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ORIGINAL RESEARCH

VALVULAR HEART DISEASE

Outcomes of Transcatheter Aortic Valve Replacement in Patients With Coexisiting Amyloidosis

Mortality, Stroke, and Readmission

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ABSTRACT

BACKGROUND Cardiac amyloidosis can coexist in patients with severe aortic stenosis. There are limited outcomes data on whether this impacts the risk of transcatheter aortic valve replacement (TAVR).

OBJECTIVES The authors aimed to investigate the effect of amyloidosis on outcomes of TAVR.

METHODS We used the Nationwide Readmissions Database to identify hospitalizations for TAVR between 2016 and 2019. The presence of a diagnosis of amyloidosis was identified. Propensity score-weighted regression analysis was used to identify the association of amyloidosis with in-hospital mortality, acute ischemic stroke, and 30-day readmission rate after TAVR.

RESULTS We identified 245,020 hospitalizations for TAVR, including 273 in patients with amyloidosis. The mean age was 79.4 $\pm$ 8.4 years. There was no difference in in-hospital mortality or 30-day readmission rate in patients with and without amyloidosis (1.8% vs 1.5%, $P = 0.622$; and 12.9% vs 12.5%, $P = 0.858$; respectively). However, there was a higher rate of acute ischemic stroke in patients with amyloidosis (6.2% vs 1.8%, $P < 0.001$). Propensity score-weighted logistic regression analysis showed the presence of amyloidosis was associated with greater odds of acute ischemic stroke (odds ratio: 3.08, 95% CI: 1.41-6.71, $P = 0.005$), but no difference in mortality (odds ratio: 0.79, 95% CI: 0.28-2.27, $P = 0.666$) or 30-day readmission rate after TAVR (HR: 0.72, 95% CI: 0.41-1.25, $P = 0.241$).

CONCLUSIONS This analysis suggests amyloidosis may be associated with a higher thromboembolic risk after TAVR that merits further investigation. (JACC Adv 2023;2:100255) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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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

AF = atrial fibrillation

AL = light chain amyloidosis

AS = aortic stenosis

ATTR = transthyretin amyloidosis

CA = cardiac amyloidosis

CMR = cardiac magnetic resonance

NRD = Nationwide Readmissions Database

TAVR = transcatheter aortic valve replacement

TEE = transesophageal echocardiography

Amyloidosis is a systemic disease characterized by extracellular deposition of misfolded proteins resulting in progressive organ dysfunction.[1] The 2 predominant amyloid proteins causing cardiac amyloidosis (CA) are transthyretin amyloidosis (ATTR) and light chain amyloidosis (AL). They result in myocardial stiffening and thickening, causing a restrictive cardiomyopathy. The increasing use of bone scintigraphy and cardiac magnetic resonance (CMR) has led to increased recognition and diagnosis of ATTR.[2,3] Recent years have drawn attention to the coexistence of CA, mainly ATTR-CA, in 13 to 16% of aortic stenosis (AS) patients presenting for transcatheter aortic valve replacement (TAVR) when diagnostic tools for CA are implemented.[4-7] The diagnosis of CA in these cases is often challenging as characteristic echocardiographic findings of thick left ventricular myocardium can occur with isolated AS alone. Sensitive diagnostic techniques for CA such as bone scintigraphy, CMR imaging, endomyocardial biopsy, and a work-up for abnormal M-protein are not routine assessments for patients that may require TAVR.

There is a paucity of data on whether the presence of amyloidosis impacts procedural and clinical outcomes after TAVR. A systematic review of 4 observational studies suggested the coexistence of CA in patients with AS was associated with a 2-fold greater risk in all-cause mortality after a mean follow-up of 20 months.[8] However, recent single-to-dual center studies that screened for CA before TAVR found the presence of CA was not associated with post-TAVR mortality,[6,9] and mortality was lower after TAVR in both the presence and absence of CA.[6] This was supported by data from a 3-center study that found that post-TAVR survival was not affected by CA.[10] There remains a lack of randomized trial data to support these observations, and the diagnosis of amyloidosis was not captured in the PARTNER (Placement of Aortic Transcatheter Valves) trial.[11] In this analysis, we sought to leverage data from the Nationwide Readmissions Database (NRD) to determine the impact of concomitant CA in patients undergoing TAVR on in-hospital outcomes and 30-day readmission rates postprocedure.

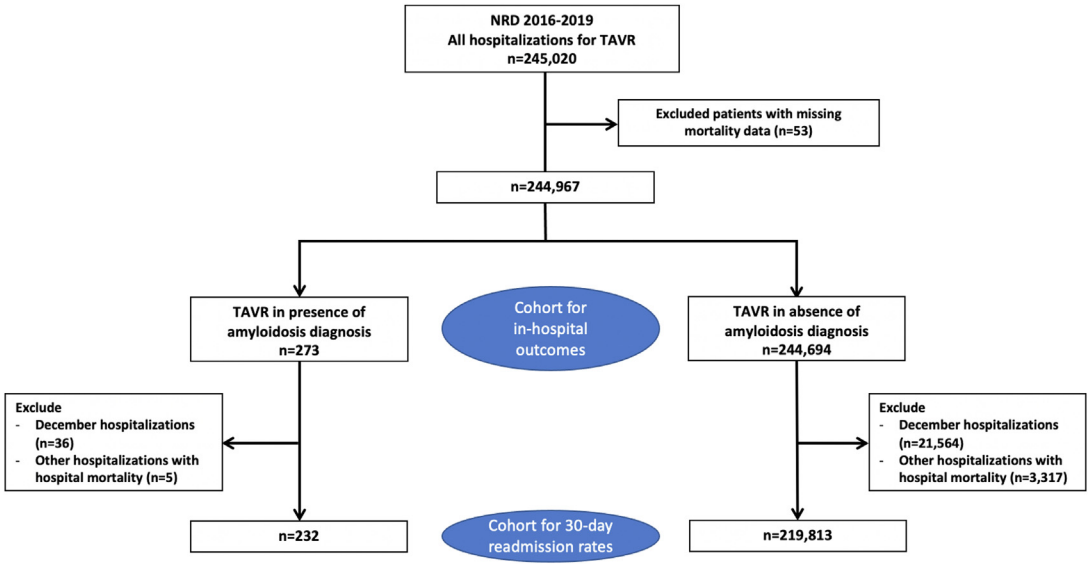
METHODS

DATA SOURCE. We queried the NRD for all hospital discharges in the United States between January 2016 and December 2019. The NRD is part of the Healthcare Cost and Utilization Project created by the Agency for Healthcare Research and Quality.[12] The 2016 to 2019 NRD includes hospital discharge data from 30 States and accounts for 56.6 to 60.4% of all hospitalizations in the United States. All data are publicly available and de-identified, and the analysis was exempt from institutional review board approval.

STUDY POPULATION AND DATA COLLECTION. All hospitalizations for TAVR were identified using the corresponding International Classification of Diseases (ICD)-10-PCS procedure codes (Supplemental Appendix). After exclusion of hospitalizations with missing mortality data, the cohort was categorized according to the presence or absence of any diagnosis of amyloidosis using the ICD-10-CM diagnoses codes E85(.x). These codes were previously used to identify CA when combined with a cardiac diagnosis.[13] The primary cohort was used for analysis of in-hospital mortality and acute ischemic stroke. The ICD-10 CM code used for identifying acute ischemic stroke (I63) was previously validated with a positive predictive value of 92.7%.[14] Seven other hospital adverse events were identified using ICD-10-CM/PCS codes: acute hemorrhagic transformation or stroke (using validated codes I60 and I61),[15] acute myocardial infarction, acute bleeding, acute kidney injury, ventricular arrhythmia, permanent pacemaker implantation, and conversion to surgical valve replacement (Supplemental Appendix). A secondary cohort was identified for analysis of the 30-day readmission rate after exclusion of hospitalizations that resulted in mortality and hospitalizations in the months of December (as the NRD does not cross the calendar year). All baseline medical comorbidities were identified using ICD-10-CM diagnoses codes (Supplemental Appendix).

STATISTICAL ANALYSIS. Baseline characteristics and crude outcomes were compared in patients with and without amyloidosis using the Student's *t*-test for continuous variables and the chi-squared test for categorical variables. Length of hospital stay, a continuous variable with skewed distribution, was compared using the Mann-Whitney *U* test. Using the primary cohort, propensity score-weighted logistic regression analysis was used to generate an odds ratio (OR) for the association of amyloidosis with in-hospital mortality, acute hospital stroke, and other hospital adverse events. Propensity score weighing was done using survey weights, in addition to the following baseline variables: age, sex, prior pacemaker or defibrillator, prior myocardial infarction, prior coronary artery bypass grafting, prior stroke, atrial fibrillation (AF), chronic kidney disease, chronic obstructive lung disease, hypertension, diabetes

FIGURE 1 Flow Diagram of Study Population



Flow diagram of primary cohort for analysis of in-hospital outcomes and secondary cohort for analysis of 30-day readmission rates.
NRD = Nationwide Readmissions Database; TAVR = transcatheter aortic valve replacement.

mellitus, chronic heart failure, insurance, median household income, hospital bed-size, hospital urban-rural location, and hospital teaching status. Matching was done using Kernel matching,[16] where every subject was matched with the weighted average of control subjects, followed by logistic regression analysis. Using the same method, propensity score-weighted linear regression analysis was used to generate a regression coefficient for the association of amyloidosis with hospital length of stay. Using the secondary cohort, propensity score-weighted Cox regression analysis was used to generate a hazard ratio (HR) for the association of amyloidosis with the 30-day readmission rate. For each test, a 2-sided P value of <0.05 was used to indicate statistical significance, and a 95% CI was reported. All statistical analyses were performed using the statistical software Stata (StataCorp, version 16.0), and the weighted values of observations provided by NRD were used.

RESULTS

BASELINE CHARACTERISTICS. We identified 245,020 hospitalizations for TAVR in the United States between 2016 and 2019. After exclusion of hospitalizations with missing mortality data, the primary cohort consisted of 273 TAVR procedures in patients with amyloidosis and 244,694 TAVR procedures in patients without amyloidosis (Figure 1). The mean age was 79.4 ± 8.4 years, and there was a lower percentage of females among patients with amyloidosis (31% vs 44%, $P = 0.001$). Patients with amyloidosis were more likely to have AF and chronic kidney disease, but less likely to have a history of prior coronary artery bypass grafting, hypertension, or diabetes. A higher percentage of TAVR procedures in patients with amyloidosis were performed in large metropolitan areas (81% vs 60%, $P < 0.001$), coinciding with a higher median household income (Table 1).

CRUDE OUTCOMES. There was no difference in in-hospital mortality or 30-day readmission rate in patients with and without amyloidosis who underwent TAVR (1.8% vs 1.5%, $P = 0.622$; and 12.9% vs 12.5%, $P = 0.858$; respectively). However, there was a higher rate of acute ischemic stroke in patients with amyloidosis (6.2% vs 1.8%, $P < 0.001$). There was also a higher rate of acute overall stroke including hemorrhagic transformation/stroke (7.2% vs 1.8%, $P < 0.001$). Rates of other hospital adverse events are outlined in Table 2. In a sub-analysis including only patients who had TAVR on hospital day 0 (greater

TABLE 1 Baseline Characteristics of Patients in TAVR Study Cohort

	Amyloidosis (n = 273)		No Amyloidosis (n = 244,694)		*P* Value[a]
Age, y	79.4 ± 8.6		79.4 ± 8.4		0.948
Female	84	31	110,412	45	**0.001**
Prior pacemaker or defibrillator	45	16	29,433	12	0.075
Prior myocardial infarction	22	8	29,920	12	0.144
Prior coronary artery bypass graft	23	8	43,861	18	**0.002**
Prior stroke	52	19	34,351	14	0.059
Atrial fibrillation	142	52	96,022	39	**0.001**
Chronic kidney disease (subgroup: ESRD)	145 (39)	53 (14)	89,077 (9,389)	36 (4)	**<0.001**
Chronic obstructive lung disease	48	18	57,825	24	0.071
Hypertension	38	14	59,612	24	**0.002**
Diabetes mellitus	69	25	92,672	38	**0.001**
Orthostatic hypotension	4	1.5	1,958	0.8	0.228
Pulmonary hypertension	19	7.0	17,402	7.1	0.996
Chronic heart failure	203	74	178,813	73	0.714
Median household income, quartile	2.9 ± 1.1		2.6 ± 1.1		**<0.001**
Insurance					0.779
Medicare	245	90	220,874	90	
Medicaid	6	2	2,870	1	
Private	17	6	15,333	6	
Self-pay/Other/Missing data	5	2	5,617	2	
Hospital bedsize					0.333
Small	6	2	11,615	5	
Medium	56	21	52,844	21	
Large	211	77	180,235	74	
Hospital urban-rural location					**<0.001**
Large metropolitan area	222	81	146,571	60	
Small metropolitan area	48	18	95,743	39	
Nonmetropolitan	3	1	2,380	1	
Hospital teaching status					0.135
Metropolitan nonteaching	14	5	25,853	11	
Metropolitan teaching	256	94	216,461	88	
Nonmetropolitan	3	1	2,380	1	

Values are n () or mean ± SD. $P < 0.05$ resembling statistical significance are in **bold**. [a]*P* value is based on the chi-squared test for categorical variables and the Student's *t*-test for continuous variables.

ESRD = end-stage renal disease; TAVR = transcatheter aortic valve replacement.

likelihood that timing of stroke was after TAVR), there was a similar higher rate of acute ischemic stroke in patients with amyloidosis (5.5% vs 1.6%, $P = 0.002$).

ADJUSTED OUTCOMES. Propensity score-weighted logistic regression analysis showed the presence of amyloidosis was not associated with any difference in-hospital mortality (OR: 0.79, 95% CI: 0.28-2.27, $P = 0.666$) or 30-day readmission rate after TAVR (HR: 0.72, 95% CI: 0.41-1.25, $P = 0.241$). However, the presence of amyloidosis was associated with higher acute ischemic stroke during hospitalization (OR: 3.08, 95% CI: 1.41-6.71, $P = 0.005$) (Figure 2). This association persisted in the sub-analysis which only included patients who had TAVR on hospital day 0 (OR: 3.31, 95% CI: 1.38-7.90, $P = 0.007$).

DISCUSSION

In this observational analysis including 273 TAVR hospitalizations in patients with severe AS and a concomitant diagnosis of amyloidosis, we found no difference in in-hospital mortality or 30-day readmission rate after TAVR compared to patients with lone AS. The presence of amyloidosis was, however, associated with an approximate 3-fold greater odds of developing acute ischemic stroke during hospitalization (Central Illustration).

TABLE 2 Unmatched Outcomes in Patients With and Without Amyloidosis Who Underwent TAVR

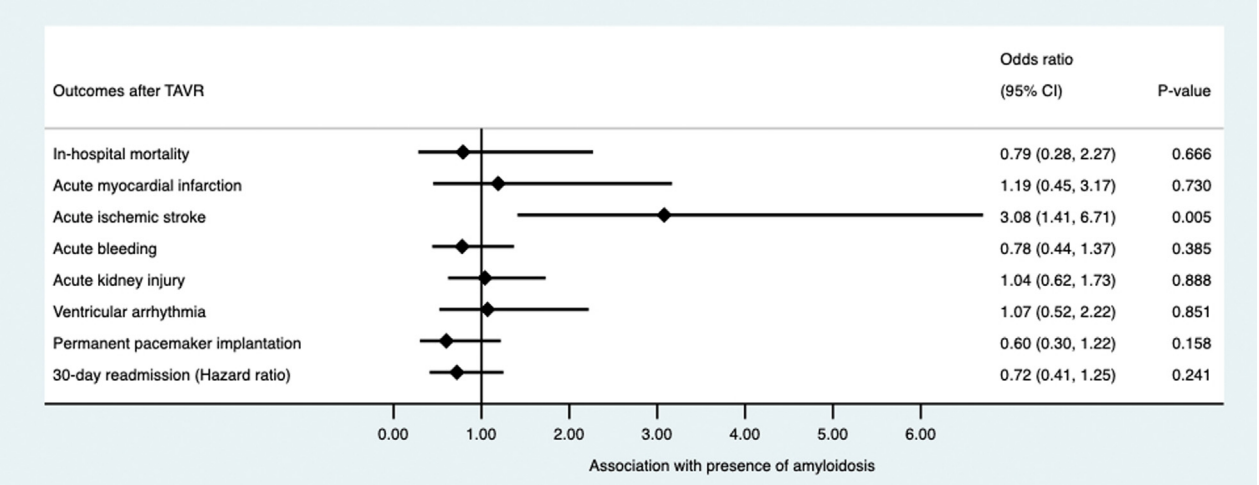
In-Hospital Outcomes	Amyloidosis (n = 273)		No Amyloidosis (n = 244,964)		*P* Value[a]
Mortality	5	1.8	3,621	1.5	0.622
Acute stroke	20	7.2	4,447	1.8	**<0.001**
Ischemic stroke	17	6.2	4,334	1.8	**<0.001**
Hemorrhagic transformation or stroke	8	2.9	212	0.1	**<0.001**
Acute myocardial infarction	10	3.7	5,634	2.3	0.189
Acute bleeding	33	12.1	35,479	14.5	0.430
Acute kidney injury	46	16.8	25,212	10.3	**0.007**
Ventricular arrhythmia	17	6.2	8,816	3.6	**0.042**
Permanent pacemaker implantation	18	6.6	19,974	8.2	0.367
Conversion to surgical replacement	0		185	0.1	0.773
Length of hospital stay, days	3 (1-8)		2 (1-5)		**0.004**
30-d Readmission Rate	**Amyloidosis (n = 232)**		**No Amyloidosis (n = 219,813)**		***P* Value**
All-cause readmission	30	12.9	27,250	12.4	0.858

Values are n () or median (IQR). $P < 0.05$ resembling statistical significance are in **bold**. [a]*P* value is based on the chi-squared test for categorical variables and the Mann-Whitney *U* test for continuous variables.

IQR = interquartile range; TAVR = transcatheter aortic valve replacement.

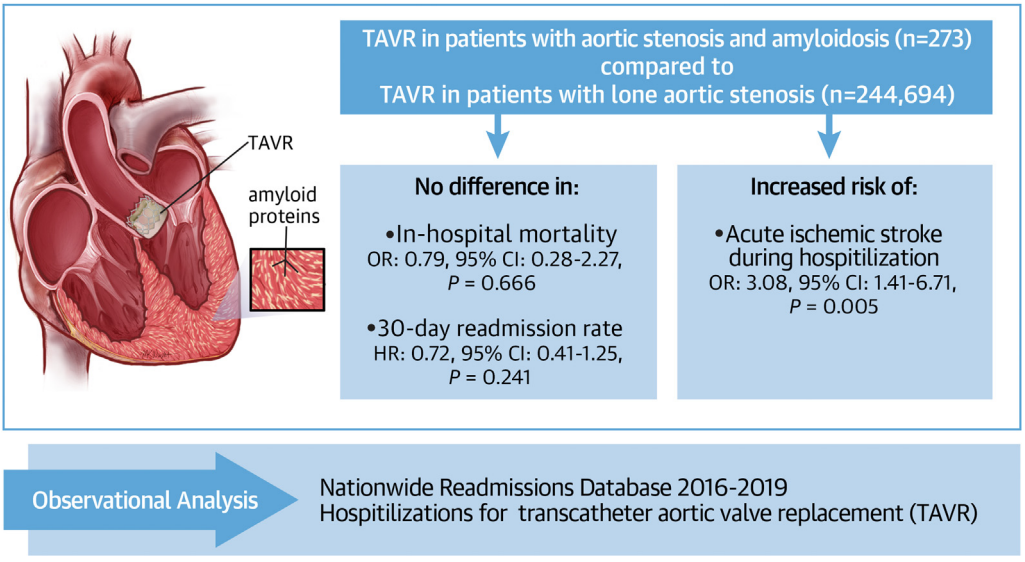
The current literature reports an expected prevalence of CA in 13% to 16% of patients presenting for TAVR, based on small studies that used bone scintigraphy to screen for ATTR-CA.[4-7] The prevalence of AL-CA, as identified by free light chain measurement and CMR, is much lower and accounts for <1% of TAVR recipients.[9] The overall lower prevalence of amyloidosis in this NRD analysis may be related to either underdiagnosis of CA (as bone scintigraphy is not routinely used in pre-TAVR work-up) or

FIGURE 2 Association of Amyloidosis With Outcomes After TAVR



Association of amyloidosis with in-hospital outcomes and 30-day readmission rate after TAVR. Propensity score-weighted logistic regression analysis was used to generate OR for in-hospital outcomes, and Cox proportional hazards regression analysis was used to generate a HR for 30-day readmission rate.

CENTRAL ILLUSTRATION **Procedural Outcomes After TAVR in Dual Aortic Stenosis-Amyloidosis Pathology**



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under-reporting (as ATTR and AL-specific ICD10 codes only started in 2018). The higher percentage of TAVR procedures in patients with amyloidosis in large metropolitan areas may be due to restriction of the procedure to large medical centers with, perhaps, more experienced practitioners.

In general, the limited available literature supports the idea that the presence of concurrent CA with severe AS does not impact the risk of mortality after TAVR. This has been demonstrated in recent studies that screened for ATTR-CA before TAVR.[6,7,9,10] However, there is a paucity of randomized multicenter data to support this. In one retrospective study, CA was associated with higher mortality in patients with severe AS, however a high percentage of patients had low-flow AS physiology and only 44% received TAVR.[17] It is possible that although CA may increase mortality in patients with severe AS,[8] TAVR may improve outcomes regardless of the presence of CA.[6] This analysis supports the current limited data that short-term mortality and readmission after TAVR is not affected by the presence of amyloidosis.

The pathophysiology behind the observed higher ischemic stroke risk in patients with CA after TAVR is multifactorial and possibly reflects the higher cardioembolic risk in patients with amyloidosis. On one hand, patients with CA have a higher prevalence of AF, likely due to impaired ventricular relaxation and elevated filling pressures causing atrial dilation.[18] AF is prevalent in between 40% and 71% of patients with wild-type ATTR-CA,[19,20] and is reported in 52% of amyloidosis patients in this study cohort. However, it is likely that myocardial amyloid infiltration of the bilateral atria and atrial dysfunction predisposes to intracardiac thrombi irrespective of AF.[21,22] An autopsy study of amyloid hearts showed the prevalence of intracardiac thrombi was 33%, with higher frequency and more fatal embolic events in AL-CA despite the lower prevalence of AF.[23] These thrombi were found predominantly in the right and left atria and atrial appendages, and the presence of AF was independently associated with the risk of thromboembolism.[23] Similar incidences of intracardiac thrombi (22%-30%) were identified in CA patients using transesophageal echocardiography (TEE).[24-26] The high incidence of intracardiac thrombi in patients with CA might explain the higher acute ischemic stroke risk after TAVR in this analysis, which was present even after adjusting for AF and other risk factors for stroke.

Whether any specific precautions peri-TAVR can help reduce procedural stoke risk in patients with CA deserves to be further studied. There is lack of randomized data on the benefits of cerebral embolic protection devices in general.[27] Anticoagulation may not be a simple answer, as patients with systemic amyloidosis may have associated cerebral amyloid angiopathy and carry a risk of intracerebral hemorrhage,[28] although this does not necessarily apply to ATTR-CA. A high percentage of patients

with CA and AF also have intracardiac thrombi on TEE despite being on anticoagulation,[25,26] and the incidence of thrombi does not seem to correlate with CHA2DS2-VASc score.[26,29] Current expert opinion recommends anticoagulation for patients with CA and AF irrespective of CHA2DS2-VASc score, and TEE before cardioversion irrespective of anticoagulation status.[30] However, there are currently no specific peri-TAVR anticoagulation recommendations for patients with CA, and the latest 2020 American College of Cardiology/American Heart Association guidelines place a general Class IIb recommendation for either dual antiplatelet therapy or anticoagulation for the first 3 months after TAVR for patients with low bleeding risk.[31] It is also unclear if medical therapy with TTR stabilizers or therapies that suppress TTR production in patients with ATTR-CA would impact their periprocedural stroke risk.

There are several limitations to this study. It is a retrospective analysis with reliance on administrative data and ICD codes for systemic amyloidosis. It does not specify amyloid type or extent of organ involvement, although systemic amyloidosis codes have been previously used in epidemiological studies to correlate with CA when used with a cardiac diagnosis.[2,13] ATTR and AL-specific ICD codes were only introduced in 2018 and are likely both under-reported and underdiagnosed. The prevalence of amyloidosis was low compared with current literature reports, possibly due to ascertainment bias. There is no imaging data as pertains to echocardiographic, CMR, or bone scintigraphy findings. There is also no data collected on antiplatelet or anticoagulant therapy, or procedural details as procedure time, number of pacing runs, number of post-dilations and use of emboli-prevention devices which could impact procedural stroke risk.[32] The observed higher stroke risk in patients with amyloidosis may be due to a referral bias for these patients for being in a later stage in their disease, or due to concomitant comorbidities that were not included in the multivariable analyses. Overall, the observational findings of this analysis are at best hypothesis generating and need to be interpreted within the context of the small number of CA cases and limitations of the NRD. However, the observed higher stroke risk post-TAVR attributed to CA highlights the potential for a greater thromboembolic risk that merits further investigation.

CONCLUSIONS

In this observational analysis, TAVR in dual AS-amyloidosis pathology was associated with a higher risk of acute stroke compared to lone AS, but no difference in in-hospital mortality or 30-day readmission rates. This suggests a potential association with a higher thromboembolic risk after TAVR that merits further investigation.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE: In this nationwide observational analysis, TAVR in dual AS-amyloidosis pathology was associated with a higher risk of acute ischemic stroke after TAVR compared to lone AS. There was no difference in in-hospital mortality or 30-day readmission rates.

TRANSLATIONAL OUTLOOK: The observed higher risk of stroke highlights the potential for greater thromboembolic risk after TAVR that deserves to be further studied.

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