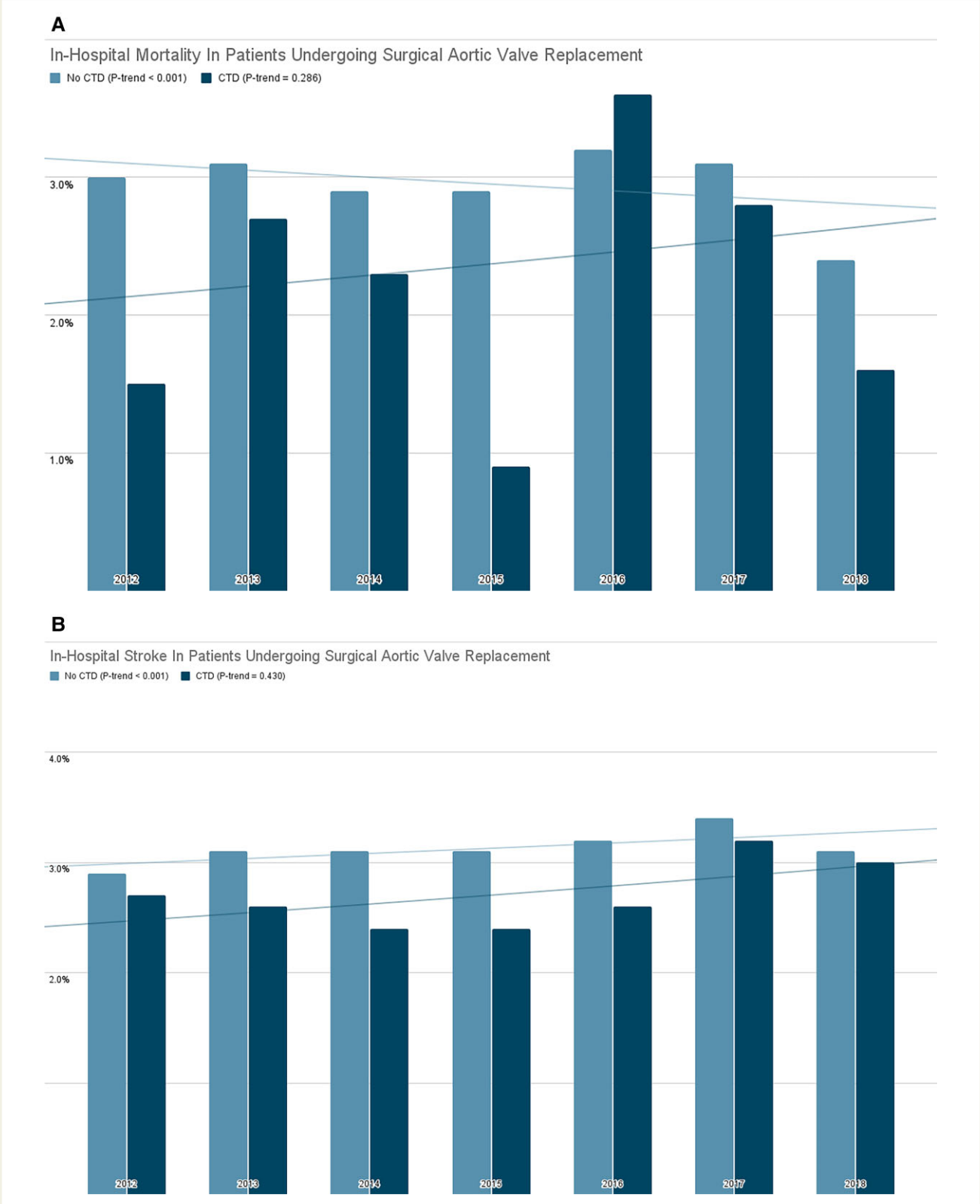


Figure 3 Outcome trends in surgical aortic valve replacement. Temporal trends of (*A*) in-hospital mortality, (*B*) stroke in patients undergoing surgical aortic valve replacement with and without autoimmune connective tissue diseases.

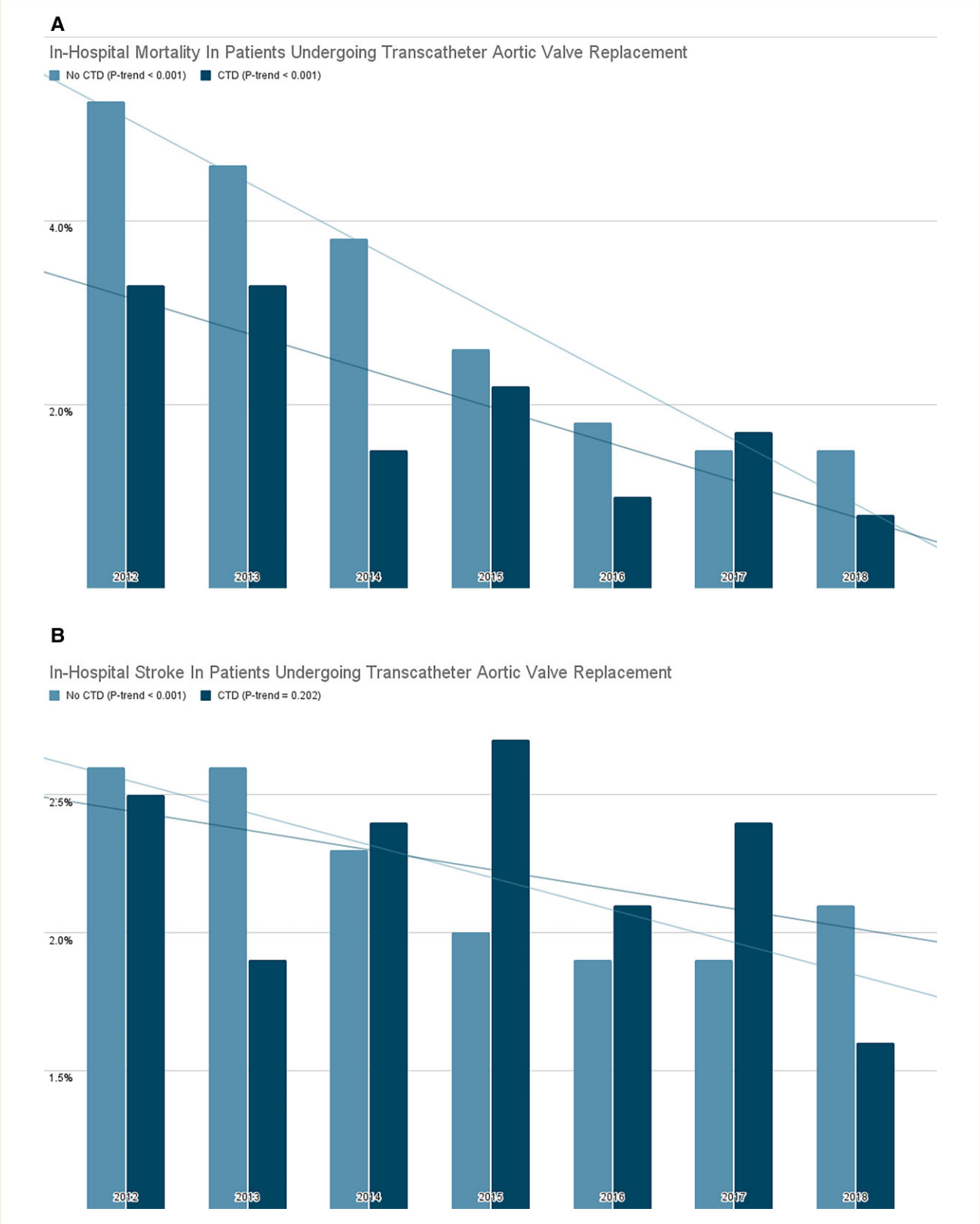


Figure 4 Outcome trends in transcatheter aortic valve replacement. Temporal trends of (*A*) in-hospital mortality, (*B*) stroke in patients undergoing transcatheter aortic valve replacement with and without autoimmune connective tissue diseases.

inflammatory profiles of CTD patients are different from those of their non-CTD counterparts. Thus, investigating the use of cerebral protection devices in this patient population is warranted due to a lack of available evidence.

This study is not without its limitations. Being derived from an extensive database not explicitly established to follow AVR or autoimmune CTD patients, many variables of interest such as other echocardiographic findings, including aortic valve areas, gradients, and ejection fraction; angiographic findings; medications used during hospitalization and chronic immunosuppressive agents; procedural success or failure and outpatient course were not recorded and, thus, could not be evaluated. In addition to this, our dataset lacked significant details regarding surgical risk; most notably, our dataset did not include the score of the STS. While we were able to obtain many significant baseline characteristics about the patient population, we lacked certain important elements, including the lack of specific serological data supporting the diagnosis, which may have led to some of the CTD patients' misdiagnosis on less-specific markers. In addition, disease activity information was limited, given the absence of serologic markers. The dataset also lacked details about heart failure control, i.e. New York Heart Association functional classification, the number of medications used, percent of patients on guideline-directed medical therapy, medication compliance, and symptoms. Additionally, the definition of diseases and procedure relies on the ICD-9 and ICD-10 coding, which may be subject to coding errors as the data were used primarily for billing purposes, allocation bias, and selection bias.[29] Another limitation would be the logistical limits of following patients and tracking them for readmission within the same year and state, thus limiting the examination of readmission outcomes and long-term follow-up. However, using an extensive database gives our current study significant advantages; the large sample size that the NRD provides with approximately 35 million admissions a year enables researchers to obtain a nationally representative sample.

Conclusions

Outcomes for patients with autoimmune CTDs requiring AVR are comparable to their non-CTD counterparts. A comprehensive heart team approach in selecting patients for AVR should consider patients with a CTD for AVR. CTD should be included in a global assessment plan for the patient and not be a primary factor in determining the risk of interventions.

What is known?

- Patients with autoimmune connective tissue diseases (CTDs) have frequent aortic valvular lesions requiring valvular replacement.
- The Society of Thoracic Surgeons (STS) score includes immunosuppressive treatment as an independent risk factor for higher surgical risk.

What is new?

- Irrespective of the aortic valve replacement approach, patients with autoimmune connective tissue diseases (CTDs) did not have worse in-hospital or 30-day outcomes than patients without CTD.

Lead author biography

Heba Wassif, MD, MPH, FACC, is a clinical cardiologist and Director of Inpatient Clinical Cardiology in the Cleveland Clinic main campus. Dr. Wassif earned her medical degree from Cairo University, Cairo, Egypt, and a master's in public health from Johns Hopkins Bloomberg School of Public Health, Baltimore, MD. Dr. Wassif received her specialty training as a general cardiology fellow at The Johns Hopkins Hospital Heart & Vascular Institute, Baltimore, MD, followed by a fellowship in interventional cardiology at Harvard Medical School, Brigham, and Women's Hospital, Boston.

Data availability

The study data are available from the corresponding author upon reasonable request for researchers authorized to access the data by the AHRQ.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Conflict of interest: None declared.

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