University of Zurich[UZH]

Zurich Open Repository and Archive
University of Zurich
Main Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2018

Impact of Preexisting Left Bundle Branch Block in Transcatheter Aortic Valve Replacement Recipients

Fischer, Quentin ; Himbert, Dominique ; Webb, John G ; Eltchaninoff, Helene ; et al ; Nietlispach, Fabian ; Maisano, Francesco

Abstract: BACKGROUND The impact of preexisting left bundle branch block (LBBB) in transcatheter aortic valve replacement (TAVR) recipients is unknown. The aim of this study was to determine the impact of preexisting LBBB on clinical outcomes after TAVR. METHODS AND RESULTS This multicenter study evaluated 3404 TAVR candidates according to the presence or absence of LBBB on baseline ECG. TAVR complications and causes of death were defined according to Valve Academic Research Consortium-2 definitions. Follow-up outpatient visits or telephone interviews were conducted at 30 days, 12 months, and yearly thereafter. Echocardiography examinations were performed at baseline, at hospital discharge, and at 1-year follow-up. Preexisting LBBB was present in 398 patients (11.7%) and was associated with an increased risk of permanent pacemaker implantation (PPI; 21.1% versus 14.8%; adjusted odds ratio, 1.51; 95% CI, 1.12-2.04) but not death (7.3% versus 5.5%; adjusted odds ratio, 1.33; 95% CI, 0.84-2.12) at 30 days. At a mean follow-up of 22±21 months, there were no differences between patients with and without preexisting LBBB in overall mortality (adjusted hazard ratio, 0.94; 95% CI, 0.75-1.18) and cardiovascular mortality (adjusted hazard ratio, 0.90; 95% CI, 0.68-1.21). In a subanalysis of 2421 patients without PPI at 30 days and with complete follow-up about the PPI, preexisting LBBB was not associated with an increased risk of PPI or sudden cardiac death. Patients with preexisting LBBB had a lower left ventricular ejection fraction (LVEF) at baseline and at 1-year follow-up (P <0.001 for both), but those with low LVEF exhibited a similar increase in LVEF over time after TAVR compared with patients with no preexisting LBBB (P=0.327). CONCLUSIONS Preexisting LBBB significantly increased the risk of early (but not late) PPI after TAVR, without any significant effect on overall mortality or cardiovascular mortality. Preexisting LBBB was associated with lower LVEF pre-TAVR but did not prevent an increase in LVEF post-TAVR similar to patients without LBBB.

DOI: https://doi.org/10.1161/CIRCINTERVENTIONS.118.006927

Posted at the Zurich Open Repository and Archive, University of Zurich
ZORA URL: https://doi.org/10.5167/uzh-164896
Journal Article
Published Version

Originally published at:
Fischer, Quentin; Himbert, Dominique; Webb, John G; Eltchaninoff, Helene; et al; Nietlispach, Fabian; Maisano, Francesco (2018). Impact of Preexisting Left Bundle Branch Block in Transcatheter Aortic Valve Replacement Recipients. Circulation. Cardiovascular Interventions, 11(11):e006927.
DOI: https://doi.org/10.1161/CIRCINTERVENTIONS.118.006927

Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Impact of Preexisting Left Bundle Branch Block in Transcatheter Aortic Valve Replacement Recipients

See Editorial by Gulati and Wang

Quentin Fischer, MD et al

BACKGROUND: The impact of preexisting left bundle branch block (LBBB) in transcatheter aortic valve replacement (TAVR) recipients is unknown. The aim of this study was to determine the impact of preexisting LBBB on clinical outcomes after TAVR.

METHODS AND RESULTS: This multicenter study evaluated 3404 TAVR candidates according to the presence or absence of LBBB on baseline ECG. TAVR complications and causes of death were defined according to Valve Academic Research Consortium-2 definitions. Follow-up outpatient visits or telephone interviews were conducted at 30 days, 12 months, and yearly thereafter. Echocardiography examinations were performed at baseline, at hospital discharge, and at 1-year follow-up. Preexisting LBBB was present in 398 patients (11.7%) and was associated with an increased risk of permanent pacemaker implantation (PPI; 21.1% versus 14.8%; adjusted odds ratio, 1.51; 95% CI, 1.12–2.04) but not death (7.3% versus 5.5%; adjusted odds ratio, 1.33; 95% CI, 0.84–2.12) at 30 days. At a mean follow-up of 22±21 months, there were no differences between patients with and without preexisting LBBB in overall mortality (adjusted hazard ratio, 0.94; 95% CI, 0.75–1.18) and cardiovascular mortality (adjusted hazard ratio, 0.90; 95% CI, 0.68–1.21). In a subanalysis of 2421 patients without PPI at 30 days and with complete follow-up about the PPI, preexisting LBBB was not associated with an increased risk of PPI or sudden cardiac death. Patients with preexisting LBBB had a lower left ventricular ejection fraction (LVEF) at baseline and at 1-year follow-up (P <0.001 for both), but those with low LVEF exhibited a similar increase in LVEF over time after TAVR compared with patients with no preexisting LBBB (P=0.327).

CONCLUSIONS: Preexisting LBBB significantly increased the risk of early (but not late) PPI after TAVR, without any significant effect on overall mortality or cardiovascular mortality. Preexisting LBBB was associated with lower LVEF pre-TAVR but did not prevent an increase in LVEF post-TAVR similar to patients without LBBB.

Downloaded from http://ahajournals.org by on February 21, 2019

The full author list is available on page 8.

Key Words: aortic valve ■ bundle-branch block ■ cause of death ■ echocardiography ■ follow-up studies ■ transcatheter aortic valve replacement

© 2018 American Heart Association, Inc.

https://www.ahajournals.org/journal/circinterventions

WHAT IS KNOWN

- Preexisting right bundle branch block has been identified as the most important risk factor for permanent pacemaker implantation post-transcatheter aortic valve replacement, and some studies have shown an increased mortality risk among patients with preexisting right bundle branch block. However, no specific data exist on the impact of preexisting left bundle branch block on transcatheter aortic valve replacement outcomes.

WHAT THE STUDY ADDS

- In transcatheter aortic valve replacement recipients, preexisting left bundle branch block increases the risk of permanent pacemaker implantation but not mortality at 30 days.
- Preexisting left bundle branch block does not associate with increased mortality or heart failure hospitalization at 2-year follow-up, and most patients improve their left ventricular ejection fraction over time.

The prevalence of left bundle branch block (LBBB) is <1% in the general population but increases in case of underlying cardiomyopathy, as well as with age, from ≈0.5% at 50 years to 5% at 80 years.[1] LBBB has been associated with an increased risk of adverse outcomes, including major cardiac events and mortality.[2–4] Indeed, LBBB results in persistent asynchronous ventricular activation,[5] which may lead to a redistribution of myocardial blood flow with septal hypoperfusion, left ventricular (LV) remodeling with ventricular dilatation, asymmetrical hypertrophy, mitral regurgitation, and reduction of LV ejection fraction (LVEF).[6–8] This may become a vicious cycle with progressive LV failure, which often correlates with further progression of the conduction abnormality as well.

Transcatheter aortic valve replacement (TAVR) is a well-established therapy for patients with aortic stenosis and intermediate-to-prohibitive surgical risk.[9] However, the occurrence of conduction disturbances and the need for permanent pacemaker implantation (PPI) remain the most frequent complications of TAVR.[10] Preexisting right bundle branch block (RBBB) has been identified as the most important risk factor for PPI post-TAVR,[10] and some studies have shown an increased mortality risk among patients with preexisting RBBB.[11,12] However, no specific data exist on the impact of preexisting LBBB on TAVR outcomes. Therefore, the aim of this study was to evaluate the impact of preexisting LBBB on clinical outcomes in patients undergoing TAVR.

METHODS

Population

The data, analytic methods, and study materials will be available to other researchers for purposes of reproducing the results (the author for correspondence should be contacted for the data). A total of 4513 patients underwent TAVR in 18 centers between February 2005 and October 2017. Of these, 4434 patients with high-quality ECGs at baseline were included in the present analysis and grouped according to the presence of baseline complete LBBB. Patients with complete RBBB (n=434) or previous pacemaker (n=596) were excluded from the study, leading to a final study population of 3404 patients. Patients with incomplete LBBB were considered as no preexisting LBBB. TAVR indication, valve type, and approach were determined by each center's heart team. Clinical outcomes were defined according to the Valve Academic Research Consortium-2 definitions.[13]

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 ECG.[14] PPI was mainly performed if third-degree or advanced second-degree atrioventricular block 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.[15] However, the final indication for PPI was at the discretion of the physician responsible for the patient, with no prospective or centralized control about the decision and reasons for PPI. Therefore, the possibility of PPI out of current guideline recommendations in some cases cannot be excluded. Data were collected in accordance to the ethics committee of each participating center, and all patients provided signed informed consent for the procedures.

Follow-Up

Follow-up was undertaken by telephone and on-site clinical visit at 1 month, 1 year, and yearly thereafter. Follow-up was obtained in 97.2% of patients (94 patients, 2.8% of the study population, were lost to follow-up), and the mean follow-up was 22±21 months. Complete follow-up about the time for PPI was obtained in a subgroup of 2564 patients (75.3%). Rate of complete follow-up was similar in both groups (77.1% in the LBBB group versus 75.1% in the no-LBBB group; P=0.372).

Complete echocardiography examinations were obtained at baseline (3349 patients; 98.4% of the population), at hospital discharge/1-month follow-up (2819 patients; 88.6% of patients alive at hospital discharge), and at 1-year follow-up (1689 patients; 58.0% of the patients at risk at 1-year follow-up). Changes in LVEF were analyzed in all patients with complete echocardiography at the 3 time points.

Outcomes

The primary outcomes of this analysis were (1) PPI and (2) cumulative all-cause mortality. Secondary outcomes were cardiovascular death, sudden cardiac death (SCD), and changes in LVEF over time. All outcomes were evaluated according to the

Downloaded from http://ahajournals.org by on February 21, 2019

presence of baseline LBBB. Morphology of the QRS on baseline ECG was available in all patients. Methods used to assess causes of death were published previously.[16] Cardiovascular death was defined according to Valve Academic Research Consortium-2 criteria. SCD was defined, in accordance with the World Health Organization definition, as a death occurring within 1 hour of symptom onset if witnessed or within the previous 24 hours if unwitnessed. Patients with known terminal disease or an identifiable noncardiac cause of sudden death were not considered to have experienced SCD.[17]

Statistical Analysis

Qualitative variables were expressed as number (percentage), whereas continuous data were presented as mean±SD or median (interquartile range) depending on their distribution. Survival rates were summarized using Kaplan-Meier estimates including all events ≤24-month follow-up, and log-rank tests were used to compare groups. Differences between groups in clinical outcomes were analyzed using a logistic regression (30-day outcomes) or Cox proportional-hazards models to adjust for baseline differences between groups. The variables included in the model were age, sex, atrial fibrillation, chronic kidney disease, LVEF <50%, and mean gradient. An ANOVA for repeated measures model with interaction was used to analyze the changes in LVEF over time. Posterior comparisons were performed using the Tukey post hoc test. All tests were 2 sided at the 0.05 significance level. Statistical analyses were conducted with the statistical package SAS, version 9.3 (SAS Institute, Cary, NC).

RESULTS

The main clinical characteristics, echocardiographic, and procedural findings of the study population are shown in Table 1. Patients in the LBBB group were older, had a higher operative risk, and a lower baseline LVEF (P <0.03 for all). There were no differences between groups about the procedural findings, approach, and transcatheter valve type.

The 30-day outcomes according to preexisting LBBB are shown in Table 2. At 30 days, the mortality rate was similar in the preexisting LBBB and no-LBBB groups (7.3% versus 5.5%; adjusted odds ratio, 1.33; 95% CI, 0.84–2.12; P=0.217). PPI occurred in 21.1% of patients with preexisting LBBB compared with 14.8% in the no-LBBB group (adjusted odds ratio, 1.51; 95% CI, 1.12–2.04; P=0.006). At 30 days, no patient had a cardiac resynchronization therapy, and pacemaker type (single versus dual chamber) was similar in both groups (adjusted odds ratio, 1.08; 95% CI, 0.43–2.73; P=0.864). The PPI rate was higher in those patients receiving a self-expandable valve (23.1% versus 8.7% for balloon-expandable valves; P<0.001), as well as during the second (2012–2017) versus first (2005–2011) study time periods (16.9% versus 13.9%; P=0.015). The rate of LBBB pre-TAVR was similar in the first and second study time periods (11.5% versus 12.0%; P=0.630).

Table 1. Baseline and Procedural Findings of the Study Population, According to Preexisting LBBB

Variables	LBBB (n=398)	No LBBB (n=3006)	*P* Value
Baseline clinical characteristics			
Age, y	82.0±7.1	81.0±8.1	0.014
Men	218 (54.8)	1392 (46.3)	0.002
Body mass index, kg/m^2	26.5±5.0	26.7±5.1	0.452
Hypertension	302 (75.9)	2237 (75.1)	0.725
Diabetes mellitus	104 (26.1)	878 (29.4)	0.172
Atrial fibrillation	133 (33.9)	814 (27.8)	0.01
Previous cardiac surgery	97 (25.8)	624 (23.0)	0.226
Coronary artery disease	203 (51.0)	1438 (48.1)	0.275
Complete or no need for revascularization	278 (74.3)	2117 (75.3)	0.697
Chronic obstructive pulmonary disease	92 (23.1)	679 (22.8)	0.875
Chronic kidney disease (eGFR, <60 mL/min)	213 (56.2)	1444 (50.1)	0.026
Peripheral artery disease	75 (19.6)	529 (19.0)	0.794
STS score, %	6.2±4.0	5.5±3.2	0.024
Echocardiographic findings			
Left ventricular ejection fraction, %	48.8±16.3	56.9±12.9	<0.001
Left ventricular ejection fraction ≤50%	186 (48.4)	757 (25.8)	<0.001
Mean transaortic gradient, mm Hg	44.0±16.2	48.6±16.8	<0.001
sPAP>60 mm Hg	42 (14.9)	240 (11.8)	0.130
Procedural findings			
Primary access			0.626
Transfemoral	319 (80.2)	2444 (81.3)	
Subclavian	13 (3.3)	62 (2.1)	
Transapical	54 (13.6)	424 (14.1)	
Transaortic	7 (1.8)	40 (1.3)	
Valve type			0.355
Self-expandable	191 (48.1)	1369 (45.6)	
Balloon expandable	206 (51.9)	1630 (54.4)	
Implantation success (VARC-2)	336 (85.9)	2471 (83.4)	0.206
Median length of stay, d (IQR)	7 (5–13.5)	7 (5–12)	0.347

eGFR indicates estimated glomerular filtration rate; IQR, interquartile range; LBBB, left bundle branch block; sPAP, systolic pulmonary artery pressure; STS, Society of Thoracic Surgeons; and VARC-2, Valve Academic Research Consortium-2.

In the no-LBBB group, a total of 2463 (72.4%) patients had a completely normal ventricular conduction, whereas 278 (9.2%), 10 (0.3%), 66 (2.2%), and 189 (6.3%) patients had a left anterior hemiblock, a left posterior hemiblock, an incomplete LBBB, and a nonspecific intraventricular conduction delay, respectively. The 30-day PPI rate was 14.3% in those patients with normal ventricular conduction versus 16.9% in

Downloaded from http://ahajournals.org by on February 21, 2019

Table 2. Thirty-Day Outcomes, According to the Presence of Preexisting LBBB

Variables	LBBB (n=398)	No LBBB (n=3006)	OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Death	29 (7.3)	165 (5.5)	1.43 (0.95–2.17)	0.089	1.33 (0.84–2.12)	0.217
Cardiovascular death	25 (6.3)	141 (4.7)	1.44 (0.93–2.25)	0.106	1.39 (0.85–2.27)	0.189
Stroke	16 (4.0)	105 (3.5)	1.15 (0.67–1.97)	0.619	0.85 (0.45–1.62)	0.633
Myocardial infarction	7 (1.8)	36 (1.2)	1.61 (0.70–3.68)	0.263	1.27 (0.50–3.19)	0.618
Major or life-threatening bleeding event	60 (15.1)	413 (13.8)	1.26 (0.93–1.70)	0.135	1.35 (0.98–1.86)	0.067
New pacemaker	84 (21.1)	445 (14.8)	1.37 (1.04–1.81)	0.023	1.51 (1.12–2.04)	0.006
Moderate or severe aortic regurgitation	37 (10.8)	282 (10.8)	0.92 (0.63–1.34)	0.668	0.81 (0.53–1.23)	0.322

LBBB indicates left bundle branch block; and OR, odds ratio.

patients with left anterior hemiblock (*P*=0.249), 20.0% in patients with a left posterior hemiblock (*P*=0.610), 16.7% in patients with an incomplete LBBB (*P*=0.594), and 14.4% in patients with a nonspecific intraventricular conduction delay (*P*=0.991).

Late Clinical Outcomes

At a mean follow-up of 22±21 months, 914 patients (26.9%) had died. Cardiovascular death occurred in 573 patients (16.8%), including heart failure (HF) death in 154 patients (4.5%) and SCD in 84 patients (2.5%). Late clinical events post-TAVR grouped according to preexisting LBBB are shown in Table 3. There were no differences between groups in late all-cause mortality (adjusted hazard ratio, 0.84; 95% CI, 0.64–1.08; *P*=0.173) or cardiovascular mortality (adjusted hazard ratio, 0.74; 95% CI, 0.51–1.05; *P*=0.093). The Kaplan-Meier curves for clinical events (mortality, cardiovascular mortality, and hospitalization for HF) ≤2-year follow-up are shown in Figure 1.

The cumulative rate of PPI was higher in the preexisting LBBB group (22.9% versus 16.5%; hazard ratio, 1.40; 95% CI, 1.11–1.78; *P*=0.006). However, this was because of an increased PPI rate early after TAVR (median time of PPI, 4 [interquartile range, 1–7] days), and no differences between groups were observed in the PPI rate after the first 30 days post-TAVR (preexisting LBBB, 2.2%; no preexisting LBBB, 1.9%; adjusted hazard ratio, 0.95; 95% CI, 0.45–2.03; *P*=0.904). The Kaplan-Meier curves for PPI and SCD are shown in Figure 2. There were no differences in late (>30 days) sudden death or PPI between groups.

LVEF Changes After TAVR

Patients in the preexisting LBBB group had a baseline LVEF significantly lower than patients with no preexisting

Table 3. Late Outcomes After TAVR, According to the Presence of Preexisting LBBB

Variables	LBBB (n=398)	No LBBB (n=3006)	HR (95% CI)	*P* Value	Adjusted HR (95% CI)	*P* Value
Late outcomes (>30 d)*						
Death	79 (21.4)	641 (22.6)	0.91 (0.71–1.16)	0.431	0.84 (0.64–1.08)	0.173
Cardiovascular death	43 (11.5)	364 (12.7)	0.86 (0.62–1.20)	0.384	0.74 (0.51–1.05)	0.093
Stroke	6 (1.6)	44 (1.5)	1.09 (0.43–2.77)	0.863	1.15 (0.41–3.24)	0.789
Myocardial infarction	0	12 (0.4)	…	…	…	…
New pacemaker	7 (2.2)	50 (1.9)	1.22 (0.53–2.79)	0.642	0.95 (0.45–2.03)	0.904
Hospitalization for HF	39 (10.1)	239 (8.2)	1.20 (0.84–1.70)	0.319	1.07 (0.74–1.55)	0.706
Cumulative outcomes†						
Death	108 (27.1)	806 (26.8)	1.01 (0.81–1.24)	0.978	0.94 (0.75–1.18)	0.596
Cardiovascular death	68 (17.1)	505 (16.8)	1.01 (0.78–1.32)	0.938	0.90 (0.68–1.21)	0.509
Stroke	22 (5.5)	149 (4.9)	1.16 (0.73–1.82)	0.533	1.09 (0.68–1.76)	0.735
Myocardial infarction	7 (1.8)	48 (1.6)	1.20 (0.55–2.62)	0.650	1.16 (0.52–2.64)	0.713
New pacemaker	91 (22.9)	495 (16.5)	1.41 (1.12–1.78)	0.004	1.40 (1.11–1.78)	0.006
Hospitalization for HF	52 (13.1)	320 (10.7)	1.20 (0.89–1.62)	0.243	1.05 (0.76–1.44)	0.785

LBBB indicates left bundle branch block; HF, heart failure; HR, hazard ratio; and TAVR, transcatheter aortic valve replacement.

*Late outcomes were defined by outcomes occurring after the first 30 d post-TAVR. Patients whose events occurred before 30 d were excluded of this analysis.

†Cumulative outcomes were showed without time censure.

Downloaded from http://ahajournals.org by on February 21, 2019

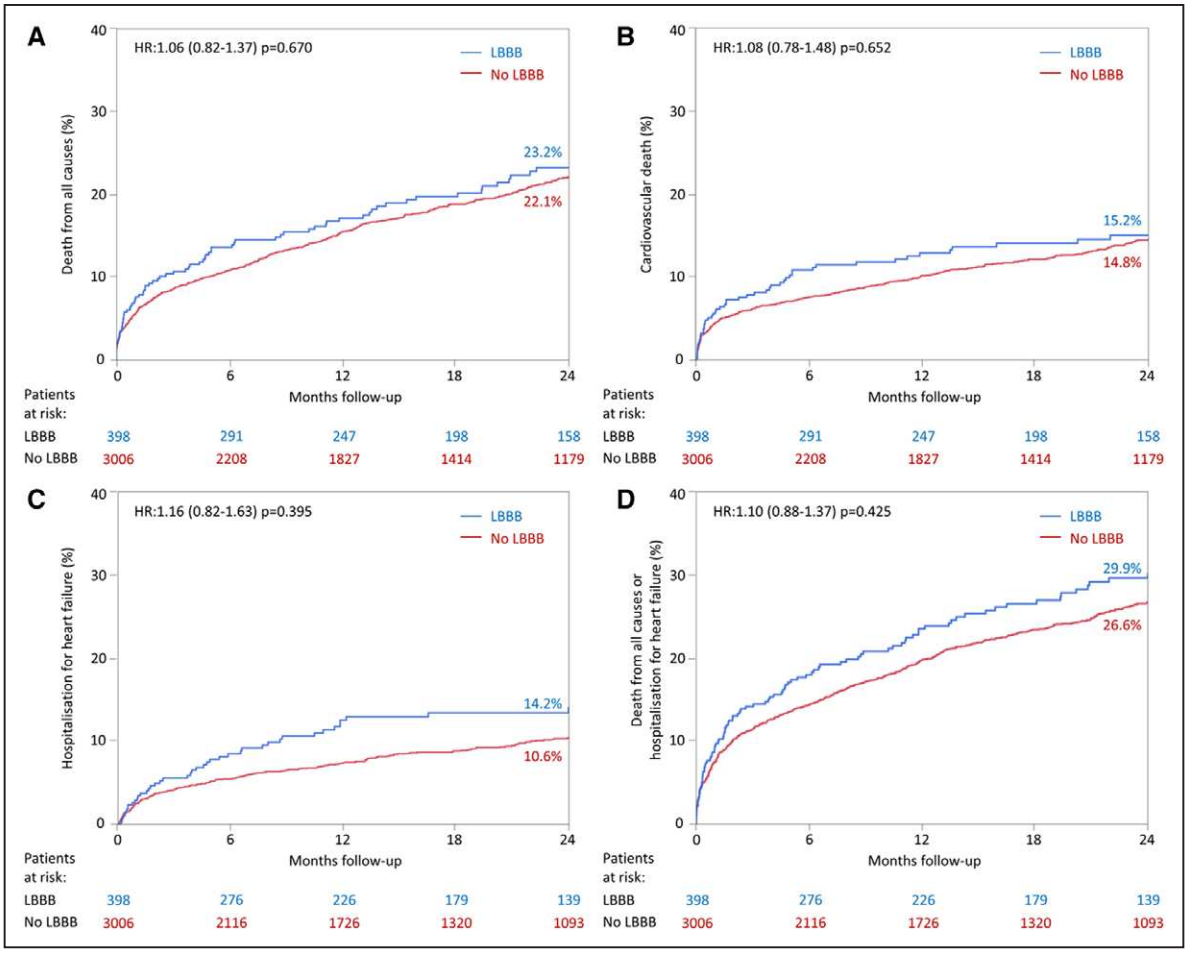

Figure 1. Clinical events at 2-y follow-up, according to preexisting left bundle branch block (LBBB).
A, Kaplan-Meier curves at 2-y follow-up for overall mortality according to the presence of preexisting LBBB. **B**, Kaplan-Meier curves at 2-y follow-up for cardiovascular mortality according to the presence of preexisting LBBB. **C**, Kaplan-Meier curves at 2-y follow-up for hospitalization for heart failure according to the presence of preexisting LBBB. **D**, Kaplan-Meier curves at 2-y follow-up for overall mortality or hospitalization for heart failure according to the presence of preexisting LBBB. HR indicates hazard ratio.

LBBB (48.4±0.8% versus 57.0±0.2%; *P*<0.001). At discharge, LVEF increased in both groups (51.3±0.8% in the preexisting LBBB group, Δ+2.9±0.7% versus 58.4±0.2% in the no preexisting LBBB group, Δ+1.4±0.2%). LVEF continued to increase in both groups during follow-up (at 12-month follow-up: 52.6±0.9% in the preexisting LBBB group, Δ+4.2±0.9% versus 59.1±0.3% in the no preexisting LBBB, Δ+2.0±0.3%). Despite a lower LVEF in the preexisting LBBB group, the relative increase of the LVEF 1 year post-TAVR was not significantly different between the 2 groups (*P*=0.085; Figure 3A). Likewise, among patients with baseline LVEF ≤50%, LVEF increased from 38.8±0.4% at baseline to 46.2±0.6% at hospital discharge (Δ+7.4±0.4%) and reached 50.2±0.6% 1 year after TAVR (Δ+11.4±0.6%). LVEF increased in both groups at discharge (42.0±1.1% in the preexisting LBBB group, Δ+7.3±0.9% versus 47.4±0.6% in the no preexisting LBBB group, Δ+7.4±0.5%) and continued to increase in both groups during follow-up (45.6±1.3% in the preexisting LBBB group, Δ+10.9±1.3% versus 51.6±0.6% in the no preexisting LBBB group at 1 year, Δ+11.5±0.6%; Figure 3B). Among patients with baseline LVEF <50%, similar changes in LVEF over time were observed in the preexisting LBBB and no preexisting LBBB groups (*P*=0.327).

DISCUSSION

In patients undergoing TAVR, preexisting LBBB was associated with an increased risk of PPI but not mortality at 30 days. Preexisting LBBB had no deleterious effect on late outcomes, including overall and cardiovascular mortality. Patients with preexisting LBBB exhibited a lower LVEF pre-TAVR but experienced a similar degree of increase in LVEF at 1-year follow-up compared with those patients with no significant conduction disturbances pre-TAVR.

Previous studies have shown a prevalence of LBBB in TAVR candidates close to 10%,[12,16,18] and the slightly higher rate observed in our study (≈12%) may be related to the exclusion of patients with other conduction abnormalities, such as RBBB or those with prior

Downloaded from http://ahajournals.org by on February 21, 2019

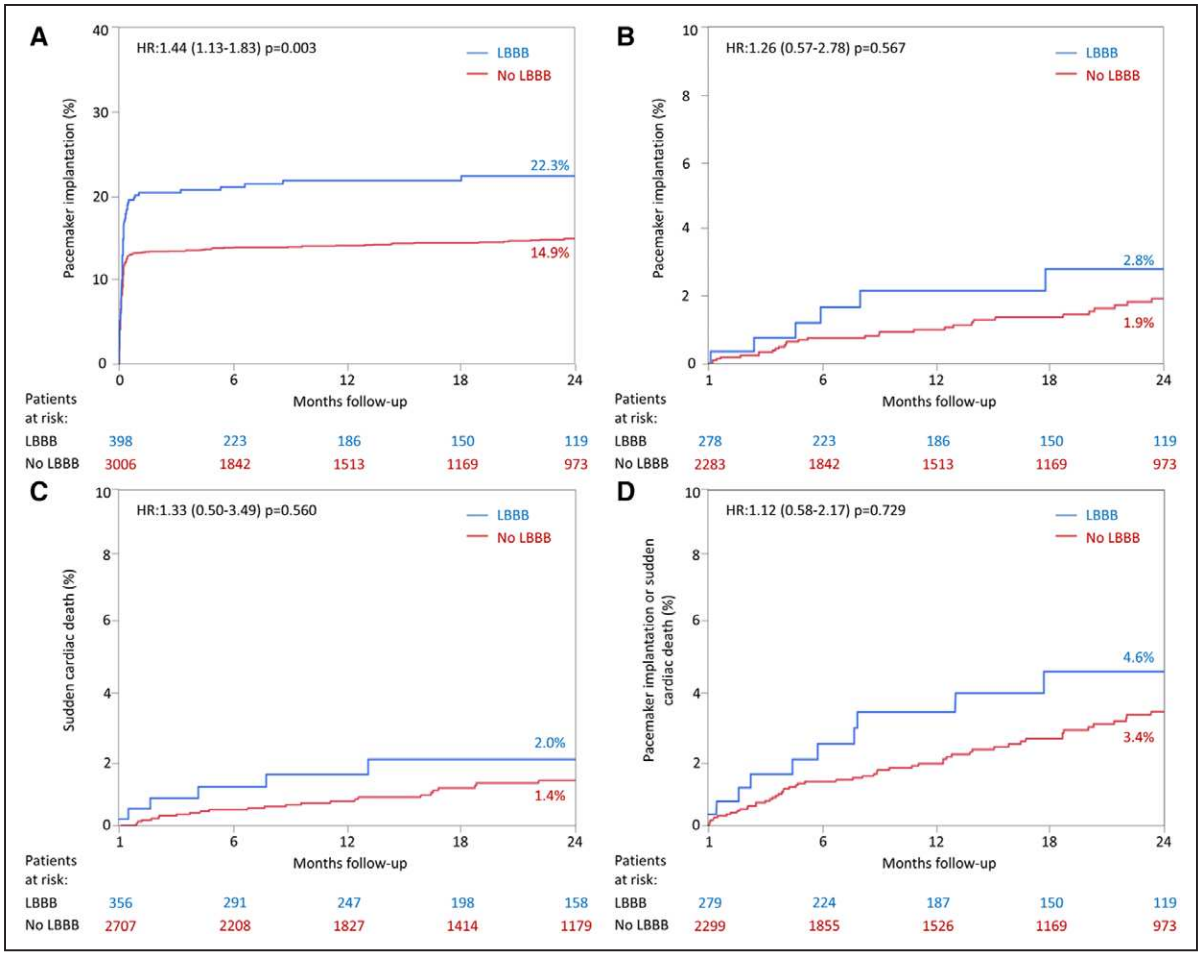

Figure 2. Permanent pacemaker implantation and sudden cardiac death at 2-y follow-up, according to preexisting left bundle branch block (LBBB). **A**, Kaplan-Meier curves at 2-y follow-up for permanent pacemaker implantation (PPI) according to the presence of preexisting LBBB. **B**, Kaplan-Meier curves for PPI between 30 d and 2 y according to the presence of preexisting LBBB in patients with no PPI at 30-d follow-up. **C**, Kaplan-Meier curves for sudden cardiac death (SCD) between 30 d and 2 y according to the presence of preexisting LBBB in patients with no PPI at 30-d follow-up. **D**, Kaplan-Meier curves for SCD or PPI between 30 d and 2 y according to the presence of preexisting LBBB in patients with no PPI at 30-d follow-up. HR indicates hazard ratio.

pacemaker. The development of ventricular conduction disorders, particularly LBBB, can result from either intrinsic conduction system degeneration or an extrinsic insult from a variety of cardiovascular diseases.[19] Several factors have been associated with LBBB development, including LV hypertrophy, increased cardiac volume, hypertension, valvular heart disease, cardiomyopathies, myocarditis, and coronary artery disease.[20,21] Most patients with severe aortic stenosis have many of these risk factors, and this may explain the higher rate of LBBB in this population compared with the general population.

The rates of PPI after TAVR are highly variable but average 13%,[10] and no significant decrease in the incidence of PPI has been observed in the past years, despite the increasing experience of centers/operators and the use of newer generation valve systems.[10,22] Multiple risk factors have been identified as independent predictors for PPI post-TAVR, like valve type, LV outflow tract calcium load, implantation depth, or preexisting RBBB.[10,23] The His bundle bifurcates into the right and left bundles at the inferior border of the membranous septum, with the latter emerging beneath the noncoronary cusp. Therefore, valve implantation that overlaps the distal membranous septum may affect both the right and left bundles and lead to complete heart block. Electrophysiological studies showed that aortic valve implantation increases the risk of conduction disturbances, most likely by increasing the His-ventricle interval or inducing an infra-Hisian block.[24] Our study was the first to highlight that baseline LBBB significantly increases the risk of PPI after TAVR. Importantly, the increased risk occurred early after TAVR, probably secondary to the mechanical compression of the His bundle during valve implantation, and no significant increase in the rate of late PPI or SCD was observed at 2-year follow-up. This provides some reassurance about the management of these patients in the absence of advanced conduction disturbances during the hospitalization period and contrasts with the results observed in the presence of new-onset LBBB post-TAVR, which seems to determine an increased risk of PPI and SCD within

Downloaded from http://ahajournals.org by on February 21, 2019

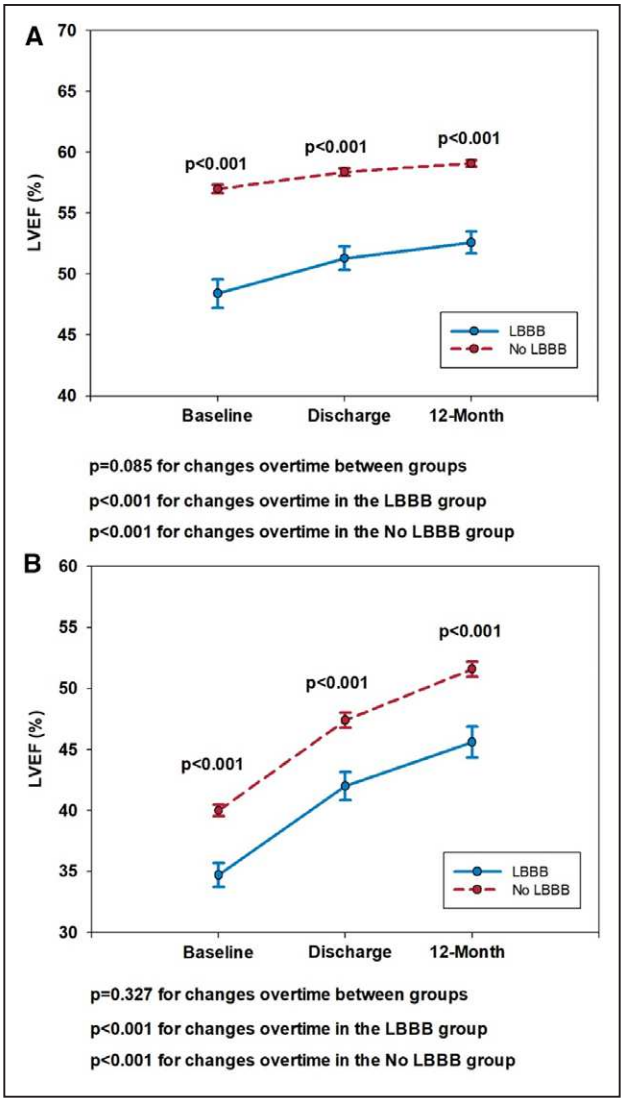

Figure 3. Changes in left ventricular ejection fraction (LVEF) after transcatheter aortic valve replacement (TAVR), according to preexisting left bundle branch block (LBBB).
A, LVEF changes over time in overall population. **B**, LVEF changes over time after TAVR in patients with LVEF <50% at baseline.

the months after the procedure.[10,16,25] Interestingly, the presence of preexisting LBBB has already been identified as an important risk factor for PPI after surgical aortic valve replacement.[26] These results should be taken into account in the preparation of the TAVR procedures, considering the use of a valve type associated with a lower risk of conduction disturbance issues and a high (more aortic) transcatheter valve positioning in those patients with preexisting LBBB, to decrease the PPI after TAVR.

Several studies in nonaortic stenosis populations have shown the negative effects of LBBB on long-term (≥10 years) outcomes, particularly in elderly patients and in the presence of underlying heart disease.[27–33] The lack of increase in mortality risk at 2-year follow-up in our study may be because of the positive effects related to the treatment of aortic stenosis and the increase in the LVEF post-TAVR along with the shorter follow-up compared with prior studies in the general population and in patients with other cardiomyopathies. A continuous follow-up of such patients will be important in determining the impact of preexisting LBBB on longer term clinical outcomes post-TAVR.

In patients with HF and reduced LVEF, LBBB is associated with an increased incidence of sudden death, all-cause mortality, and acute HF.[34–36] In contrast, we failed to find an increase in the rate of hospitalizations for HF among TAVR recipients with preexisting LBBB, despite a lower LVEF in this group. This could be partially explained by a similar improvement in LV function in patients with and without preexisting LBBB within the months after TAVR. Unlike other studies in patients with other cardiac diseases, even those patients with LBBB and reduced LVEF at inclusion experienced similar improvement in LVEF than patients without LBBB during follow-up. A recent study found that patients with LBBB and mild-to-moderate LV dysfunction (LVEF between 36% and 50%) have exceedingly poor outcomes. At 5 years, 59% of patients had died, further decreased their LVEF ≤35%, had a sustained ventricular arrhythmia, or required device implantation.[37] LBBB results in dysynchronous electrical activation of the ventricles and inefficient contraction of the LV and may lead to progressive LV failure. This process may be disrupted by cardiac resynchronization therapy, and the indication for resynchronization should be evaluated in patients with complete LBBB and persistent LVEF ≤35% after TAVR. However, the results of the present study showing significant improvements in LVEF in a high proportion of patients strongly suggest that this evaluation should not be performed immediately but several months after the TAVR procedure.

Study Limitations

Given the nonrandomized nature of the study, the presence of unmeasured confounders that may influence the relationship between LBBB and outcomes cannot be excluded.

Although the causes of death at each center were defined according to the Valve Academic Research Consortium-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. Depth of implant, degree of LV outflow tract calcification, and duration of the PR interval on baseline ECG were not available in most patients, precluding an analysis of the impact of these factors in PPI rates. In addition, echocardiographic data at 1-year follow-up were available in ≈60% of patients. Data about the use of atrioventricular node–blocking medications, which may affect the PPI, were not available. Finally, the indication for PPI during follow-up was not collected in all centers.

Downloaded from http://ahajournals.org by on February 21, 2019

Conclusions

The results of this study show that preexisting LBBB increased the risk for PPI early post-TAVR. However, preexisting LBBB in TAVR recipients was not associated with increased mortality or HF hospitalization at 2-year follow-up, and there were significant improvements in LVEF in most patients. This suggests that the possible use of specific therapies, including cardiac resynchronization therapy, should be delayed by several months to avoid implementing unnecessary treatment. Future studies should determine the longer term outcomes of such patients.

ARTICLE INFORMATION

Received May 8, 2018; accepted August 11, 2018.

Authors

Quentin Fischer, MD; Dominique Himbert, MD; John G. Webb, MD; Helene Eltchaninoff, MD; Antonio J. Muñoz-García, MD, PhD; Corrado Tamburino, MD, PhD; Luis Nombela-Franco, MD, PhD; Fabian Nietlispach, MD, PhD; Cesar Moris, MD, PhD; Marc Ruel, MD; Antonio E. Dager, MD; Vicenç Serra, MD; Asim N. Cheema, MD; Ignacio J. Amat-Santos, MD, PhD; Fabio Sandoli de Brito, MD; Henrique Ribeiro, MD, PhD; Alexandre Abizaid, MD; Rogério Sarmento-Leite, MD; Eric Dumont, MD; Marco Barbanti, MD; Eric Durand, MD, PhD; Juan H. Alonso Briales, MD; Claire Bouleti, MD, PhD; Sebastiano Immè, MD; Francesco Maisano, MD; Raquel del Valle, MD; Luis Miguel Benitez, MD; Bruno García del Blanco, MD; Mélanie Côté, MSc; François Philippon, MD, FRCPC, FHRS; Marina Urena, MD, PhD; Josep Rodés-Cabau, MD

Correspondence

Josep Rodés-Cabau, MD, Quebec Heart and Lung Institute, Laval University, 2725 Chemin Ste-Foy, G1V 4GS, Quebec City, Quebec, Canada. Email josep.rodes@criucpq.ulaval.ca

Affiliations

Department of Cardiology, Quebec Heart and Lung Institute, Laval University, Canada (Q.F., E.D., M.C., F.P., J.R.-C.). Department of Cardiology, Assistance Publique-Hôpitaux de Paris, Bichat Hospital, France (D.H., C.B., M.U.). Department of Cardiology, St. Paul's Hospital, Vancouver, British Columbia, Canada (J.G.W., M.B.). Department of Cardiology, Hôpital Charles Nicolle, University of Rouen, France (H.E., E.D.). Department of Cardiology, Hospital Universitario Virgen de la Victoria, Universidad de Málaga, Spain (A.J.M.-G., J.H.A.B.). Department of Cardiology, Ferrarotto Hospital, University of Catania, Italy (C.T., M.B., S.I.). Instituto Cardiovascular, Hospital Clinico San Carlos, IdISSC, Madrid, Spain (L.N.-F.). Department of Cardiology, University Heart Center, Transcatheter Valve Clinic, Zurich, Switzerland (F.N., F.M.). Department of Cardiology, Hospital Universitario Central de Asturias, Oviedo, Spain (C.M., R.d.V.). Department of Cardiology, Ottawa Heart Institute, University of Ottawa, Ontario, Canada (M.R.). Department of Cardiology, Clìnica de Occidente de Cali, Colombia (A.E.D., L.M.B.). Department of Cardiology, Hospital Universitari Vall d'Hebron, Barcelona, Spain (V.S., B.G.d.B.). Department of Cardiology, St. Michael's Hospital, Toronto University, Ontario, Canada (A.N.C.). Department of Cardiology, Hospital Clinico Universitario de Valladolid, Spain (I.J.A.-S.). Department of Cardiology, Hospital Israelita Albert Einstein, São Paulo, Brazil (F.S.d.B). Department of Cardiology, Heart Institute-InCor, University of São Paulo, Brazil (H.R.). Department of Cardiology, Instituto Dante Pazzanese de Cardiologia, São Paulo, Brazil (A.A.). Department of Cardiology, Instituto de Cardiologia do Rio Grande do Sul, Porto Alegre, Brazil (R.S.-L.).

Acknowledgments

Dr Rodés-Cabau holds the Canadian Research Chair Foundation Famille Jacques Larivière for the Development of Structural Heart Disease Interventions.

Disclosures

Dr Rodés-Cabau has received research grants from Edwards Lifesciences and Medtronic. Drs Webb, Eltchaninoff, and Dumont are consultants for Edwards Lifesciences. Dr Tamburino is a consultant for Edwards Lifesciences, Medtronic, CeloNova, and Abbott. Dr Nietlispach has served as a consultant for Edwards Lifesciences, Medtronic, and St. Jude Medical and has received speaker fees from Jude Medical and Biotronik. Dr Moris has served as a proctor and advisor for Medtronic. Dr Ruel has served as a proctor for Medtronic and has received a research grant from Edwards Lifesciences. Dr de Brito has served as a proctor for Edwards Lifesciences and Medtronic. Dr Sarmento-Leite has served as a proctor for Medtronic CoreValve implantation. Dr Himbert is a consultant for Edwards Lifesciences and has served as a proctor for Edwards Lifesciences and Medtronic. Dr Maisano has served as a consultant to Abbott Vascular, Medtronic, St. Jude Medical, and Valtech Cardio; has received royalties from Edwards Lifesciences; and is a cofounder of 4Tech. The other authors report no conflicts.

REFERENCES

1. Francia P, Balla C, Paneni F, Volpe M. Left bundle-branch block–pathophysiology, prognosis, and clinical management. *Clin Cardiol*. 2007;30:110–115. doi: 10.1002/clc.20034
2. Schneider JF, Thomas HE Jr, Sorlie P, Kreger BE, McNamara PM, Kannel WB. Comparative features of newly acquired left and right bundle branch block in the general population: the Framingham study. *Am J Cardiol*. 1981;47:931–940. doi: 10.1016/0002-9149(81)90196-X
3. Eriksson P, Hansson PO, Eriksson H, Dellborg M. Bundle-branch block in a general male population: the study of men born 1913. *Circulation*. 1998;98:2494–2500.
4. Brilakis ES, Wright RS, Kopecky SL, Reeder GS, Williams BA, Miller WL. Bundle branch block as a predictor of long-term survival after acute myocardial infarction. *Am J Cardiol*. 2001;88:205–209. doi: 10.1016/S0002-9149(01)01626-5
5. Vernooy K, van Deursen CJ, Strik M, Prinzen FW. Strategies to improve cardiac resynchronization therapy. *Nat Rev Cardiol*. 2014;11:481–493. doi: 10.1038/nrcardio.2014.67
6. Grines CL, Bashore TM, Boudoulas H, Olson S, Shafer P, Wooley CF. Functional abnormalities in isolated left bundle branch block. The effect of interventricular asynchrony. *Circulation*. 1989;79:845–853.
7. Verbeek XA, Vernooy K, Peschar M, Van Der Nagel T, Van Hunnik A, Prinzen FW. Quantification of interventricular asynchrony during LBBB and ventricular pacing. *Am J Physiol Heart Circ Physiol*. 2002;283:H1370–H1378. doi: 10.1152/ajpheart.00051.2002
8. Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. *J Am Coll Cardiol*. 2005;46:2183–2192. doi: 10.1016/j.jacc.2005.01.071
9. Puri R, Chamandi C, Rodriguez-Gabella T, Rodés-Cabau J. Future of transcatheter aortic valve implantation—evolving clinical indications. *Nat Rev Cardiol*. 2018;15:57–65. doi: 10.1038/nrcardio.2017.116
10. Auffret V, Puri R, Urena M, Chamandi C, Rodriguez-Gabella T, Philippon F, Rodés-Cabau J. Conduction disturbances after transcatheter aortic valve replacement: current status and future perspectives. *Circulation*. 2017;136:1049–1069. doi: 10.1161/CIRCULATIONAHA.117.028352
11. Watanabe Y, Kozuma K, Hioki H, Kawashima H, Nara Y, Kataoka A, Nagura F, Nakashima M, Shirai S, Tada N, Araki M, Takagi K, Yamanaka F, Yamamoto M, Hayashida K. Pre-existing right bundle branch block increases risk for death after transcatheter aortic valve replacement with a balloon-expandable valve. *JACC Cardiovasc Interv*. 2016;9:2210–2216. doi: 10.1016/j.jcin.2016.08.035
12. Auffret V, Webb JG, Eltchaninoff H, Muñoz-García AJ, Himbert D, Tamburino C, Nombela-Franco L, Nietlispach F, Morís C, Ruel M, Dager AE, Serra V, Cheema AN, Amat-Santos IJ, de Brito FS Jr, Lemos PA, Abizaid A, Sarmento-Leite R, Dumont E, Barbanti M, Durand E, Alonso Briales JH, Vahanian A, Bouleti C, Immè S, Maisano F, Del Valle R, Benitez LM, García Del Blanco B, Puri R, Philippon F, Urena M, Rodés-Cabau J. Clinical impact of baseline right bundle branch block in patients undergoing transcatheter aortic valve replacement. *JACC Cardiovasc Interv*. 2017;10:1564–1574. doi: 10.1016/j.jcin.2017.05.030
13. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB; Valve Academic Research Consortium (VARC)-2. Updated standardized endpoint definitions for

Downloaded from http://ahajournals.org by on February 21, 2019

transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. *Eur Heart J*. 2012;33:2403–2418. doi: 10.1093/eurheartj/ehs255

14. Surawicz B, Childers R, Deal BJ, Gettes LS, Bailey JJ, Gorgels A, Hancock EW, Josephson M, Kligfield P, Kors JA, Macfarlane P, Mason JW, Mirvis DM, Okin P, Pahlm O, Rautaharju PM, van Herpen G, Wagner GS, Wellens H; American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; American College of Cardiology Foundation; Heart Rhythm Society. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. *J Am Coll Cardiol*. 2009;53:976–981. doi: 10.1016/j.jacc.2008.12.013
15. Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; Heart Rhythm Society. 2012 ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2013;127:e283–e352. doi: 10.1161/CIR.0b013e318276ce9b
16. Urena M, Webb JG, Eltchaninoff H, Muñoz-García AJ, Bouleti C, Tamburino C, Nombela-Franco L, Nietlispach F, Moris C, Ruel M, Dager AE, Serra V, Cheema AN, Amat-Santos IJ, de Brito FS, Lemos PA, Abizaid A, Sarmento-Leite R, Ribeiro HB, Dumont E, Barbanti M, Durand E, Alonso Briales JH, Himbert D, Vahanian A, Immè S, Garcia E, Maisano F, del Valle R, Benitez LM, García del Blanco B, Gutiérrez H, Perin MA, Siqueira D, Bernardi G, Philippon F, Rodés-Cabau J. Late cardiac death in patients undergoing transcatheter aortic valve replacement: incidence and predictors of advanced heart failure and sudden cardiac death. *J Am Coll Cardiol*. 2015;65:437–448. doi: 10.1016/j.jacc.2014.11.027
17. Fishman GI, Chugh SS, Dimarco JP, Albert CM, Anderson ME, Bonow RO, Buxton AE, Chen PS, Estes M, Jouven X, Kwong R, Lathrop DA, Mascette AM, Nerbonne JM, O'Rourke B, Page RL, Roden DM, Rosenbaum DS, Sotoodehnia N, Trayanova NA, Zheng ZJ. Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. *Circulation*. 2010;122:2335–2348. doi: 10.1161/CIRCULATIONAHA.110.976092
18. Erkapic D, Kim WK, Weber M, Möllmann H, Berkowitsch A, Zaltsberg S, Pajitnev DJ, Rixe J, Neumann T, Kuniss M, Sperzel J, Hamm CW, Pitschner HF. Electrocardiographic and further predictors for permanent pacemaker requirement after transcatheter aortic valve implantation. *Europace*. 2010;12:1188–1190. doi: 10.1093/europace/euq094
19. Schneider JF, Thomas HE Jr, Kreger BE, McNamara PM, Kannel WB. Newly acquired left bundle-branch block: the Framingham study. *Ann Intern Med*. 1979;90:303–310. doi: 10.7326/0003-4819-90-3-303
20. Hiss RG, Lamb LE. Electrocardiographic findings in 122,043 individuals. *Circulation*. 1962;25:947–961.
21. Ostrander LD Jr. Bundle-branch block: an epidemiologic study. *Circulation*. 1964;30:872–881.
22. Auffret V, Lefevre T, Van Belle E, Eltchaninoff H, Iung B, Koning R, Motreff P, Leprince P, Verhoye JP, Manigold T, Souteyrand G, Boulmier D, Joly P, Pinaud F, Himbert D, Collet JP, Rioufol G, Ghostine S, Bar O, Dibie A, Champagnac D, Leroux L, Collet F, Teiger E, Darremont O, Folliguet T, Leclercq F, Lhermusier T, Olhmann P, Huret B, Lorgis L, Drogoul L, Bertrand B, Spaulding C, Quilliet L, Cuisset T, Delomez M, Beygui F, Claudel JP, Hepp A, Jegou A, Gommeaux A, Mirode A, Christiaens L, Christophe C, Cassat C, Metz D, Mangin L, Isaaz K, Jacquemin L, Guyon P, Pouillot C, Makowski S, Bataille V, Rodés-Cabau J, Gilard M, Le Breton H; FRANCE TAVI Investigators. Temporal trends in transcatheter aortic valve replacement in France: FRANCE 2 to FRANCE TAVI. *J Am Coll Cardiol*. 2017;70:42–55. doi: 10.1016/j.jacc.2017.04.053
23. Mauri V, Reimann A, Stern D, Scherner M, Kuhn E, Rudolph V, Rosenkranz S, Eghbalzadeh K, Friedrichs K, Wahlers T, Baldus S, Madershahian N, Rudolph TK. Predictors of permanent pacemaker implantation after transcatheter aortic valve replacement with the SAPIEN 3. *JACC Cardiovasc Interv*. 2016;9:2200–2209. doi: 10.1016/j.jcin.2016.08.034
24. Tovia-Brodie O, Ben-Haim Y, Joffe E, Finkelstein A, Glick A, Rosso R, Belhassen B, Michowitz Y. The value of electrophysiologic study in decision-making regarding the need for pacemaker implantation after TAVI. *J Interv Card Electrophysiol*. 2017;48:121–130. doi: 10.1007/s10840-016-0218-2
25. Urena M, Mok M, Serra V, Dumont E, Nombela-Franco L, DeLarochellière R, Doyle D, Igual A, Larose E, Amat-Santos I, Côté M, Cuéllar H, Pibarot P, de Jaegere P, Philippon F, Garcia del Blanco B, Rodés-Cabau J. Predictive factors and long-term clinical consequences of persistent left bundle branch block following transcatheter aortic valve implantation with a balloon-expandable valve. *J Am Coll Cardiol*. 2012;60:1743–1752. doi: 10.1016/j.jacc.2012.07.035
26. Bagur R, Manazzoni JM, Dumont É, Doyle D, Perron J, Dagenais F, Mathieu P, Baillot R, Charbonneau É, Metrás J, Mohammadi S, Côté M, Philippon F, Voisine P, Rodés-Cabau J. Permanent pacemaker implantation following isolated aortic valve replacement in a large cohort of elderly patients with severe aortic stenosis. *Heart*. 2011;97:1687–1694. doi: 10.1136/heartjnl-2011-300308
27. Prihadi EA, Leung M, Vollema EM, Ng ACT, Ajmone Marsan N, Bax JJ, Delgado V. Prevalence and prognostic relevance of ventricular conduction disturbances in patients with aortic stenosis. *Am J Cardiol*. 2017;120:2226–2232. doi: 10.1016/j.amjcard.2017.08.046
28. Fahy GJ, Pinski SL, Miller DP, McCabe N, Pye C, Walsh MJ, Robinson K. Natural history of isolated bundle branch block. *Am J Cardiol*. 1996;77:1185–1190. doi: 10.1016/S0002-9149(96)00160-9
29. Rabkin SW, Mathewson FA, Tate RB. Natural history of left bundle-branch block. *Br Heart J*. 1980;43:164–169.
30. Zhang ZM, Rautaharju PM, Soliman EZ, Manson JE, Cain ME, Martin LW, Bavry AA, Mehta L, Vitolins M, Prineas RJ. Mortality risk associated with bundle branch blocks and related repolarization abnormalities (from the Women's Health Initiative [WHI]). *Am J Cardiol*. 2012;110:1489–1495. doi: 10.1016/j.amjcard.2012.06.060
31. Eriksson P, Wilhelmsen L, Rosengren A. Bundle-branch block in middle-aged men: risk of complications and death over 28 years. The Primary Prevention Study in Göteborg, Sweden. *Eur Heart J*. 2005;26:2300–2306. doi: 10.1093/eurheartj/ehi580
32. Badheka AO, Singh V, Patel NJ, Deshmukh A, Shah N, Chothani A, Mehta K, Grover P, Savani GT, Gupta S, Rathod A, Marzouka GR, Mitrani RD, Moscucci M, Cohen MG. QRS duration on electrocardiography and cardiovascular mortality (from the National Health and Nutrition Examination Survey-III). *Am J Cardiol*. 2013;112:671–677. doi: 10.1016/j.amjcard.2013.04.040
33. Freedman RA, Alderman EL, Sheffield LT, Saporito M, Fisher LD. Bundle branch block in patients with chronic coronary artery disease: angiographic correlates and prognostic significance. *J Am Coll Cardiol*. 1987;10:73–80. doi: 10.1016/S0735-1097(87)80162-6
34. Baldasseroni S, Opasich C, Gorini M, Lucci D, Marchionni N, Marini M, Campana C, Perini G, Deorsola A, Masotti G, Tavazzi L, Maggioni AP; Italian Network on Congestive Heart Failure Investigators. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. *Am Heart J*. 2002;143:398–405. doi: 10.1067/mhj.2002.121264
35. Sumner G, Salehian O, Yi Q, Healey J, Mathew J, Al-Merri K, Al-Nemer K, Mann JF, Dagenais G, Lonn E; HOPE Investigators. The prognostic significance of bundle branch block in high-risk chronic stable vascular disease patients: a report from the HOPE trial. *J Cardiovasc Electrophysiol*. 2009;20:781–787. doi: 10.1111/j.1540-8167.2009.01440.x
36. Tabrizi F, Englund A, Rosenqvist M, Wallentin L, Stenestrand U. Influence of left bundle branch block on long-term mortality in a population with heart failure. *Eur Heart J*. 2007;28:2449–2455. doi: 10.1093/eurheartj/ehm262
37. Witt CM, Wu G, Yang D, Hodge DO, Roger VL, Cha YM. Outcomes with left bundle branch block and mildly to moderately reduced left ventricular function. *JACC Heart Fail*. 2016;4:897–903. doi: 10.1016/j.jchf.2016.07.002

Downloaded from http://ahajournals.org by on February 21, 2019