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Late Cardiac Death in Patients Undergoing Transcatheter Aortic Valve Replacement

Incidence and Predictors of Advanced Heart Failure and Sudden Cardiac Death

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ABSTRACT

BACKGROUND Little evidence exists of the burden and predictors of cardiac death after transcatheter aortic valve replacement (TAVR).

OBJECTIVES The purpose of this study was to assess the incidence and predictors of cardiac death from advanced heart failure (HF) and sudden cardiac death (SCD) in a large patient cohort undergoing TAVR.

METHODS The study included a total of 3,726 patients who underwent TAVR using balloon (57%) or self-expandable (43%) valves. Causes of death were defined according to the Valve Academic Research Consortium-2.

RESULTS At a mean follow-up of 22 ± 18 months, 155 patients had died due to advanced HF (15.2% of total deaths, 46.1% of deaths from cardiac causes) and 57 had died due to SCD (5.6% of deaths, 16.9% of cardiac deaths). Baseline comorbidities (chronic obstructive pulmonary disease, atrial fibrillation, left ventricular ejection fraction ≤40%, lower mean transaortic gradient, pulmonary artery systolic pressure >60 mm Hg; $p < 0.05$ for all) and 2 procedural factors (transapical approach, hazard ratio [HR]: 2.38, 95% confidence interval [CI]: 1.60 to 3.54; $p < 0.001$; presence of moderate or severe aortic regurgitation after TAVR, HR: 2.79, 95% CI: 1.82 to 4.27; $p < 0.001$) independently predicted death from advanced HF. Left ventricular ejection fraction ≤40% (HR: 1.93, 95% CI: 1.05 to 3.55; $p = 0.033$) and new-onset persistent left bundle-branch block following TAVR (HR: 2.26, 95% CI: 1.23 to 4.14; $p = 0.009$) were independently associated with an increased risk of SCD. Patients with new-onset persistent left bundle-branch block and a QRS duration >160 ms had a greater SCD risk (HR: 4.78, 95% CI: 1.56 to 14.63; $p = 0.006$).

CONCLUSIONS Advanced HF and SCD accounted for two-thirds of cardiac deaths in patients after TAVR. Potentially modifiable or treatable factors leading to increased risk of mortality for HF and SCD were identified. Future studies should determine whether targeting these factors decreases the risk of cardiac death. (J Am Coll Cardiol 2015;65:437–48) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AR = aortic regurgitation

AVB = atrioventricular block

HF = heart failure

LBBB = left bundle-branch block

LVEF = left ventricular ejection fraction

NOP = new-onset persistent

PASP = pulmonary artery systolic pressure

PPM = permanent pacemaker

SCD = sudden cardiac death

TAVR = transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) improves survival in patients with symptomatic aortic stenosis who are deemed to be at high or prohibitive surgical risk (1). However, in initial studies, approximately 1 of 4 patients died during the first year following TAVR despite relief of the valvular obstruction, highlighting the need to improve patient selection (2). Such efforts have reduced overall mortality after TAVR (3), mainly due to decreased incidence of noncardiac death, without significant changes in the cardiac death rate.

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The persistent risk of death from advanced heart failure (HF) and sudden cardiac death (SCD) in patients undergoing surgical aortic valve replacement (SAVR), the most common modes of death following SAVR, has long been of concern (4–7). Some studies suggested that the risks of cardiac death and SCD are increased by potentially treatable factors, such as new conduction disturbances (4,6,8,9). Although there is little evidence of the burden of death from advanced HF and SCD in patients undergoing TAVR, both accounted for approximately three-fourths of cardiac deaths in some previous studies (10–12). However, their predictors remain largely unknown. More importantly, whether potentially treatable or modifiable factors might increase the risk of death from HF and SCD after TAVR has not yet been elucidated. The objective of this study was, therefore, to assess the incidence and predictors of death from advanced HF and SCD in patients undergoing TAVR.

METHODS

STUDY POPULATION. The study included 3,726 total patients who underwent TAVR in 18 centers in North America, South America, and Europe. The indications for TAVR and approach were assessed by each center's heart team, and TAVR procedures were performed as described (1), with data prospectively collected in a dedicated database in each center. Clinical outcomes were defined according to VARC (Valve Academic Research Consortium)-2 criteria (2).

ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHY DATA. Twelve-lead electrocardiography (ECG) tracings were recorded at least at baseline, immediately after the procedure, and at hospital discharge. ECGs at baseline and at hospital discharge were obtained in 95% of patients. American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recommendations for standardization and interpretation of the electrocardiogram (13) were the basis for diagnosis of intraventricular conduction abnormalities. New-onset persistent (NOP) left bundle-branch block (LBBB) was defined as a new LBBB in a patient without a prior permanent pacemaker (PPM), which persisted at hospital discharge or until death. Primary analyses excluded patients who developed new-onset LBBB and required PPM implantation during the hospitalization period. In a supplementary analysis, patients were classified into 3 groups: NOP-LBBB (no pacemaker); new-onset persistent LBBB and pacemaker during hospitalization (NOP-LBBB-PPM); and no NOP-LBBB. A PPM was implanted if third-degree or advanced second-degree atrioventricular block (AVB) occurred at any anatomical level and was not expected to resolve, or in the presence of sinus node dysfunction and documented symptomatic bradycardia, in agreement with current recommendations (14). In the presence of new-onset LBBB with PR interval prolongation

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(>200 ms) or very wide QRS (>150 ms) not expected to normalize, indication for PPM was at the physician's discretion.

Experienced echocardiographers at each center analyzed echocardiograms. The degree of aortic regurgitation (AR) was classified according to the VARC-2 criteria (2). Left ventricular ejection fraction (LVEF) was calculated using Simpson's rule.

FOLLOW-UP. Follow-up was by telephone and/or outpatient clinic visits at 1 month after TAVR, at 1 year, and yearly thereafter. Complete follow-up was achieved in 95.9% of patients (4.1% of the study population was lost to follow-up).

DEFINITION OF CAUSES OF DEATH. Causes of death were obtained by scrutinizing medical charts and by telephone calls or interviews with families and physicians. Civil registries were consulted when necessary. Cardiovascular death was defined according to VARC-2 criteria. Any death attributable to a proximate cardiac cause or death of an unknown cause was classified as cardiac death. SCD was defined, in accordance with the World Health Organization definition, as a death occurring within 1 h of symptom onset if witnessed or within the previous 24 h if unwitnessed. Patients with known terminal disease or an identifiable noncardiac etiology of

TABLE 1 Baseline Clinical Characteristics, Procedural Findings, and 30-Day Outcomes of the Study Population (N = 3,726)

Clinical characteristics and electrocardiographic findings	
Age, yrs	81 ± 8
Male	1,866/3,718 (50.2)
Body mass index, kg/m^2	27 ± 5
NYHA functional class ≥III	2,740/3,668 (74.7)
Hypertension	2,854/3,704 (77.1)
Diabetes mellitus	1,118/3,706 (30.2)
COPD	955/3,685 (25.9)
eGFR <60 ml/min	1,864/3,638 (51.2)
Coronary artery disease	1,987/3,705 (53.6)
Complete or no need of revascularization	2,216/3,349 (66.2)
Paroxysmal/chronic AF	1,093/3,628 (30.1)
Pre-existing LBBB	330/3,540 (9.3)
Prior pacemaker	415/3,710 (11.2)
Logistic EuroSCORE, %	19.4 ± 13.0
Echocardiographic findings	
LVEF ≤40%	682/3,657 (18.6)
Mean transaortic gradient, mm Hg	47 ± 17
PASP >60 mm Hg	376/2,748 (13.7)
Procedural findings	
Approach	
Transfemoral	2,958/3,713 (79.7)
Transapical	607/3,713 (16.3)
Transaortic	69/3,713 (1.9)
Subclavian	79/3,713 (2.1)
Prosthesis type	
Self-expandable	1,559/3,717 (43.0)
Balloon-expandable	2,118/3,717 (57.0)
Moderate or severe AR	374/3,407 (11.0)
30-day outcomes	
Death	271 (7.3)
Stroke	114/3,666 (3.1)
Myocardial infarction	52/3,287 (1.6)
Major or life threatening bleeding	479/3,480 (13.8)
NOP-LBBB	471/3,539 (13.3)
PPM implantation	536/3,666 (14.6)

Values are mean ± SD or n (%).

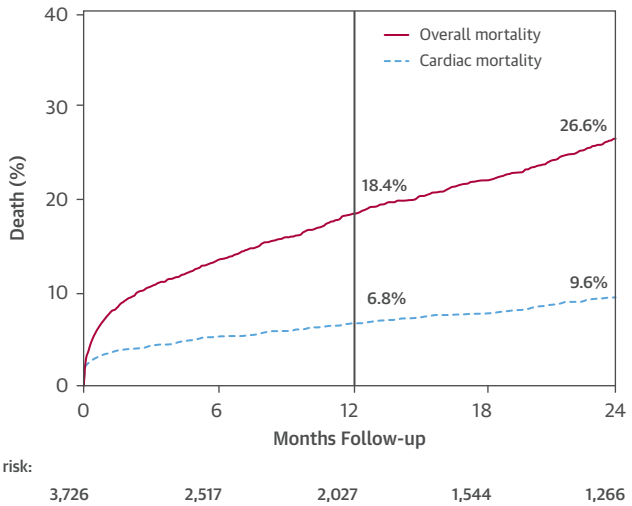
AF = atrial fibrillation; AR = aortic regurgitation; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration ratio; LBBB = left bundle-branch block; LVEF = left ventricular ejection fraction; NOP-LBBB = new-onset persistent left bundle-branch block; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PPM = permanent pacemaker.

TABLE 2 Causes of Cardiovascular Death After Transcatheter Aortic Valve Implantation (N = 663)

Cardiac death	336 (50.7)
Advanced heart failure	155 (23.4)
Sudden cardiac death	57 (8.6)
Myocardial infarction	32 (4.8)
Endocarditis	17 (2.6)
Other procedure-related cardiac complications	75 (11.3)
Noncoronary vascular related death	69 (10.4)
Other procedure-related complications	163 (24.6)
Unknown	95 (14.3)

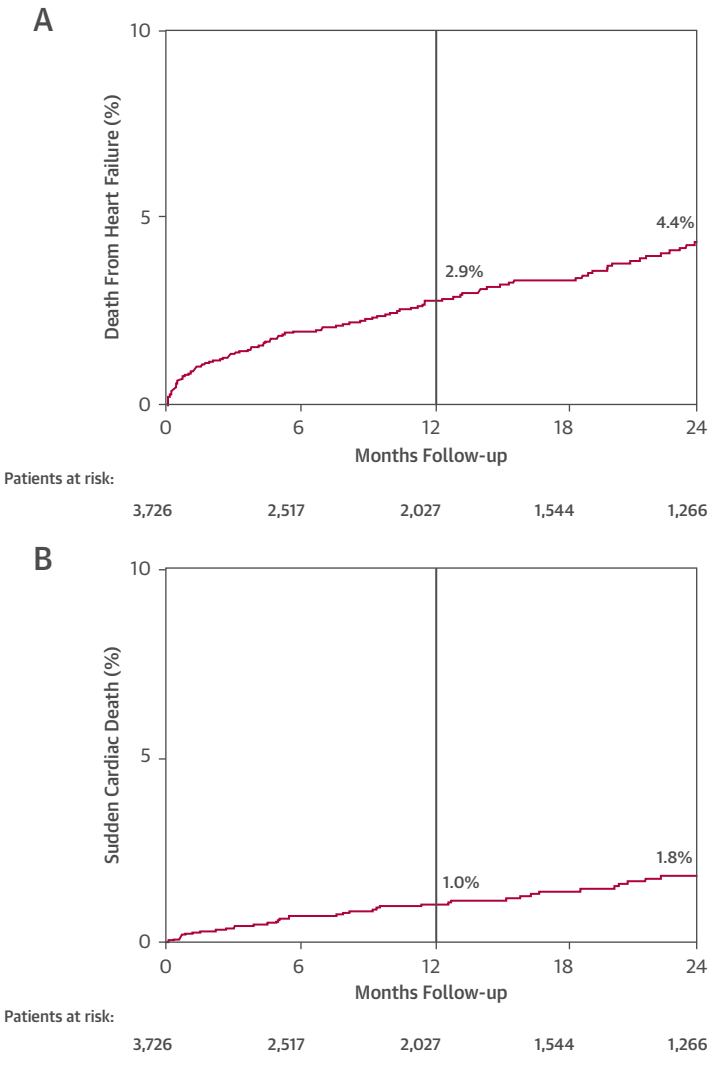
Values are n (%).

FIGURE 1 Rates of Overall and Cardiac Mortality



Kaplan-Meier curves at 2-year follow-up for overall and cardiac mortality in the study population.

FIGURE 2 Rates of Death From Advanced Heart Failure and Sudden Cardiac Death



Kaplan-Meier curves at 2-year follow-up for death from advanced heart failure **(A)** and sudden cardiac death **(B)**.

sudden death were not considered to have experienced SCD (15).

STATISTICAL ANALYSIS. Qualitative variables are expressed as n (percentage) and quantitative variables as mean ± SD. Survival rates were summarized using Kaplan-Meier estimates, and log-rank tests were used to perform comparisons between groups. Predictors of death from HF and SCD were analyzed using univariate and multivariate proportional hazard models (cumulative outcomes). Hazard proportional assumption was evaluated by means of log-minus-log survival plots. A Fine-Gray Cox model was constructed to account for death from other causes as a competing risk event for death from HF and SCD. Variables with p values <0.10 in the univariate analyses were included in the multivariate analysis. All univariate analyses were performed on complete cases.

Overall, 3.4% of data were missing, and 23.4% of patients had missing data for at least 1 variable. Missing data were assumed to be random and were dealt with through the multiple imputation procedure using the Markov Chain Monte Carlo method. Ten imputed datasets were created, and results were pooled according to Rubin's protocol (16). Multivariate models using complete-case analyses were also performed. The optimal cutoff value for QRS duration to predict SCD in patients with NOP-LBBB was defined using receiver-operating characteristic curves and the maximum Youden's index (sensitivity + specificity − 1) (17). Results with p values <0.05 were considered significant. Statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, North Carolina) and the Statistical Package for Social Sciences version 20 (SPSS Inc., IBM, Armonk, New York).

RESULTS

Table 1 shows the main clinical characteristics, echocardiographic and procedural findings, and 30-day outcomes of the study population. The mean age of the study population was 81 ± 8 years, and 50.2% of patients were males. The mean logistic EuroSCORE was 19.4 ± 13.0%. Balloon- and self-expandable valves were used in 57% and 43% of patients, respectively, and TAVR was performed through the transfemoral route in 79.7% of patients and the transapical route in 16.3%. After TAVR, moderate to severe AR was observed in 374 patients (11.0%) and NOP-LBBB occurred in 471 patients (13.3%). At 30 days after TAVR, mortality and stroke rates were 7.3% and 3.1%, respectively.

INCIDENCE OF DEATH FROM ADVANCED HF AND SCD. At a mean follow-up of 22 ± 18 months, 1,022 patients (27.4%) had died, 663 (17.8%) from cardiovascular causes. Cardiac death was confirmed in 336 patients (33.0% of deaths). Table 2 shows causes of cardiovascular death in the study population. Cumulative rates of overall mortality and cardiac mortality at 2-year follow-up were 26.6% (95% confidence interval [CI]: 25.3% to 28.8%) and 9.6% (95% CI: 8.4% to 10.8%), respectively (Figure 1). Death from advanced HF occurred in 155 patients (4.2%), accounting for 15.2% of total deaths and 46.1% of cardiac deaths. Cumulative rates of death from advanced HF at 1- and

2-year follow-up were 2.9% (95% CI: 2.3% to 3.5%) and 4.4% (95% CI: 3.7% to 5.2%), respectively (Figure 2A). A total of 57 patients died from SCD (5.6%, 16.9% of cardiac deaths), and the cumulative rates of SCD at 1- and 2-year follow-up were 1.0% (95% CI: 0.6% to 1.4%) and 1.8% (95% CI: 1.2% to 2.4%), respectively (Figure 2B).

PREDICTORS OF DEATH FROM ADVANCED HF. Table 3 shows predictors of death from advanced HF. In the multivariate analysis, baseline characteristics such as chronic obstructive pulmonary disease (hazard ratio [HR]: 1.59, 95% CI: 1.11 to 2.29; p = 0.012), pre-existing paroxysmal or chronic atrial fibrillation (HR: 2.33, 95% CI: 1.62 to 3.35; p < 0.001), LVEF ≤40% (HR: 1.68, 95% CI:1.10 to 2.56; p = 0.017), a lower mean transaortic gradient (HR: 1.11, 95% CI: 1.02 to 1.22; p = 0.040 per 10-mm Hg decrease), pulmonary artery systolic pressure [PASP] >60 mm Hg (HR: 1.99, 95% CI: 1.21 to 3.28; p = 0.007), and 2 procedural factors such as the use of the transapical route (HR: 2.38, 95% CI: 1.60 to 3.54; p < 0.001) and the presence of moderate or severe AR after TAVR (HR: 2.79, 95% CI: 1.82 to 4.27; p < 0.001) were associated with increased risk of death from advanced HF. The same predictors were found using complete-case analysis. When death from other causes was considered as a competing risk event, pre-existing paroxysmal or chronic atrial fibrillation (HR: 1.88, 95% CI: 1.34 to 2.64; p < 0.001), LVEF ≤40% (HR: 1.49, 95% CI: 1.00 to 2.26; p = 0.050), PASP >60 mm Hg (HR: 1.90, 95% CI: 1.22 to 2.96; p = 0.005), use of the transapical route (HR: 2.24, 95% CI: 1.54 to 3.26; p < 0.001), and the presence of moderate or severe AR after TAVR (HR: 2.10, 95% CI: 1.42 to 3.14; p < 0.001) were also independent predictors of death from HF.

Figure 3 shows rates of death from HF at 2-year follow-up according to use of the transapical approach and the presence of moderate or severe AR after TAVR. Online Table 1 displays differences between approach groups in baseline clinical characteristics, echocardiographic and procedural findings, and 30-day outcomes. After adjusting for these differences, the transapical approach remained an independent predictor of death from advanced HF (HR: 1.86, 95% CI: 1.20 to 2.86; p = 0.001).

Among the 374 patients with moderate or severe AR after TAVR, 135 patients (36.1%) had died at last follow-up, 25 (6.7%) due to advanced HF. A lower mean transaortic gradient (HR: 1.35, 95% CI: 1.04 to 1.85; p = 0.040 per 10-mm Hg decrease) and a PASP >60 mm Hg (HR: 3.06, 95% CI: 1.14 to 8.22; p = 0.027) were independent echocardiographic predictors of death from HF in these patients, whereas the presence of moderate or severe AR before TAVR (HR: 0.24, 95% CI: 0.07 to 0.83; p = 0.025) was an independent protective factor (Table 4).

In the subgroup of patients with LVEF ≤40% (n = 682), moderate or severe prosthesis-patient mismatch was not associated with an increased risk of death from HF (HR: 0.94, 95% CI: 0.42 to 2.09; p = 0.937).

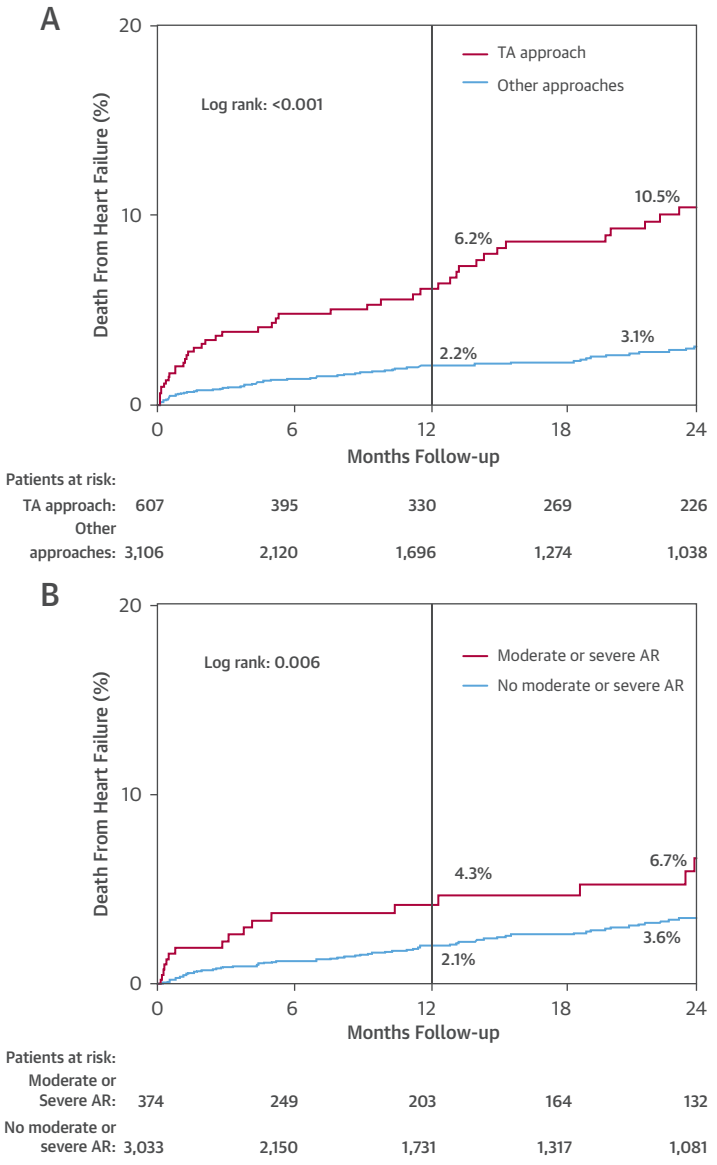
PREDICTORS OF SCD. Table 5 shows the predictors of SCD. An LVEF ≤40% before TAVR (HR: 1.93, 95% CI: 1.05 to 3.55; p = 0.033) and the occurrence of NOP-LBBB (HR: 2.26, 95% CI: 1.23 to 4.14; p = 0.009) were independently associated with an increased risk of SCD. The same predictors were found using complete-case analysis. When considering death from

TABLE 3 Univariate and Multivariate Predictors of Terminal Heart Failure Following TAVR

	Univariate HR (95% CI)	p Value	Multivariate HR* (95% CI)	p Value
Clinical characteristics and electrocardiographic findings				
Age, yrs	1.02 (0.99–1.04)	0.162		
Male	1.22 (0.90–1.67)	0.225		
Body mass index, kg/m^2	0.98 (0.94–1.01)	0.134		
NYHA functional class ≥III	1.75 (1.12–2.73)	0.014	1.19 (0.72–1.96)	0.502
Hypertension	1.33 (0.88–2.02)	0.176		
Diabetes mellitus	1.01 (0.71–1.44)	0.939		
COPD	1.54 (1.10–2.15)	0.011	1.59 (1.11–2.29)	0.012
eGFR <60 ml/min	1.36 (0.98–1.91)	0.058	0.64 (0.29–1.37)	0.248
Coronary artery disease	1.36 (0.98–1.87)	0.066	1.04 (0.61–1.77)	0.891
Complete or no need of revascularization	0.66 (0.47–0.92)	0.015	1.01 (0.59–1.71)	0.985
Paroxysmal/chronic AF	2.58 (1.87–3.56)	<0.001	2.33 (1.62–3.35)	<0.001
Pre-existing LBBB	0.73 (0.38–1.38)	0.329		
Prior pacemaker	1.60 (1.04–2.46)	0.031	0.87 (0.54–1.40)	0.564
Echocardiographic findings				
LVEF ≤40%	1.87 (1.31–2.66)	0.001	1.68 (1.10–2.56)	0.017
Mean transaortic gradient (mm Hg)†	1.22 (1.11–1.35)	<0.001	1.11 (1.02–1.22)	0.040
PASP >60 mm Hg	1.85 (1.22–2.80)	0.004	1.99 (1.21–3.28)	0.007
Procedural findings				
Transapical approach	3.16 (2.29–4.38)	<0.001	2.38 (1.60–3.54)	<0.001
Balloon-expandable prosthesis type	2.72 (1.88–3.94)	<0.001	1.06 (0.55–2.06)	0.854
Moderate or severe AR	1.83 (1.19–2.84)	0.006	2.79 (1.82–4.27)	<0.001
30-day outcomes				
Stroke	1.97 (0.97–4.01)	0.063	1.89 (0.91–3.95)	0.090
Myocardial infarction	2.48 (0.92–6.71)	0.074	2.37 (0.86–6.54)	0.097
Major or life threatening bleeding	1.39 (0.91–2.14)	0.132		
NOP-LBBB	0.95 (0.60–1.51)	0.833		
PPM implantation	0.62 (0.37–1.04)	0.070	0.78 (0.42–1.44)	0.422

*For the multivariate analysis, patients with missing data were included through the use of multiple imputation.
†Per 10-mm Hg decrease.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

FIGURE 3 Rates of Mortality From Advanced Heart Failure According to the Use of TA Approach or SAR



Kaplan-Meier curves at 2-year follow-up for death from heart failure according to the use of transapical approach **(A)** or the occurrence of moderate or severe aortic regurgitation **(B)**. AR = aortic regurgitation; TA = transapical.

other causes as a competing risk event, LVEF ≤40% (HR: 2.13, 95% CI: 1.17 to 3.87; p = 0.011) and the occurrence of NOP-LBBB (HR: 2.20, 95% CI: 1.19 to 4.06; p = 0.010) remained independent predictors of SCD. **Figure 4** shows Kaplan-Meier curves for SCD according to the presence of LVEF ≤40% and/or NOP-LBBB. When both were present concomitantly, the risk of sudden death at 1-year follow-up increased to 12.3% (95% CI: 7.1% to 22.5%).

A total of 15 patients with NOP-LBBB (3.2% of patients with NOP-LBBB) died of SCD at last follow-up. **Table 6** shows electrocardiographic predictors of SCD in patients with NOP-LBBB. The receiver-operating characteristic curve showed that the best QRS duration cut-off for predicting SCD in patients with NOP-LBBB was >160 ms, with a sensitivity of 38.5% and specificity of 87.8% (area under the curve: 0.64, standard error: 0.09). A QRS duration >160 ms at hospital discharge was associated with an increased risk of SCD in patients with NOP-LBBB (HR: 4.78, 95% CI: 1.56 to 14.63; p = 0.006). **Figure 5** shows cumulative SCD rates at 2-year follow-up in patients with NOP-LBBB according to QRS duration (>160 or ≤160 ms). In patients with QRS duration >160 ms, the rate of SCD was 9.9% at 1-year follow-up.

In a further analysis, patients were classified into 3 groups according to the occurrence of new-onset LBBB and PPM during the hospitalization period: NOP-LBBB (n = 471 [12.6%]); NOP-LBBB-PPM (n = 92 [2.5%]); and no NOP-LBBB (n = 2,976 [79.9%]). Reasons for PPM in patients with NOP-LBBB were paroxysmal or transient advanced-degree AVB in 58 patients (63.0%) and prophylactic in 34 patients (37.0%). Whereas those patients with NOP-LBBB-PPM had no increased risk of SCD compared with those with no NOP-LBBB (HR: 0.71, 95% CI: 0.09 to 5.48; p = 0.740) (Online Table 2), those with NOP-LBBB (with no PPM) had an increased risk of SCD compared with those with no NOP-LBBB (HR: 2.21, 95% CI: 1.20 to 4.09; p = 0.011). No significant differences in SCD were observed between the NOP-LBBB and NOP-LBBB-PPM groups (HR: 3.13, 95% CI: 0.38 to 25.63; p = 0.287). Online Figure 1 displays Kaplan-Meier curves for SCD according to the occurrence of NOP-LBBB (with no PPM), NOP-LBBB-PPM, or no NOP-LBBB.

DISCUSSION

Advanced HF and SCD were reportedly the most common causes of death after SAVR, accounting for >50% of total deaths in most surgical series (4–7). The percentage of both modes of death versus total deaths was much lower (~20%) in our study, in accordance with prior observations in patients undergoing TAVR (11,12). This may be attributable to the high prevalence of severe noncardiac comorbidities in this population, leading to a high incidence of death from noncardiac causes.

DEATH FROM ADVANCED HF FOLLOWING TAVR. The interplay between chronic obstructive pulmonary

disease, atrial fibrillation, left ventricular dysfunction, severe pulmonary hypertension, and overt HF is well known (18). It is not surprising that these baseline comorbidities predicted the occurrence of death from advanced HF after TAVR in our study, as all were previously identified predictors of poorer outcomes in patients undergoing TAVR (1,12) and were associated with increased risk of mortality due to HF after cardiac surgery (5–7). A lower mean transaortic gradient, another baseline factor associated with death from advanced HF following TAVR in our study, was similarly associated with a higher rate of HF recurrence, a poorer New York Heart Association functional class, and a higher rate of death from HF in patients with aortic stenosis undergoing SAVR, regardless of the presence of left ventricular dysfunction (19).

Interestingly, our study identified 2 potentially modifiable factors as independent predictors of death from HF: use of the transapical approach and the presence of moderate or severe AR after TAVR (**Central Illustration**). There are some studies suggesting that the use of the transapical (vs. transfemoral) approach may increase the risk of mortality after TAVR (10,20,21), although the causes remain largely unknown. The present study showed, for the first time to our knowledge, that an approximately 2-fold increased risk of death from HF was associated with transapical access. This suggests that the increased mortality associated with the transapical approach is driven, at least in part, by a higher rate of progression to advanced HF. Accordingly, several studies reported poorer evolution of LVEF in patients undergoing transapical (vs. transfemoral) procedures (22,23), attributable to the higher degree of myocardial injury and impairment in left ventricular apical function (24,25). This may also explain the early rise in N-terminal prohormone of B-type natriuretic peptide levels following transapical, but not transfemoral, TAVR (26). Our results suggest that alternatives to the transapical route, such as subclavian, transaortic, or carotid approaches, may be considered in patients at high risk of advanced HF for whom the transfemoral approach is not suitable.

Although the presence of residual moderate or severe AR is a well-established predictor of both overall and cardiovascular mortality after TAVR (1,27), the specific mechanisms leading to increased mortality have not yet been elucidated. An increased risk of death from HF was observed in patients with residual moderate or severe AR in this study, suggesting that progression to advanced HF may partially explain the excess rate of death. Reports indicate that this increased risk of mortality

TABLE 4 Echocardiographic Predictors of Death From Heart Failure in Patients With Moderate or Severe Aortic Regurgitation Following TAVR (n = 374)

	Univariate HR (95% CI)	p Value	Multivariate HR (95% CI)	p Value
Baseline				
LVEF, %	0.99 (0.97–1.02)	0.591		
Mean transaortic gradient, mm Hg	1.35 (1.00–1.66)*	0.048	1.35 (1.04–1.85)*	0.040
PASP >60 mm Hg	2.38 (0.91–6.93)	0.079	3.06 (1.14–8.22)	0.027
Moderate or severe MR	1.55 (0.51–4.68)	0.439		
Moderate or severe AR	0.39 (0.14–1.03)	0.058	0.24 (0.07–0.83)	0.025
Discharge				
LVEF (%)	0.99 (0.96–1.01)	0.341		
Mean gradient	1.00 (0.91–1.10)	0.980		

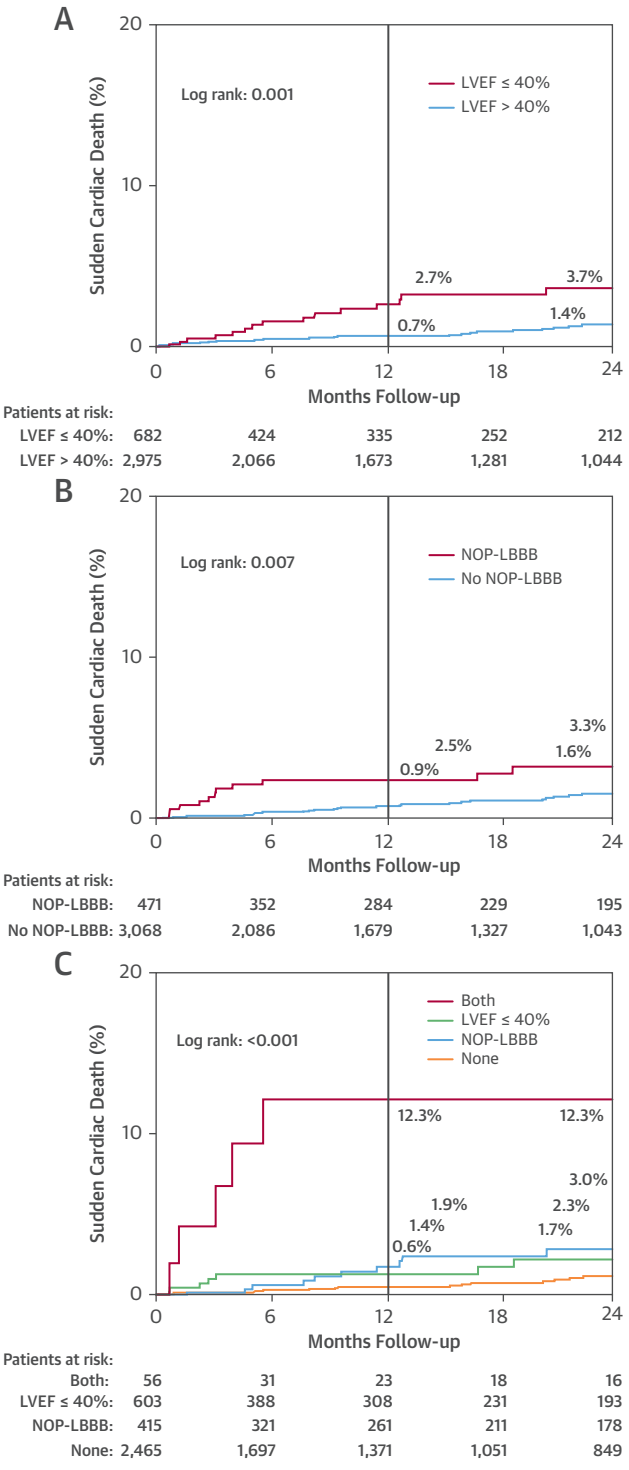
*Per 10-mm Hg decrease.
MR = mitral regurgitation; other abbreviations as in Tables 1 and 3.

TABLE 5 Univariate and Multivariate Predictors of Sudden Cardiac Death Following TAVR

	Univariate HR (95% CI)	p Value	Multivariate HR* (95% CI)	p Value
Clinical characteristics and electrocardiographic findings				
Age, yrs	1.00 (0.97–1.04)	0.862		
Male	1.30 (0.77–2.18)	0.329		
Body mass index, kg/m^2	1.00 (0.95–1.05)	0.918		
NYHA functional class ≥III	1.67 (0.82–3.40)	0.162		
Hypertension	1.32 (0.67–2.62)	0.421		
Diabetes mellitus	1.56 (0.91–2.67)	0.104		
COPD	1.34 (0.77–2.35)	0.305		
eGFR <60 ml/min	1.12 (0.65–1.94)	0.684		
Coronary artery disease	1.05 (0.62–1.77)	0.865		
Complete or no need of revascularization	0.70 (0.40–1.22)	0.206		
Paroxysmal/chronic AF	1.28 (0.73–2.26)	0.386		
Pre-existing LBBB	0.56 (0.17–1.78)	0.321		
Prior pacemaker	0.47 (0.15–1.51)	0.205		
Echocardiographic findings				
LVEF ≤40%	2.07 (1.17–3.65)	0.013	1.93 (1.05–3.55)	0.033
Mean transaortic gradient (mm Hg)†	1.22 (1.35–1.00)	0.082	1.11 (0.90–1.34)	0.134
PASP >60 mm Hg	1.09 (0.49–2.43)	0.830		
Procedural findings				
Transapical approach	0.46 (0.18–1.16)	0.101		
Balloon-expandable prosthesis type	0.85 (0.51–1.44)	0.550		
Moderate or severe AR	1.97 (1.02–3.81)	0.044	1.40 (0.64–3.05)	0.395
30-day outcomes				
Stroke	2.94 (1.06–8.14)	0.038	1.85 (0.43–7.89)	0.405
Myocardial infarction	–	–		
Major or life threatening bleeding	1.24 (0.58–2.62)	0.581		
NOP-LBBB	2.00 (1.11–3.61)	0.021	2.26 (1.23–4.14)	0.009
PPM implantation	0.94 (0.44–2.00)	0.871		

*For the multivariate analysis, patients with missing data were included through the use of multiple imputation.
†Per 10-mm Hg decrease.
Abbreviations as in Tables 1 and 3.

FIGURE 4 Rates of Sudden Cardiac Death According to the Presence of an LVEF ≤40% and/or the Occurrence of NOP-LBBB



Kaplan-Meier curves at 2-year follow-up for sudden cardiac death according to the presence of a left ventricular ejection fraction (LVEF) ≤40% **(A)**, new-onset persistent left bundle-branch block (NOP-LBBB) **(B)**, or both **(C)**.

TABLE 6 Electrocardiographic Predictors of Sudden Cardiac Death in Patients With New-Onset Persistent Left Bundle-Branch Block Following TAVR (n = 471)

	Univariate HR (95% CI)	p Value
Baseline		
QRS duration	1.01 (0.98-1.04)	0.551
PR >200 ms	—	—
Discharge		
QRS duration	1.02 (0.99-1.05)	0.162
QRS >160 ms	4.78 (1.56-14.63)	0.006
PR >200 ms	0.26 (0.03-2.20)	0.218

Abbreviations as in Tables 1 and 3.

particularly occurs in patients with a significant increment in the degree of AR following TAVR compared with baseline, probably due to a sudden increase in end-diastolic ventricular pressure that prevents the development of the compensatory mechanisms present in patients with chronic AR (28). Accordingly, we observed that the presence of significant AR before TAVR had a protective effect on the risk of death from HF in patients with residual moderate or severe AR. However, both the presence of severe pulmonary hypertension and a lower transaortic gradient before TAVR were associated with an increased risk of mortality from HF in such patients. Development of pulmonary hypertension in patients with aortic stenosis has been mainly attributed to diastolic dysfunction (29,30), which markedly reduces tolerance to acute AR. Higher pulmonary pressure levels have been associated with increased mortality in patients with significant AR after TAVR (31). The presence of lower transaortic gradients may reflect more advanced myocardial disease, even in the absence of left ventricular dysfunction (32). Whether therapies directed at reducing the degree of AR after TAVR (e.g., balloon post-dilation, valve-in-valve procedures, percutaneous closure of paravalvular leaks, high pacing rates, surgery) are associated with a reduction in the rates of mortality from advanced HF after TAVR should be further evaluated.

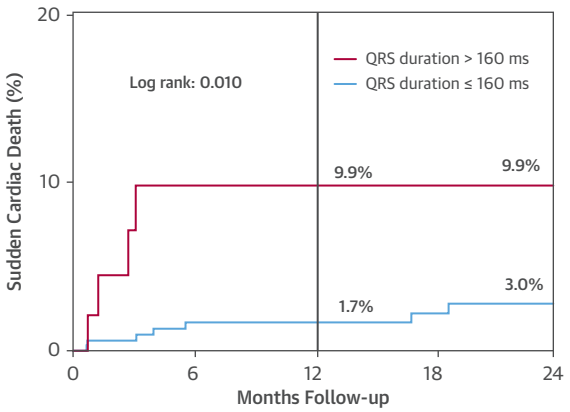
SCD FOLLOWING TAVR. The effect of NOP-LBBB on mortality after aortic valve replacement has been highly controversial in both surgical and transcatheter fields (4,9,33-36). Some studies reported an increased risk of SCD, complete AVB, or syncope in patients with NOP-LBBB following SAVR (9). In the TAVR field, although NOP-LBBB has been associated with an increased risk of complete AVB or PPM implantation during the follow-up period (35,36), no

increased rates of SCD were observed in previous studies assessing the effect of NOP-LBBB (33,34). However, differences in the definitions of both SCD and LBBB (e.g., persistent at hospital discharge vs. all), and underpowered sample sizes (all previous studies included <1,200 patients) may partially explain such differences. Although the specific causes of SCD in patients with NOP-LBBB (ventricular arrhythmia vs. advanced AVB) have not yet been elucidated, autopsy data has shown necrosis of the bundle of His and left bundle-branch due to mechanical compression by the transcatheter prosthesis (37), supporting progression to advanced AVB as a possible mechanism of SCD in such patients. Most patients with NOP-LBBB and wide QRS died within the first 6 months after TAVR, and no increased risk of SCD was observed in patients with NOP-LBBB and PPM implanted before hospital discharge, suggesting advanced AVB as the main cause of SCD in these patients. Nonetheless, no significant differences were observed between NOP-LBBB and NOP-LBBB-PPM in the risk of SCD. The ongoing MARE (Ambulatory Electrocardiographic Monitoring for the Detection of High-Degree Atrio-Ventricular Block in Patients With New-onset PeRsistent LEft Bundle Branch Block After Transcatheter Aortic Valve Implantation) study (38), with continuous ECG recording (up to 3 years) in patients with NOP-LBBB following TAVR should help to clarify this issue.

The results of our study also highlight the importance of measuring the QRS duration in patients with NOP-LBBB following TAVR. One of 10 patients with TAVR who left the hospital with NOP-LBBB and a QRS duration >160 ms died of SCD within the first months following the procedure (vs. <3% in patients with NOP-LBBB and QRS ≤160 ms) (**Central Illustration**). A higher rate of progression to advanced AVB may be responsible for the high rate of SCD in such patients, and the implantation of a preventive pacemaker before hospital discharge may be justified while awaiting results of further studies.

Considerable evidence supports the association between left ventricular dysfunction and sudden cardiac death (39). It is, therefore, not surprising that patients with LVEF ≤40% were at higher risk of SCD in this study (**Central Illustration**). Of note, patients with both NOP-LBBB and an LVEF ≤40% exhibited the highest rate of SCD (>12%) within the year following TAVR, much higher than SCD rates in the presence of only 1 of these factors (<5%). This may be secondary to the occurrence of ventricular arrhythmias, bradyarrhythmias, and/or even advanced HF due to LBBB-related mechanical dyssynchrony. A longer QRS duration was reported to be a predictor of SCD in patients with HF (40), and impairment or lack of improvement in LVEF in patients with NOP-LBBB after TAVR (41,42) may also contribute to the very high risk of SCD in patients with both factors. Although the effectiveness of implantable cardioverter-defibrillator devices in patients age >80 years, particularly in those with associated comorbidities such as renal failure and chronic pulmonary diseases (a large proportion of the TAVR population), has not been confirmed (39), future studies are needed to evaluate the usefulness (and cost-effectiveness) of implanting such devices in this high-risk group of patients. Also, cardiac resynchronization in patients with left ventricular dysfunction requiring ventricular pacing or implantable cardioverter-defibrillators has been associated with a lower risk of death or rehospitalization for heart failure (43). Whether biventricular pacing might be associated with increased survival in patients with reduced LVEF and NOP-LBBB or PPM after TAVR should be further studied.

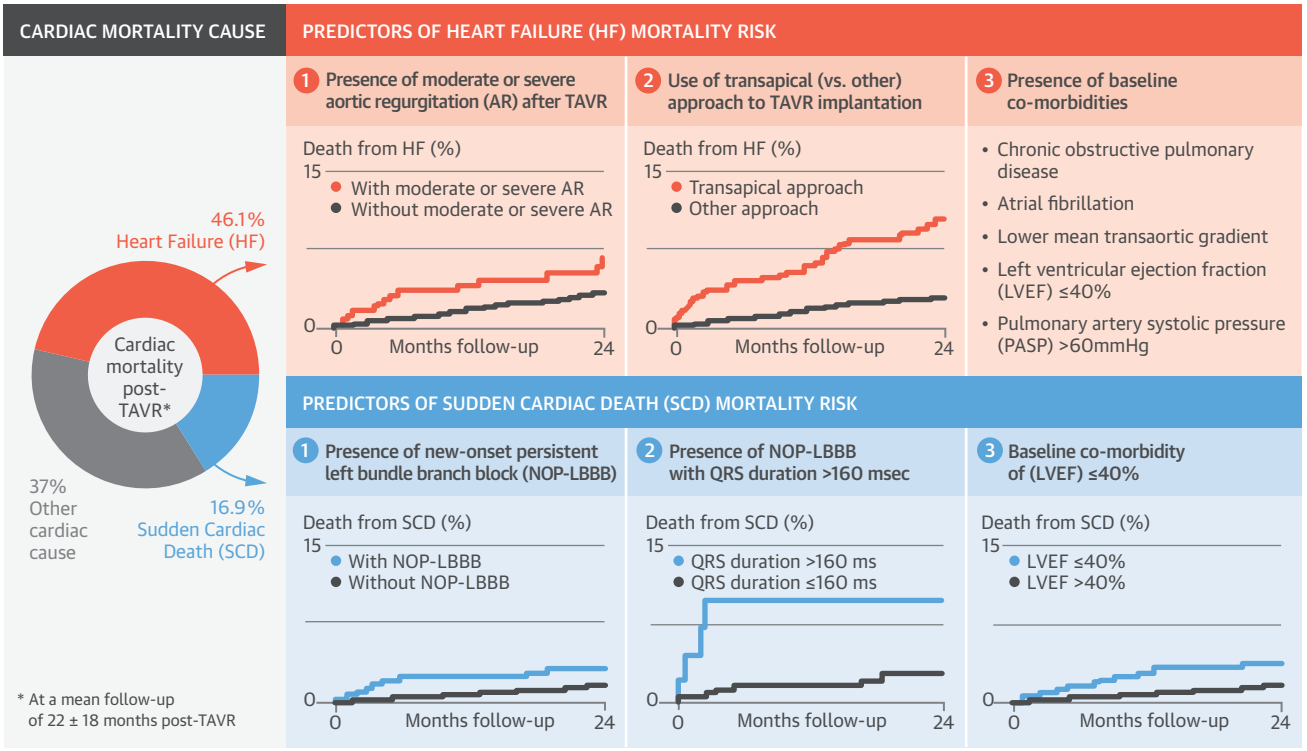
FIGURE 5 Rate of Sudden Cardiac Death in Patients With New-Onset Left Bundle-Branch Block



Kaplan-Meier curves at 2-year follow-up for sudden cardiac death in patients with new-onset left bundle-branch block, defined by the presence of a QRS duration >160 ms.

STUDY LIMITATIONS. Although the causes of death in each center were defined according to the VARC-2, no event adjudication committee was available in this study. ECG and echocardiographic findings were interpreted in each center, with no ECG or echocardiography core laboratory evaluation. No contractile reserve data was available in patients with low-flow low-gradient aortic stenosis. The occurrence of

CENTRAL ILLUSTRATION **Predictors of Death From Heart Failure and Sudden Cardiac Death in Patients Undergoing TAVR**



Urena, M. et al. J Am Coll Cardiol. 2015; 65(5):437-48.

Baseline comorbidities and procedural factors leading to an increased rate of death from heart failure and sudden cardiac death. Kaplan-Meier curves for potentially modifiable or treatable factors are shown. TAVR = transcatheter aortic valve replacement.

advanced AVB in patients with NOP-LBBB during follow-up was not prospectively collected in all participating centers and was not analyzed in order to avoid major bias. Also, the number of patients in the NOP-LBBB-PPM group was limited, and the potential protective effect of PPM in patients with NOP-LBBB should be interpreted with caution and needs further investigation. Finally, although each center collected data prospectively, data analysis was retrospective.

CONCLUSIONS

Advanced HF and SCD accounted for approximately two-thirds of cardiac deaths following TAVR, which occurred most frequently during the first 6 months after the procedure. Potentially modifiable or treatable factors leading to increased risk of mortality from HF and SCD were identified. Future studies should evaluate whether specific therapeutic strategies targeting these factors, such as alternatives to the transapical approach in patients at risk of advanced HF not suitable for transfemoral access, further treatment of residual moderate or severe AR (especially if acute increase vs. baseline), pacemaker implantation in patients with NOP-LBBB (particularly in the presence of QRS duration >160 ms), or cardiac defibrillator implantation in patients with left ventricular dysfunction, decrease these patients' risk of cardiac death. In the meantime, our results allow identification of the patients at the highest risk of dying of HF or SCD within the first months following TAVR and should contribute to improved clinical decision-making.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Predictors of cardiac death after TAVR include potentially modifiable or treatable factors, such as a transapical approach and moderate-severe residual AR, both associated with death from HF, and development of NOP-LBBB, associated with SCD, particularly in those with QRS duration >160 ms.

COMPETENCY IN PATIENT CARE: In managing patients undergoing TAVR, physicians may consider alternatives to a transapical approach in those patients at risk of advanced HF (especially in those with severely impaired ventricular function), treating residual AR (especially in those with pulmonary hypertension or no/trace AR at baseline), and implantation of a pacemaker or defibrillator in those with NOP-LBBB, QRS prolongation >160 ms, and left ventricular dysfunction.

TRANSLATIONAL OUTLOOK: Randomized trials are needed to define optimum management strategies for patients with modifiable risk factors for development of HF or cardiac death following TAVR.

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KEY WORDS aortic stenosis, heart failure, sudden cardiac death, transcatheter aortic valve implantation, transcatheter aortic valve replacement

APPENDIX For supplemental tables and a figure, please see the online version of this article.