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Clinical Impact of Baseline Right Bundle Branch Block in Patients Undergoing Transcatheter Aortic Valve Replacement

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ABSTRACT

OBJECTIVES This study sought to assess the influence of baseline right bundle branch block (RBBB) on all-cause and cardiovascular mortality as well as sudden cardiac death (SCD) among patients undergoing transcatheter aortic valve replacement (TAVR).

BACKGROUND Few data exist regarding the late clinical impact of pre-existing RBBB in TAVR recipients.

METHODS A total of 3,527 patients (mean age 82 ± 8 years, 50.1% men) were evaluated according to the presence of RBBB on baseline electrocardiography. Intraventricular conduction abnormalities were classified according to the American Heart Association, American College of Cardiology Foundation, and Heart Rhythm Society recommendations for standardization and interpretation of the electrocardiogram. TAVR complications and causes of death were defined according to Valve Academic Research Consortium 2 definitions.

RESULTS RBBB was present on baseline electrocardiography in 362 patients (10.3%) and associated with higher 30-day rates of permanent pacemaker implantation (PPI) (40.1% vs. 13.5%; $p < 0.001$) and death (10.2% vs. 6.9%; $p = 0.024$). At a mean follow-up of 20 ± 18 months, pre-existing RBBB was independently associated with all-cause mortality (hazard ratio [HR]: 1.31; 95% confidence interval [CI]: 1.06 to 1.63; $p = 0.014$) and cardiovascular mortality (HR: 1.45; 95% CI: 1.11 to 1.89; $p = 0.006$) but not with SCD (HR: 0.71; 95% CI: 0.22 to 2.32; $p = 0.57$). Patients with pre-existing RBBB and without PPI at discharge from the index hospitalization had the highest 2-year risk for cardiovascular death (27.8%; 95% CI: 20.9% to 36.1%; log-rank $p = 0.007$). In a subanalysis of 1,245 patients without PPI at discharge from the index hospitalization and with complete follow-up regarding the need for PPI, pre-existing RBBB was independently associated with the composite of SCD and PPI (HR: 2.68; 95% CI: 1.16 to 6.17; $p = 0.023$).

CONCLUSIONS Pre-existing RBBB was found in 10% of TAVR recipients and was associated with poorer clinical outcomes. Patients with baseline RBBB without permanent pacemakers at hospital discharge may be at especially high risk for high-degree atrioventricular block and/or SCD during follow-up. Future studies should evaluate strategies aimed at the early detection of patients at risk for late development of high-degree atrioventricular block.
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Within the past decade, transcatheter aortic valve replacement (TAVR) has revolutionized the management of high-risk or inoperable patients with symptomatic severe aortic stenosis (1). However, the occurrence of conduction disturbances, particularly left bundle branch block (LBBB) and atrioventricular block (AVB), and the need for permanent pacemaker implantation (PPI) remain the most frequent complications of TAVR (2,3). Indeed, the availability of newer generation transcatheter valves has not reduced but rather increased the occurrence of such complications (4).

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Pre-existing right bundle branch block (RBBB) is a well-recognized risk factor for PPI or late bradycardia post-TAVR (5,6). The prognostic impact of pre-existing RBBB has been studied in the general population, as well as among patients with heart disease, with some controversial results from 1 specific setting to another (7–13). Nonetheless, a recent meta-analysis of 19 prospective cohort studies demonstrated higher risks for all-cause and cardiovascular mortality in patients with RBBB (14). Yet data regarding the impact of pre-existing RBBB on clinical outcomes of TAVR recipients remain scarce (15).

The purpose of this study was to evaluate the impact of pre-existing RBBB on clinical outcomes in patients undergoing TAVR with both balloon- and self-expandable valves.

METHODS

STUDY POPULATION. This was a multicenter study including a total of 3,726 patients who underwent TAVR. Of these, 3,527 patients with analyzable electrocardiograms at baseline were included in the present analysis and grouped according to the presence of baseline complete RBBB (either isolated or associated with left fascicular block). Patients with incomplete RBBB were considered as patients with no RBBB. TAVR indication, valve type, and approach were determined by each center's "heart team." Procedures were performed as described elsewhere (16). Clinical outcomes were defined according to the Valve Academic Research Consortium (VARC) 2 definitions (17).

ELECTROCARDIOGRAPHY AND ECHOCARDIOGRAPHY. Twelve-lead electrocardiographic tracings were recorded at baseline and at hospital discharge. Intraventricular conduction abnormalities were classified according to the American Heart Association, American College of Cardiology Foundation, and Heart Rhythm Society recommendations for standardization and interpretation of the electrocardiogram (18). PPI was performed if third-degree or advanced second-degree AVB occurred at any anatomic level and was not expected to resolve or in the presence of sinus node dysfunction and documented symptomatic bradycardia, in agreement with current recommendations (19). In the presence of new-onset LBBB with PR interval prolongation (>200 ms) or very wide QRS interval (>150 ms) not expected to normalize, indication for PPI was at the physician's discretion.

Experienced echocardiographers analyzed echocardiograms at each center. The degree of aortic regurgitation was classified according to the VARC-2 criteria (17).

ABBREVIATIONS AND ACRONYMS

AVB = atrioventricular block
CI = confidence interval
HR = hazard ratio
LBBB = left bundle branch block
PPI = permanent pacemaker implantation
RBBB = right bundle branch block
SCD = sudden cardiac death
TAVR = transcatheter aortic valve replacement
VARC = Valve Academic Research Consortium

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TABLE 1 Baseline Clinical Characteristics, Procedural Findings, and 30-Day Outcomes of the Study Population (N = 3,527)

	RBBB (n = 362)	No RBBB (n = 3,165)	p Value
Baseline clinical characteristics			
Age, yrs	81.7 ± 7.3	81.4 ± 7.6	0.70
Male	211/361 (58.4)	1,553/3,163 (49.1)	0.001
Body mass index, kg/m^2	27.2 ± 5.2 (n = 357)	26.7 ± 5.1 (n = 3,135)	0.18
NYHA functional class III or IV	268/359 (74.7)	2,327/3,116 (74.7)	1.00
Hypertension	269/360 (74.7)	2,437/3,155 (77.2)	0.29
Diabetes mellitus	104/360 (28.9)	952/3,154 (30.2)	0.63
Paroxysmal/chronic atrial fibrillation	109/357 (30.5)	932/3,088 (30.2)	0.90
Previous pacemaker	14/361 (3.9)	385/3,154 (12.2)	<0.001
Coronary artery disease	213/360 (59.2)	1,687/3,152 (53.5)	0.044
Complete or no need for revascularization	199/314 (63.4)	1,902/2,874 (66.2)	0.35
Chronic obstructive pulmonary disease	108/361 (29.9)	800/3,141 (25.5)	0.076
Chronic kidney disease (eGFR <60 ml/min)	182/354 (51.4)	1,596/3,094 (51.6)	0.96
Logistic EuroSCORE, %	17.3 (10.4–26.0) (n = 267)	16.5 (10.2–25.3) (n = 2,280)	0.79
Echocardiographic findings			
Left ventricular ejection fraction ≤40%	60/354 (16.9)	585/3,112 (18.8)	0.43
Mean transaortic gradient, mm Hg	47.6 ± 16.3 (n = 331)	46.7 ± 16.7 (n = 2,942)	0.24
sPAP >60 mm Hg	37/259 (14.3)	315/2,320 (13.6)	0.78
Procedural findings			
Approach			0.55
Transfemoral	291/361 (80.6)	2,510/3,157 (79.5)	
Transapical	52/361 (14.4)	525/3,157 (16.6)	
Transaortic	9/361 (2.5)	57/3,157 (1.8)	
Subclavian	9/361 (2.5)	65/3,157 (2.1)	
Valve type			0.034
Balloon-expandable	221/362 (61.0)	1,741/3,157 (55.1)	
Self-expandable	141/362 (39.0)	1,416/3,157 (44.9)	
Moderate or severe aortic regurgitation	36/332 (10.8)	325/2,895 (11.2)	0.86
30-day outcomes			
Death	37/362 (10.2)	217/3,165 (6.9)	0.024
Stroke	10/357 (2.8)	99/3,117 (3.2)	0.75
Myocardial infarction	5/318 (1.6)	41/2,782 (1.5)	1.00
Major or life-threatening bleeding	51/343 (14.9)	406/2,952 (13.8)	0.62
New-onset persistent LBBB	4/353 (1.1)	461/3,098 (14.9)	<0.001
New pacemaker*	137/342 (40.1)	370/2,738 (13.5)	<0.001

Values are mean ± SD, n/N (%) for categorical data, and median (interquartile range) for continuous data. *Among patients without previous pacemakers.

eGFR = glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; LBBB = left bundle branch block; NYHA = New York Heart Association; RBBB = right bundle branch block; sPAP = systolic pulmonary artery pressure.

FOLLOW-UP. Follow-up was performed by telephone and/or on-site clinical visit at 1 month post-TAVR at 1 year and yearly thereafter. Complete follow-up was achieved in 95.1% of patients (4.9% of the study population was lost to follow-up). Complete follow-up regarding the need for PPI was obtained in a subgroup of 1,720 patients (48.8%), including 1,245 (72.3%) without PPI at baseline or during the index hospitalization.

OUTCOMES. The primary outcome of this analysis was cumulative all-cause mortality. Secondary outcomes were cardiovascular death and sudden cardiac death (SCD). All outcomes were evaluated according to the presence of baseline RBBB. Methods used to assess causes of death were previously published (20). Cardiovascular death was defined according to VARC-2 criteria. 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 sudden death were not considered to have experienced SCD (21).

In a subanalysis, the impact of baseline RBBB on PPI and the composite of SCD and PPI were evaluated among patients with complete follow-up regarding the need for PPI and without PPI at discharge of the index hospitalization (i.e., PPI either at baseline or during the index hospitalization).

STATISTICAL ANALYSIS. Qualitative variables are expressed as number (percentage), and continuous data are presented as mean ± SD or median (interquartile range) depending on their distribution, which was assessed using the Kolmogorov-Smirnov test. Survival rates were summarized using Kaplan-Meier estimates, and log-rank tests were used to compare groups. Predictors of all-cause death, cardiovascular death, and SCD were analyzed using univariate and multivariate proportional hazards models (cumulative outcomes). Predictors of PPI and of the composite of PPI and SCD were evaluated among patients with complete follow-up regarding the need for permanent pacemaker and without PPI at discharge from the index hospitalization. The proportional hazards assumption was tested by plotting log-minus-log survival. Each variable showing significant departure from hazard proportionality was subsequently entered as a time-varying covariate in the multivariate Cox model. Fine and Gray Cox models were also constructed to account for death from other causes as a competing-risk event for cardiovascular death and SCD. Variables with p values <0.10 in univariate analysis were included in the multivariate analysis. All univariate analyses were performed on complete cases. To account for the multicenter design of the study, a multilevel hierarchical mixed-effects analysis

using the center of enrollment as a random effect was performed to analyze the potential effect of heterogeneity across centers.

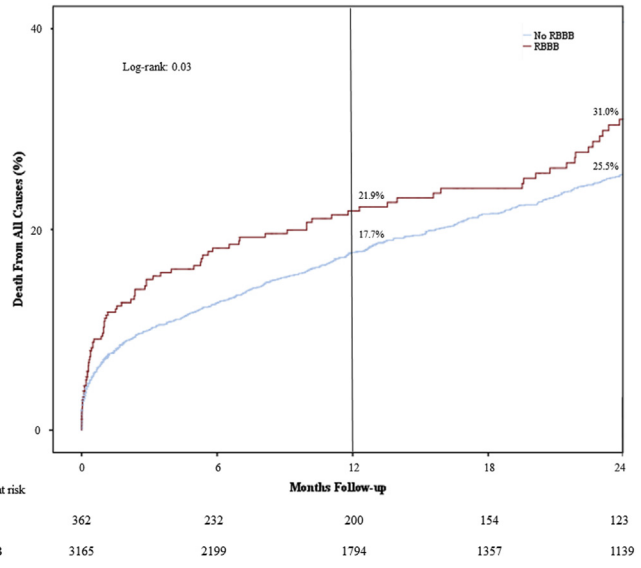
Overall, 4.66% of data were missing, and 42.4% of patients had at least 1 missing value. For the purposes of multivariate analysis, missing data were assumed to be random and were handled by multiple imputation using chained equations. Twenty imputed datasets were created, and results were pooled according to Rubin's rule (22) and are reported as adjusted hazard ratios (HRs) with their 95% confidence intervals (CIs). All tests were 2 sided at the 0.05 significance level. Statistical analyses were conducted using Stata release 13 (StataCorp, College Station, Texas) and SPSS version 22 (IBM, Armonk, New York).

RESULTS

PATIENTS. 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 82 ± 8 years, 50.1% were men, and 362 (10.3%) presented with RBBB. Within the RBBB group, 229 patients (63.3%) had isolated RBBB, whereas 123 (34.0%) and 10 (2.7%) had associated left anterior and posterior fascicular block, respectively. Patients with RBBB were more often men with more frequent histories of coronary artery disease and a trend toward more chronic obstructive pulmonary disease. Regarding procedural findings, the rate of balloon-expandable valves was higher among patients with RBBB. At 30 days, mortality was higher in the RBBB group (10.2% vs. 6.9%; p = 0.024). PPI was required in 40.1% of patients with RBBB at 30 days post-TAVR compared with 13.5% in the no-RBBB group (p < 0.001). The rate of PPI was similar in patients with isolated RBBB (39.4%) compared with those with RBBB and left anterior fascicular block (36.1%) (p = 0.64).

INCIDENCE OF ALL-CAUSE AND SPECIFIC CAUSES OF DEATH ACCORDING TO THE PRESENCE OF BASELINE RBBB. At a mean follow-up of 20 ± 18 months, a total of 975 patients (27.6%) had died. Cumulative rates of overall mortality at 2-year follow-up were 25.5% (95% CI: 23.8% to 27.4%) in the no-RBBB group and 31.0% (95% CI: 25.7% to 37.0%) in the RBBB group (log-rank p = 0.03) (Figure 1). Cardiovascular death occurred in 637 patients (18.1%), including SCD in 57 patients (1.6%). Cumulative rates of cardiovascular death at 2-year follow-up were 23.5% (95% CI: 18.7% to 29.1%) in the RBBB group and 17.4% (95% CI: 15.9% to 19.0%) in the no-RBBB group (log-rank p = 0.007) (Figure 2A). The 2-year rates of SCD were 1.0% (95% CI: 0.3% to 4.2%) and 2.0% (95% CI: 1.4% to 2.7%), respectively (log-rank p = 0.28) (Figure 3). When further stratifying patients by the presence of pre-existing RBBB and PPI at discharge from index hospitalization, patients with RBBB but no PPI had a higher rate of 2-year cardiovascular death (27.8%; 95% CI: 20.9% to 36.1%) compared with other subgroups that had comparable cardiovascular mortality (log-rank p = 0.007) (Figure 2B).

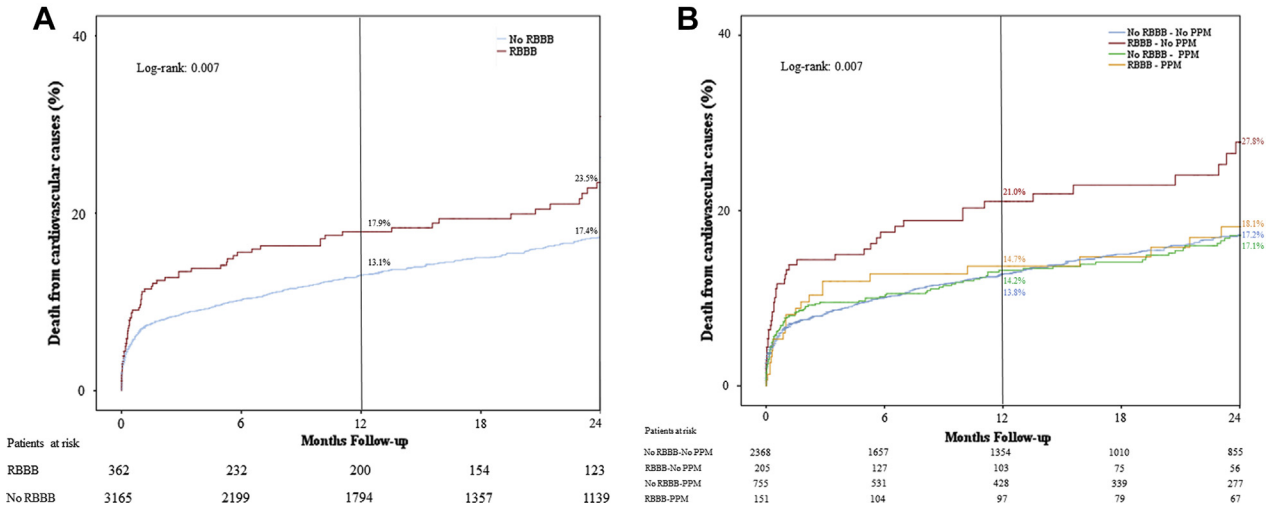
FIGURE 1 Rates of All-Causes Mortality



Kaplan-Meier curves at 2-year follow-up for overall mortality according to the presence of pre-existing right bundle branch block (RBBB).

PREDICTORS OF ALL-CAUSE AND SPECIFIC CAUSES OF DEATH ACCORDING TO THE PRESENCE OF BASELINE RBBB. Table 2 shows predictors of all-cause death. In multivariate analysis, baseline RBBB was associated with increased risk for all-cause death (HR: 1.25; 95% CI: 1.01 to 1.56; p = 0.041). Hazards' proportionality was not met for some variables, which were subsequently entered in the model as time varying (Online Table 1). The addition of these interactions did not change the association between baseline RBBB and mortality post-TAVR (HR: 1.25; 95% CI: 1.01 to 1.55; p = 0.044). In multilevel analysis, RBBB remained significantly associated with all-cause death (HR: 1.31; 95% CI: 1.06 to 1.63; p = 0.014).

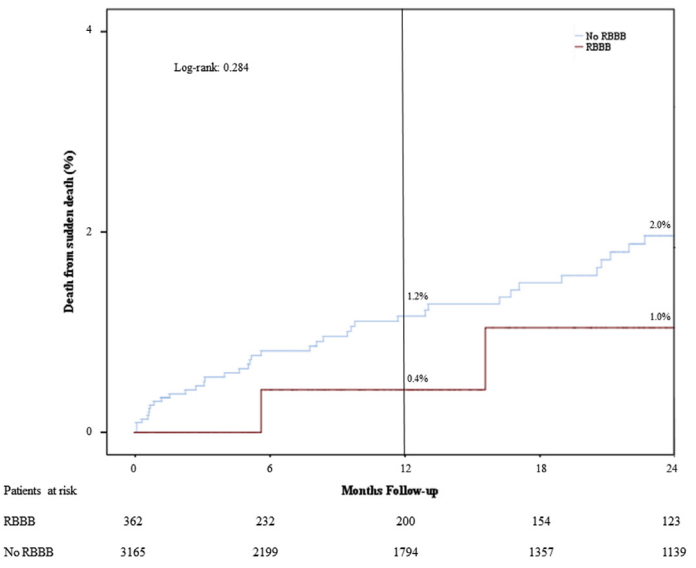
FIGURE 2 Rates of Cardiovascular Mortality



(A) Kaplan-Meier curves at 2-year follow-up for cardiovascular mortality according to the presence of pre-existing right bundle branch block (RBBB). **(B)** Kaplan-Meier curves at 2-year follow-up for cardiovascular mortality according to the presence of pre-existing RBBB and the presence of a permanent pacemaker (PPM) at discharge from the index hospitalization.

Table 3 summarizes predictors of cardiovascular death. After adjustment for confounders, baseline RBBB associated with a higher risk for cardiovascular death (HR: 1.38; 95% CI: 1.06 to 1.80; p = 0.018).

FIGURE 3 Rates of Sudden Cardiac Death



Kaplan-Meier curves at 2-year follow-up for sudden cardiac death according to the presence of pre-existing right bundle branch block (RBBB).

Significant departure from proportionality of hazards was demonstrated for some variables. However, results of the time-varying Cox model (Online Table 2) were consistent with the primary analysis regarding the impact of baseline RBBB (HR: 1.36; 95% CI: 1.04 to 1.78; p = 0.023). Furthermore, when death from other causes was considered as a competing risk event in a Fine and Gray Cox model, baseline RBBB was also significantly associated with cardiovascular death (sub-HR: 1.39; 95% CI: 1.06 to 1.83; p = 0.016). Heterogeneity between centers had no significant effect on the impact of RBBB in hierarchical analysis (HR: 1.45; 95% CI: 1.11 to 1.89; p = 0.006).

The factors associated with SCD are detailed in Table 4. In multivariate analysis, pre-existing RBBB was not associated with SCD (HR: 0.67; 95% CI: 0.20 to 2.18; p = 0.50). This result was confirmed in a time-varying Cox model, as hazards' proportionality was not met in the primary analysis (HR: 0.65; 95% CI: 0.20 to 2.13; p = 0.48) (Online Table 3). Competing risk analysis reached consistent results (sub-HR: 0.64; 95% CI: 0.20 to 2.05; p = 0.45). Similarly, RBBB was not associated with SCD in a multilevel mixed-effects analysis (HR: 0.71; 95% CI: 0.22 to 2.32; p = 0.57).

IMPACT OF BASELINE RBBB ON THE NEED FOR PPI AND SCD AT FOLLOW-UP. In a subanalysis, the

occurrence of SCD, need for PPI, and their composite were evaluated in patients without PPI at discharge of the index hospitalization and with complete follow-up regarding the need for PPI (n = 1,245, including 88 patients with pre-existing RBBB). Online Table 4 provides a comparison of patients included and excluded from this analysis. Included patients were younger, were more often female, and exhibited a higher burden of comorbidities despite a similar logistic European System for Cardiac Operative Risk Evaluation score.

At a mean follow-up of 23 ± 18 months, 63 patients (5.1%) presented the composite of SCD or PPI: 26 patients experienced SCD (2.1%), and PPI was required in 37 patients (3.0%). In multivariate analysis, pre-existing RBBB was not associated with SCD (HR: 1.70; 95% CI: 0.48 to 6.04; p = 0.41) but tended to associate with PPI (HR: 2.51; 95% CI: 0.88 to 7.19; p = 0.085) (Online Tables 5 and 6). Baseline RBBB was significantly associated with the composite of SCD or need for PPI (HR: 2.51; 95% CI: 1.10 to 5.75; p = 0.029) (**Table 5**). The results were confirmed in a time-varying Cox model because of violation of the assumption of proportionality of hazards (HR: 2.64; 95% CI: 1.16 to 6.02; p = 0.02) (Online Table 7). There was no significant effect of heterogeneity across centers in the multilevel analysis, as RBBB remained associated with the composite of SCD or need for PPI (HR: 2.68; 95% CI: 1.16 to 6.17; p = 0.023).

TABLE 2 Univariate and Multivariate Predictors of All-Cause Death Following Transcatheter Aortic Valve Replacement

	Univariate HR (95% CI)	p Value	Multivariate HR* (95% CI)	p Value
Baseline clinical characteristics				
Pre-existing RBBB	1.21 (1.00–1.47)	0.05	1.25 (1.01–1.56)	0.041
Age, yrs	1.01 (1.003–1.02)	0.009	1.02 (1.01–1.03)	0.003
Male	1.21 (1.07–1.38)	0.003	1.23 (1.07–1.42)	0.003
Body mass index, kg/m^2	0.73 (0.65–0.83)	<0.001	0.99 (0.98–1.01)	0.41
NYHA functional class III or IV	1.53 (1.30–1.81)	<0.001	1.16 (0.97–1.38)	0.115
Hypertension	0.97 (0.83–1.12)	0.65		
Diabetes mellitus	1.08 (0.94–1.23)	0.30		
Paroxysmal/chronic atrial fibrillation	1.65 (1.45–1.88)	<0.001	1.43 (1.24–1.65)	<0.001
Previous pacemaker	1.29 (1.07–1.55)	0.007	0.91 (0.73–1.12)	0.36
Coronary artery disease	1.19 (1.05–1.35)	0.007	0.93 (0.75–1.14)	0.47
Complete or no need for revascularization	0.75 (0.65–0.85)	<0.001	0.90 (0.72–1.12)	0.34
Chronic obstructive pulmonary disease	1.34 (1.17–1.53)	<0.001	1.29 (1.11–1.50)	0.001
Chronic kidney disease (eGFR <60 ml/min)	1.21 (1.06–1.37)	0.004	1.15 (1.00–1.32)	0.053
Logistic EuroSCORE	1.01 (1.008–1.02)	<0.001	1.01 (0.99–1.01)	0.08
Echocardiographic findings				
Left ventricular ejection fraction ≤40%	1.18 (1.03–1.36)	0.017	1.08 (0.90–1.30)	0.39
Mean transaortic gradient	1.39 (1.21–1.59)	<0.001	0.995 (0.99–0.998)	0.041
sPAP >60 mm Hg	1.29 (1.06–1.55)	0.009	1.17 (0.95–1.44)	0.13
Procedural findings				
Nontransfemoral approach	1.50 (1.30–1.73)	<0.001	1.29 (1.09–1.53)	0.004
Moderate or severe aortic regurgitation	1.49 (1.24–1.80)	<0.001	1.61 (1.30–1.98)	<0.001
30-day outcomes				
Stroke	2.04 (1.55–2.69)	<0.001	1.94 (1.44–2.61)	<0.001
Myocardial infarction	2.42 (1.60–3.66)	<0.001	2.16 (1.32–3.56)	0.002
Major or life-threatening bleeding	2.18 (1.87–2.53)	<0.001	1.97 (1.67–2.32)	<0.001
New-onset persistent LBBB	0.75 (0.62–0.92)	0.005	0.98 (0.78–1.22)	0.84
New pacemaker	0.82 (0.68–0.99)	0.036	0.89 (0.71–1.10)	0.28

*For the multivariate analysis, patients with missing data were included through the use of multiple imputations.
CI = confidence interval; HR = hazard ratio; other abbreviations as in Table 1.

DISCUSSION

The present analysis demonstrated a prevalence of RBBB of 10.3% among TAVR candidates. RBBB was associated with higher 30-day PPI and mortality rates. Also, RBBB was an independent predictor of midterm all-cause and cardiovascular mortality. The impact of RBBB on cardiovascular mortality was related primarily to patients without PPI at discharge from index hospitalization. In those patients, RBBB was associated with more than 2-fold higher risk for the composite of SCD and PPI.

Previous studies have reported inconsistent findings regarding the prognostic impact of RBBB on mortality among healthy participants or patients with heart disease (7–13). In the general population or in the acute phase of myocardial infarction, a higher incidence of RBBB was observed in men with hypertension and diabetes mellitus, and such patients were more likely to develop congestive heart failure or to harbor underlying cardiac diseases (10–12). However, RBBB was not associated with increased mortality in these studies. Zhang et al. (13), analyzing 66,450 participants from the Women's Health Initiative, demonstrated an increased risk for death from coronary heart disease among women with RBBB and baseline cardiovascular disease over 14-year follow-up. Nonetheless, RBBB was not associated with all-cause death or death from coronary heart disease in women free of baseline cardiovascular disease. On the contrary, among 18,411 patients without previous myocardial infarction or chronic heart failure from the Copenhagen City Heart Study, Bussink et al. (7) identified RBBB as a significant predictor of all-cause and cardiovascular mortality in both sexes. Recently,

TABLE 3 Univariate and Multivariate Predictors of Cardiovascular Death Following Transcatheter Aortic Valve Replacement

	Univariate HR (95% CI)	p Value	Multivariate HR* (95% CI)	p Value
Baseline clinical characteristics				
Pre-existing RBBB	1.26 (0.995–1.59)	0.055	1.38 (1.06–1.80)	0.018
Age, yrs	1.01 (1.003–1.03)	0.013	1.02 (1.01–1.03)	0.003
Male	1.16 (0.996–1.36)	0.056	1.17 (0.98–1.40)	0.08
Body mass index, kg/m^2	0.73 (0.62–0.85)	<0.001	1.00 (0.98–1.02)	0.82
NYHA functional class III or IV	1.50 (1.22–1.85)	<0.001	1.10 (0.88–1.38)	0.38
Hypertension	0.98 (0.82–1.19)	0.87		
Diabetes mellitus	1.09 (0.92–1.29)	0.33		
Paroxysmal/chronic atrial fibrillation	1.59 (1.35–1.87)	<0.001	1.38 (1.15–1.65)	0.001
Previous pacemaker	1.25 (0.997–1.58)	0.053	0.86 (0.66–1.12)	0.26
Coronary artery disease	1.13 (0.97–1.32)	0.13		
Complete or no need for revascularization	0.77 (0.65–0.91)	0.002	0.95 (0.79–1.15)	0.63
Chronic obstructive pulmonary disease	1.26 (1.06–1.49)	0.007	1.20 (0.99–1.45)	0.06
Chronic kidney disease (eGFR <60 ml/min)	1.20 (1.03–1.41)	0.023	1.10 (0.92–1.31)	0.29
Logistic EuroSCORE	1.02 (1.01–1.02)	<0.001	1.01 (1.00–1.02)	0.045
Echocardiographic findings				
Left ventricular ejection fraction ≤40%	1.25 (1.05–1.48)	0.012	1.21 (0.97–1.52)	0.09
Mean transaortic gradient	1.37 (1.16–1.62)	<0.001	0.998 (0.993–1.00)	0.60
sPAP >60 mm Hg	1.29 (1.02–1.63)	0.03	1.19 (0.93–1.53)	0.17
Procedural findings				
Nontransfemoral approach	1.57 (1.32–1.86)	<0.001	1.40 (1.14–1.73)	0.002
Moderate or severe aortic regurgitation	1.62 (1.29–2.04)	<0.001	1.68 (1.30–2.18)	<0.001
30-day outcomes				
Stroke	2.46 (1.80–3.36)	<0.001	2.32 (1.66–3.26)	<0.001
Myocardial infarction	3.20 (2.05–5.00)	<0.001	2.61 (1.51–4.52)	0.001
Major or life-threatening bleeding	2.49 (2.07–2.98)	<0.001	2.33 (1.91–2.85)	<0.001
New-onset persistent LBBB	0.72 (0.56–0.93)	0.01	0.93 (0.71–1.23)	0.61
New pacemaker	0.73 (0.57–0.92)	0.009	0.74 (0.56–0.99)	0.043

*For the multivariate analysis, patients with missing data were included through the use of multiple imputations.
Abbreviations as in Tables 1 and 2.

pooling data from 19 prospective cohort studies including 201,437 participants, Xiong et al. (14) demonstrated a significantly increased risk for all-cause and cardiac mortality in patients with RBBB. Although the exact mechanism by which RBBB increases mortality remains elusive, it has been hypothesized that through its association with fibrosis of the conduction system, RBBB might contribute to bradyarrhythmias and tachyarrhythmias (23,24). Moreover, among patients with prior myocardial infarction or chronic heart failure, RBBB is associated with lower left ventricular ejection fraction (9,25). Finally, patients with acquired RBBB more often harbor numerous comorbidities (such as right ventricular or chronic pulmonary diseases) and cardiovascular risk factors underlying, sometimes undiagnosed, cardiac diseases, which may, at least partly, explain the increased mortality in such patients.

Several studies have highlighted the significant role of RBBB in the development of post-TAVR high-degree AVB and the requirement for PPI in the immediate post-operative period (5). The high incidence of new-onset LBBB post-TAVR could explain such a strong association. Yet only 1 recent study specifically assessed the clinical impact of RBBB post-TAVR (15). This Japanese multicenter registry reached similar conclusions as the present analysis regarding overall and cardiovascular mortality at a median follow-up of 16 months. However, the cohort was limited (n = 749), included exclusively balloon-expandable valve recipients, and provided no data regarding SCD and the need for PPI during follow-up. This is of particular importance when trying to explain the potential causes of increased mortality in those patients harboring RBBB.

In the specific setting of TAVR, the occurrence of late conduction disturbances may also be an issue. Because of the close anatomic relationship between the aortic annulus and the nodal-Hisian conduction system, these disturbances often stem from a direct insult to the left bundle branch (26). New-onset LBBB develops in 10% to 60% of patients (depending on valve type), mainly during TAVR or within 24 h of the procedure, persists at discharge in approximately 50% of patients (10% to 37%), and is associated with a higher risk for PPI at follow-up (26,27). Also, new-onset LBBB may be associated with SCD post-TAVR (20). Obviously, among patients with baseline RBBB, the occurrence of new-onset LBBB will generate PPI during the index hospitalization and is therefore unlikely to result in serious and unexpected late adverse events. However, in some cases, post-TAVR conduction disturbances may also be a slowly evolving phenomenon. In a cohort of 130 self-expandable valve recipients, Chorianopoulos et al. (6) demonstrated a 3.8% rate of significant bradycardia >96 h post-TAVR, baseline RBBB being the only independent predictor of such events. New-onset LBBB occurs >3 months following TAVR in approximately 1% of patients (28) and may evolve toward high-degree AVB as late as more than 1 year post-TAVR (29). The occurrence of such late conduction disorders in patients with pre-existing RBBB may lead to hospitalization for heart failure because of high-degree AVB or even to SCD. Actually, 1 case of compression of the conduction system, evidenced by autopsy, in a patient with pre-existing RBBB who died suddenly 21 days post-TAVR was recently reported (30).

TABLE 4 Univariate and Multivariate Predictors of Sudden Cardiac Death Following Transcatheter Aortic Valve Replacement

	Univariate HR (95% CI)	p Value	Multivariate HR* (95% CI)	p Value
Baseline clinical characteristics				
Pre-existing RBBB	0.49 (0.15–1.58)	0.23	0.67 (0.20–2.18)	0.50
Age	1.00 (0.97–1.04)	0.84		
Male	1.31 (0.78–2.20)	0.31		
Body mass index	0.83 (0.49–1.41)	0.49		
NYHA functional class III or IV	1.66 (0.81–3.39)	0.17		
Hypertension	1.33 (0.67–2.63)	0.42		
Diabetes mellitus	1.01 (0.71–1.45)	0.95		
Paroxysmal/chronic atrial fibrillation	1.28 (0.73–2.25)	0.39		
Previous pacemaker	0.47 (0.15–1.50)	0.20		
Coronary artery disease	1.04 (0.62–1.77)	0.88		
Complete or no need for revascularization	0.70 (0.40–1.22)	0.21		
Chronic obstructive pulmonary disease	1.35 (0.77–2.36)	0.30		
Chronic kidney disease (eGFR <60 ml/min)	1.11 (0.64–1.92)	0.71		
Logistic EuroSCORE	1.01 (0.99–1.03)	0.57		
Echocardiographic findings				
Left ventricular ejection fraction ≤40%	2.06 (1.16–3.64)	0.013	2.29 (1.22–4.31)	0.01
Mean transaortic gradient	0.98 (0.97–1.00)	0.09	0.99 (0.97–1.00)	0.15
sPAP >60 mm Hg	1.09 (0.49–2.43)	0.83		
Procedural findings				
Nontransfemoral approach	0.45 (0.19–1.05)	0.07	0.51 (0.21–1.21)	0.13
Balloon-expandable valve type	0.87 (0.52–1.47)	0.61		
Moderate or severe aortic regurgitation	1.98 (1.02–3.83)	0.04	1.56 (0.75–3.25)	0.23
30-day outcomes				
Stroke	2.96 (1.07–8.22)	0.04	2.36 (0.73–7.60)	0.15
Myocardial infarction	-	-		
Major or life-threatening bleeding	1.22 (0.58–2.59)	0.60		
New-onset persistent LBBB	1.98 (1.10–3.57)	0.02	2.02 (1.05–3.90)	0.035
New pacemaker	0.94 (0.44–2.00)	0.88		

*For the multivariate analysis, patients with missing data were included through the use of multiple imputations.
Abbreviations as in Tables 1 and 2.

The present study has several clinical implications. Following the current trend toward simplification of TAVR procedures, some teams suggested that early discharge post-TAVR may be a reasonable option, especially among balloon-expandable valve recipients (31). Our findings suggest that such a strategy may not be suitable for patients with pre-existing RBBB. Whether a strategy of prolonged, continuous monitoring proves beneficial and cost effective in such patients remains to be elucidated. Interestingly, 1 recent study suggested that a significant proportion of patients requiring PPI post-TAVR actually have clinically relevant arrhythmias before the procedure, and thus the inclusion of a pre-procedural period of electrocardiographic monitoring in the TAVR work flow may help identify patients with conduction abnormalities that are not expected to resolve and could lead to an overall reduction in the length of hospital stay (32). Another potential solution to reconcile the safe management of patients with RBBB with the current quest for shorter hospital stay may be more "aggressive" strategies relying on systematic electrophysiological studies or implantable monitoring devices. Some investigators identified specific electrophysiological measurements as predictors of high-degree AVB development post-TAVR (33), but to date there is no strong evidence supporting the use of invasive strategies in routine clinical practice, although several ongoing studies (Online Table 8) will likely shed more light on the natural history of conduction

TABLE 5 Univariate and Multivariate Predictors of Sudden Cardiac Death or New Pacemaker Implantation Following Transcatheter Aortic Valve Replacement Among Patients Without Baseline Pacemaker or Pacemaker Implantation During Index Hospitalization (n = 1,245)

	Univariate HR (95% CI)	p Value	Multivariate HR* (95% CI)	p Value
Baseline clinical characteristics				
Pre-existing RBBB	2.33 (1.11–4.90)	0.025	2.51 (1.10–5.75)	0.029
Age	0.99 (0.96–1.03)	0.69		
Male	1.24 (0.76–2.04)	0.39		
Body mass index	0.90 (0.54–1.49)	0.68		
NYHA functional class III or IV	0.79 (0.44–1.43)	0.44		
Hypertension	1.51 (0.75–3.06)	0.25		
Diabetes mellitus	0.96 (0.56–1.65)	0.88		
Paroxysmal/chronic atrial fibrillation	0.98 (0.54–1.75)	0.93		
Coronary artery disease	1.19 (0.72–1.96)	0.50		
Complete or no need for revascularization	0.78 (0.46–1.31)	0.35		
Chronic obstructive pulmonary disease	1.39 (0.83–2.31)	0.21		
Chronic kidney disease (eGFR <60 ml/min)	1.10 (0.66–1.85)	0.71		
Logistic EuroSCORE	1.01 (0.99–1.03)	0.29		
Echocardiographic findings				
Left ventricular ejection fraction ≤40%	1.37 (0.80–2.36)	0.25		
Mean transaortic gradient	0.98 (0.96–0.995)	0.012	0.98 (0.96–0.99)	0.012
sPAP >60 mm Hg	1.22 (0.60–2.49)	0.59		
Procedural findings				
Nontransfemoral approach	1.05 (0.61–1.81)	0.87		
Balloon-expandable valve type	0.87 (0.53–1.43)	0.58		
Discharge QRS duration	1.01 (1.005–1.02)	0.001	1.01 (0.998–1.02)	0.10
30-day outcomes				
Stroke	3.82 (1.53–9.55)	0.004	3.34 (1.20–9.34)	0.02
Major or life-threatening bleeding	1.20 (0.61–2.36)	0.60		
New-onset persistent LBBB	1.85 (1.11–3.09)	0.018	1.58 (0.83–3.00)	0.17

*For the multivariate analysis, patients with missing data were included through the use of multiple imputations.
Abbreviations as in Tables 1 and 2.

disturbances following TAVR and provide insights into their optimal therapy.

STUDY LIMITATIONS. Given the nonrandomized nature of the study, the presence of unmeasured confounders that may influence the relationship between RBBB and outcomes cannot be excluded. Although the causes of death at each center were defined according to the VARC-2 criteria, no event adjudication committee was available in this study. Electrocardiographic and echocardiographic findings were interpreted at each center, with no electrocardiographic or echocardiographic core laboratory evaluation. Data regarding the use of atrioventricular node-blocking medications, which may affect the need for PPI, were not available. Finally, the need for PPI, as well as the indication for PPI, during follow-up was not prospectively recorded in all centers.

CONCLUSIONS

Pre-existing RBBB was found in 10.3% of TAVR recipients and was associated with a higher risk for all-cause and cardiovascular mortality, especially among patients without pacemakers at hospital discharge. A meaningful association between pre-existing RBBB and the composite of PPI and SCD during follow-up also emerged among patients without PPI at hospital discharge. Future studies should evaluate strategies aimed at the early detection of patients at risk for late development of high-degree AVB. Meanwhile, prolonged monitoring may be considered in patients with pre-existing RBBB.

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PERSPECTIVES

WHAT IS KNOWN? RBBB has been associated with higher risks for all-cause and cardiovascular death in the general population and is a recognized risk factor of post-operative PPI post-TAVR. However, little is known regarding the midterm prognosis of pre-existing RBBB following TAVR.

WHAT IS NEW? Baseline RBBB was present in 10% of TAVR recipients and was associated with an increased risk for PPI at 30 days. After a mean follow-up of about 2 years, baseline RBBB was associated with a significant increase in the risk for all-cause and cardiovascular mortality but not SCD. Among patients without PPI at discharge of the index hospitalization, RBBB associated with a higher risk for a composite of SCD or need for PPI.

WHAT IS NEXT? Future studies are required to elucidate the optimal management of TAVR recipients with RBBB, especially by evaluating the optimal pre- and post-TAVR monitoring strategies as well as invasive strategies such as systematic electrophysiological studies, implantable monitoring devices, or "prophylactic" PPI in selected cases.

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KEY WORDS outcomes, permanent pacemaker implantation, right bundle branch block, sudden cardiac death, transcatheter aortic valve replacement

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