Risk Stratification of New Persistent Left Bundle Branch Block After Transcatheter Aortic Valve Implantation

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Previous studies reported that new-onset persistent left bundle branch block (NOP-LBBB) was related to worse outcomes after transcatheter aortic valve implantation (TAVI). However, these results can be confounded by the presence of permanent pacemaker (PPM) implantation before and after TAVI. Long-term outcomes and the risk stratification of NOP-LBBB not having PPM implantation before and after TAVI have not been fully investigated. This is an international, multicenter, retrospective study of patients who underwent TAVI from July 31, 2007, to May 8, 2020. A total of 2,240 patients were included, and 17.5% of patients developed NOP-LBBB. NOP-LBBB was associated with cardiac mortality (adjusted hazard ratio [aHR] 1.419, 95% confidence interval [CI] 1.014 to 1.985, p = 0.041) and the composite outcomes of cardiac mortality and/or heart failure readmission (aHR 1.313, 95% CI 1.027 to 1.678, p = 0.030). Patients who developed NOP-LBBB with pre-TAVI left ventricular ejection fraction (LVEF) <40% were significantly associated with cardiac mortality (aHR 2.049, 95% CI 1.039 to 4.041, p = 0.038), heart failure (aHR 3.990, 95% CI 2.362 to 6.741, p <0.001), and the composite outcome (aHR 2.729, 95% CI 1.703 to 4.374, p <0.001). Although NOP-LBBB with pre-TAVI LVEF >40% had a significant decrease in LVEF 6 to 12 months after TAVI (−1.8 ± 9.7% vs +0.6 ± 8.1%, p = 0.003), NOP-LBBB with pre-TAVI LVEF <40% had a significant increase in LVEF 6 to 12 months after TAVI (+9.7 ± 13.6% vs +13.0 ± 11.7%, p = 0.157). In conclusion, patients with NOP-LBBB without pre-TAVI and post-TAVI PPM developed significantly worse long-term outcomes, especially in patients with pre-TAVI LVEF <40%. Further prospective investigation should be undertaken. **(Am J Cardiol 2022;175:80−87)**

Transcatheter aortic valve implantation (TAVI) has revolutionized the traditional management of severe symptomatic aortic stenosis. Indeed, TAVI has been found to be an excellent alternative to surgical aortic valve replacement concerning overall mortality and heart failure (HF) readmission in patients at low to high risk for adult cardiac surgery,[1−6] which ultimately led to a significant increase in TAVI volumes. Despite improvements in TAVI technology and procedural experiences, new left bundle branch block (LBBB) has remained the most common complication after the conventional TAVI procedure. The incidence remains high at around 25% (4% to 65%), but a significant proportion (about 50%) has a spontaneous resolution of the conduction disturbance during the post-TAVI hospitalization.[7−17] However, a certain amount of new LBBB patients (10% to 15%) still required a new permanent pacemaker (PPM) implantation after TAVI.[7−17] Previous studies of long-term outcomes of the new LBBB included patients with pre-TAVI and post-TAVI PPM implantation.[7−17] Since pre-TAVI and post-TAVI PPM implantation can be a cofounding factor of worse outcomes after TAVI, long-term outcomes of new LBBB without pre-TAVI and post-TAVI PPM have not been clearly investigated.[7−17] In this present study, we used a multicenter international dataset to investigate clinical outcomes of the new LBBB after excluding patients with pre-TAVI and post-TAVI PPM.

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Methods

This is an international, multicenter, retrospective study of consecutive patients who underwent TAVI from July 31, 2007, to May 8, 2020, at the participating hospitals. All patients with preexisting LBBB and cardiac implantable electronic devices (CIEDs) such as PPM, implantable cardioverter-defibrillator, or cardiac resynchronization therapy were excluded from this study, and all CIED implantations after the index TAVI procedure. We collected patient characteristics, pre-TAVI and post-TAVI data of electrocardiogram and echocardiography, and intraprocedural data. The risk of adult cardiac surgery was evaluated using the latest version of the Society of Thoracic Surgery risk prediction model.[18,19] Although the Medtronic CoreValve (Medtronic, Minneapolis, Minnesota), the Edwards SAPIEN Valve (Edwards Lifesciences, Irvine, California), and the Edwards SAPIEN XT were considered the early generation devices, the Edwards SAPIEN 3, Medtronic Evolut R, and Medtronic Evolut PRO were considered as the new generation prostheses. Patients receiving other types of TAVI valves were excluded from this study. This study used data extracted from the TAVI research registry approved by institutional review boards at each hospital respectively. All patients provided signed informed consent for the data collection, and the need for consent to participate in this retrospective study was waived in view of the anonymous research design.

In this study, similar to previous studies, the new-onset persistent LBBB (NOP-LBBB) was determined as a new LBBB occurring during the hospitalization period for the TAVI procedure and persisting until the hospital discharge.[9–13,15–17] This also included patients who died without resolving the new LBBB during the same hospitalization. At the participating hospitals, patient selection and the required procedural technique for TAVI were decided by their interventional cardiologists and 2 cardiac surgeons, per the Centers for Medicare & Medicaid Services policy.[20] Outpatient clinic visits, telephone contacts, and a review of medical records were used to conduct the longitudinal follow-up. In this study, long-term outcomes included all-cause and cardiac mortality, HF readmission, and the composite outcome of cardiac mortality and/or HF readmission. In patients who had multiple HF-related hospitalizations, only the first admission was counted in this study.

Qualitative variables were reported as number (percentage) and quantitative variables as mean ± SD or median (interquartile range) based on each variable distribution. Categorical variables were compared with Pearson's chi-square test or Fisher's exact test. Mann-Whitney *U* test and Wilcoxon-signed rank test were used for quantitative variables with non-normal distribution. Two-sided Student's *t* test was used for quantitative variables with normal distribution. All p values were 2-sided, and p values <5% were considered significant. Survival rates were reported by Kaplan-Meier analysis, and a log-rank test was used to compare the outcome between groups. Cox proportional hazard models (cumulative outcomes) were used to evaluate outcomes after TAVI, and all multivariate models were adjusted based on baseline differences with a p <5%. The quantitative values were evaluated with linear spline regression analysis. The transitional point where the slope of the risk relation changed was chosen to convert the analyzed quantitative variables to the categorical ones. The linear spline regression analysis was performed with R Statistical Software package Version 3.5.1 for Mac (R Foundation for Statistical Computing, Vienna, Austria). All other analyses were performed with IBM SPSS Statistical Software Version 27 (Armonk, New York).

Results

At the participating 5 centers during the study duration, 2,240 patients were ultimately included in our analysis (Supplementary Figure 1). The median of the observational period was 1.8 (interquartile range 0.8 to 3.2) years after TAVI, and 393 patients (17.5%) developed NOP-LBBB. The baseline characteristics are listed in Table 1. During the study period, the development of NOP-LBBB was significantly associated with cardiac mortality and the composite outcome of cardiac mortality and/or HF admission (Figure 1, Table 2). The detailed analysis of long-term outcomes with NOP-LBBB was reported separately (Supplementary Figures 2 to 5). Preexisting left ventricular (LV) ejection fraction (LVEF) <40% was associated with post-TAVI cardiac mortality, HF readmission, and the composite outcome in patients with and without NOP-LBBB (Supplementary Figure 6). After excluding 112 patients with missing echocardiographic data, patients were classified into 4 groups (Supplementary Figure 1). Baseline characteristics of the newly classified groups were listed in Supplementary Table 1. The event-free period of cardiac mortality, HF readmission, and the composite outcome was significantly different in these groups (Figure 2, Supplementary Table 2). Especially, the worst outcomes were observed in patients who developed NOP-LBBB in the setting of pre-TAVI LVEF <40%. The detailed analysis of long-term outcomes with the newly classified groups was reported separately (Supplementary Figures 7 to 10).

In patients who had available data on LVEF before TAVI and 6 to 12 months after TAVI, chronologic changes in LVEF were listed (Figure 3, Table 3). Patients with NOP-LBBB had a significant decrease in LVEF 6 to 12 months after TAVI (Figure 3, Table 3). These findings were similarly observed in patients with pre-TAVI LVEF >40% (Figure 3, Table 3). Conversely, regardless of the development of NOP-LBBB, patients with pre-TAVI LVEF <40% had a significant improvement in post-TAVI LVEF, but both patients still remained in the range of moderately reduced LVEF (<50%) 6 to 12 months after TAVI (Figure 3, Table 3).

Discussion

The main findings of the present international, multicenter study are summarized as follows: (1) the development of NOP-LBBB was significantly associated with cardiac mortality and the composite of cardiac mortality and/or HF readmission without cofounding effects from the presence of pre-TAVI and post-TAVI PPM, (2) pre-TAVI LVEF <40% can help stratify the risk of post-TAVI long-term

Table 1
Baseline characteristics between patients with and without NOP-LBBB

	NOP-LBBB (n=393)	No LBBB (n=1847)	p-Value
Baseline characteristics			
Men	162 (41.2 %)	845 (45.7 %)	0.101
Age (years)	80.3 ± 7.8	80.9 ± 7.4	0.158
BMI (kg/m^2)	28.7 ± 7.5	27.2 ± 6.2	<0.001
Hypertension	338 (86.0 %)	1601 (86.8 %)	0.684
Diabetes mellitus	146 (37.2 %)	583 (31.6 %)	0.033
CKD	179 (45.7 %)	937 (50.8 %)	0.063
Hyperlipidemia	261 (66.4 %)	1114 (60.4 %)	0.026
Prior stroke	35 (8.9 %)	170 (9.2 %)	0.847
PAD	54 (13.7 %)	222 (12.0 %)	0.354
Pre-existing CAD	191 (53.4 %)	762 (46.9 %)	0.027
Prior PCI	83 (22.0 %)	354 (19.7 %)	0.308
Prior CABG	66 (16.8 %)	227 (12.3 %)	0.016
Prior SAVR	9 (2.3 %)	59 (3.2 %)	0.342
History of AF	83 (21.2 %)	457 (24.7 %)	0.134
STS score	5.3 ± 3.6	5.5 ± 4.2	0.908
Baseline ECG			
Pre-existing RBBB	7 (1.8 %)	145 (7.9 %)	<0.001
Pre-existing LAFB	36 (9.2 %)	115 (6.3 %)	0.037
Pre-existing AVB*	39 (9.9 %)	176 (9.6 %)	0.828
Pre-existing NICD	6 (1.5 %)	32 (1.7 %)	0.767
Baseline PR (milliseconds)	181.0 ± 36.2	180.5 ± 36.5	0.986
Baseline QRS (milliseconds)	97.2 ± 16.8	100.9 ± 24.2	0.524
Baseline TTE			
LVEF (%)	55.7 ± 12.3	55.8 ± 12.2	0.658
LVEF less than 40 %	50 (13.4 %)	232 (13.2 %)	0.900
Vmax (m/sec)	4.2 ± 0.9	4.2 ± 0.8	0.911
AVA (cm^2)	0.8 ± 0.3	0.7 ± 0.2	0.001
Mean AVPG (mmHg)	46.4 ± 19.4	48.5 ± 17.8	0.048
Procedural value			
Self-expanding valve	225 (57.3 %)	980 (53.1 %)	0.133
BAV before deployment	244 (63.7 %)	1159 (64.7 %)	0.719
BAV after deployment	70 (18.2 %)	294 (16.3 %)	0.375
New-generation valve	258 (65.6 %)	1257 (68.1 %)	0.347

*All of the pre-existing AVB were either first or second-degree of AVB.

AF = atrial fibrillation; AVA = aortic valvular area; AVB = atrioventricular block; AVPG = aortic valvular pressure gradient; BAV = balloon aortic valvuloplasty; BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CKD = chronic kidney disease; ECG = electrocardiogram; LAFB = left anterior fascicular block; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NICD = nonspecific interventricular conduction delay; NOP-LBBB = new-onset persistent left bundle branch block; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; RBBB = right bundle branch block; SAVR = surgical aortic valve replacement; STS = Society of Thoracic Surgery; TTE = transthoracic echocardiography; Vmax = maximum transvalvular aortic velocity.

outcomes, and (3) the association of NOP-LBBB and pre-TAVI LVEF <40% was significantly related to worse outcomes.

NOP-LBBB is a common sequela in the conventional TAVI procedure, but the clinical impact of post-TAVI NOP-LBBB has been controversial.[7–17] We hypothesized the controversy was related to the concomitant PPM in patients with NOP-LBBB. Therefore, this study excluded all patients with preexisting LBBB and all CIED implantations before/after TAVI to minimize the cofounding effects. The study design allowed us to evaluate the causal relations between the development of NOP-LBBB and long-term outcomes more precisely. Indeed, similar to previous studies, NOP-LBBB was associated with cardiac mortality and the composite outcome.[12–14,16,17] These results were similarly observed regardless of the type or generation of TAVI prostheses. However, it has been unclear whether other factors are associated with worse outcomes in patients with NOP-LBBB.

Our study showed that pre-TAVI LVEF <40% could potentially stratify long-term outcomes in patients with and without post-TAVI NOP-LBBB. Regardless of the type or generation of TAVI prostheses, the development of NOP-LBBB in patients with pre-TAVI LVEF <40% was significantly associated with worse outcomes. To our best knowledge, this is the first study to show that pre-TAVI LVEF <40% could potentially stratify long-term outcomes after TAVI in both patients with and without NOP-LBBB.

As previous studies showed, patients with NOP-LBBB had a significant reduction in post-TAVI LVEF.[10,11,14–16] In contrast, it is also well known that patients with pre-TAVI LVEF 30% to 50% have a favorable chance of recovering from LVEF after TAVI.[21–24] In this study, patients who developed NOP-LBBB in the setting of pre-TAVI

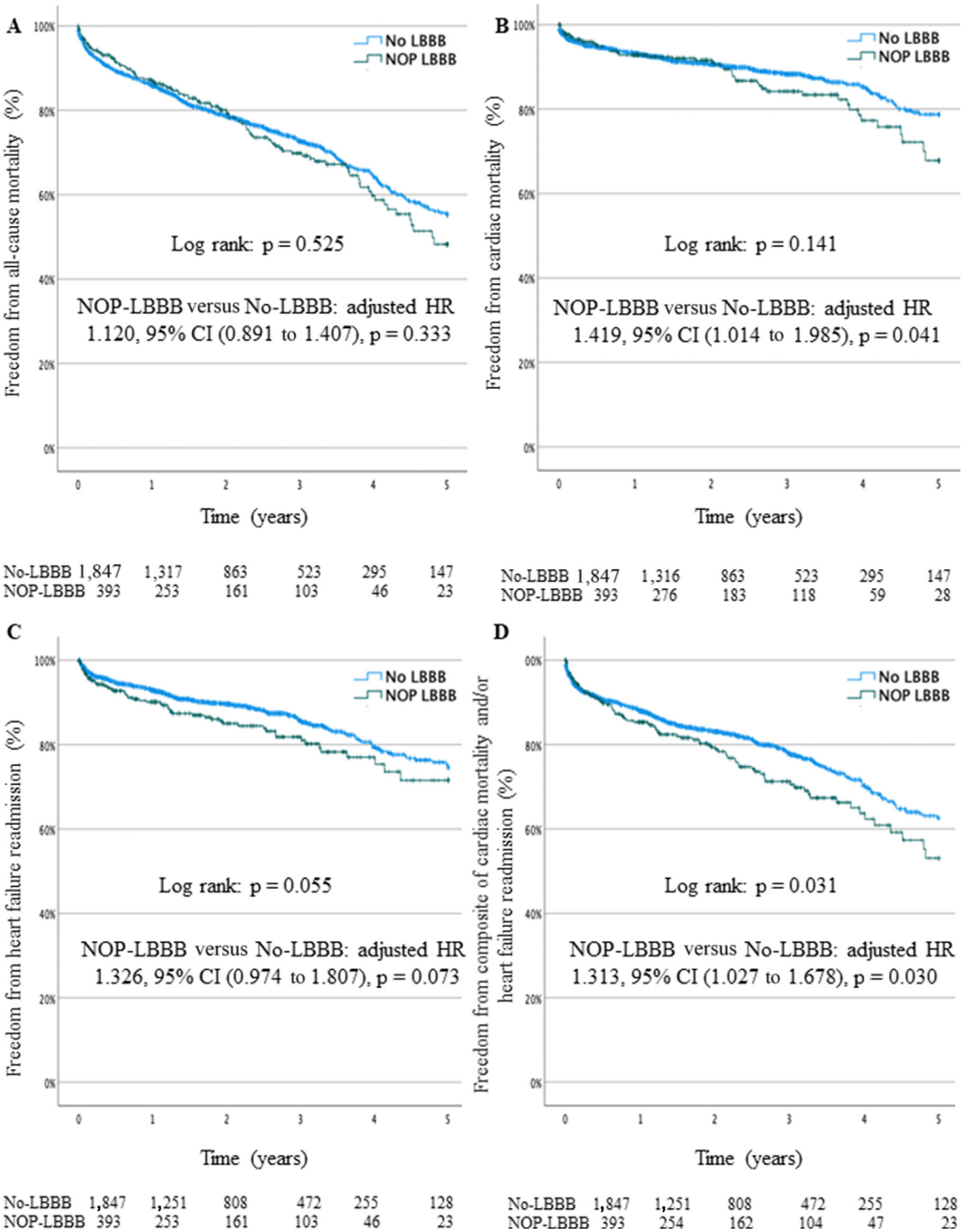

Figure 1. Long-term clinical outcomes between patients with and without NOP-LBBB
Cumulative incidence curves for long-term: all-cause mortality (*A*), cardiac mortality (*B*), heart failure readmission (*C*), and composite of cardiac mortality and/or heart failure readmission (*D*). No-LBBB = no new-onset persistent left bundle branch block.

LVEF <40% demonstrated a dramatic increase in post-TAVI LVEF. This finding suggests that worse outcomes in patients with NOP-LBBB with pre-TAVI LVEF <40% were not solely associated with the preexisting LV systolic dysfunction. Because our study excluded all CIEDs, the subsequent progression to high-grade atrioventricular block after NOP-LBBB cannot explain the worse outcomes.

As Table 3 listed, patients with pre-TAVI LVEF <40% had a large amount of cardiovascular co-morbidities. Perhaps, the preexisting myocardial fibrosis (MF) can be

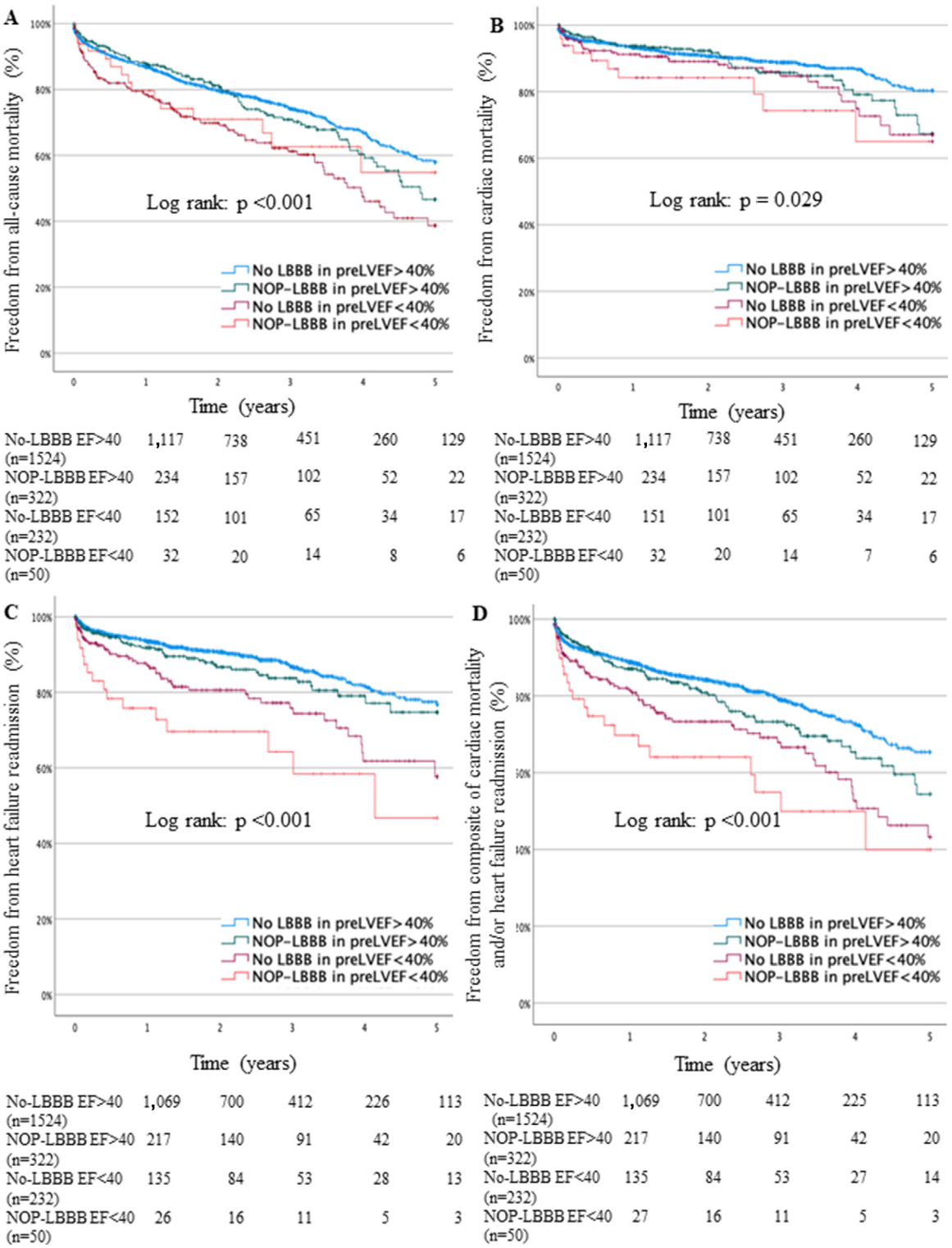

Figure 2. Long-term clinical outcomes in newly stratified patient groups. Cumulative incidence curves for long-term: all-cause mortality (*A*), cardiac mortality (*B*), heart failure readmission (*C*), and composite of cardiac mortality and/or heart failure readmission (*D*). EF = ejection fraction; No-LBBB = no new-onset persistent left bundle branch block.

related to their worse outcomes.[25] Whereas TAVI improved LVEF dramatically in patients with pre-TAVI LVEF <40%, most of this patient group remained in the moderately reduced LVEF (<50%), and the underlying MF could suppress the potential procedural benefit.[25] It can be beneficial to obtain cardiac magnetic resonance imaging before TAVI to evaluate the MF burden, especially for patients with preexisting LV systolic dysfunction.[26]

In patients with NOP-LBBB, especially in the setting of pre-TAVI LVEF <40%, the development of new

Table 2
Unadjusted and adjusted association of NOP-LBBB with post-TAVI outcomes

	NOP-LBBB(n=393)	No-LBBB(n=1847)	Unadjusted HR(95% CI)	p-Value	Adjusted HR(95% CI)	p-Value
All-cause mortality	107 (27.2 %)	468 (25.3 %)	1.070 (0.868-1.321)	0.525	1.120 (0.891-1.407)	0.333
Cardiac mortality	52 (13.2 %)	194 (10.5 %)	1.259 (0.927-1.710)	0.141	1.419 (1.014-1.985)	0.041
Heart failure admission	59 (15.0 %)	222 (12.0 %)	1.326 (0.994-1.768)	0.055	1.326 (0.974-1.807)	0.073
Composite of cardiac mortality and/or heart failure admission	95 (24.2 %)	356 (19.3 %)	1.282 (1.022-1.608)	0.031	1.313 (1.027-1.678)	0.030

HR = hazard ratio; LVEF = left ventricular ejection fraction; No-LBBB = no new-onset persistent left bundle branch block; NOP-LBBB = new-onset persistent left bundle branch block; TAVI = transcatheter aortic valve implantation.

intracardiac dyssynchrony is highly suspected of causing the worse outcomes.[15–17] Recent self-expanding TAVI valves are repositionable, and this unique design enables the TAVI team to minimize the implantation depth and the subsequent injury to the conduction system.[27,28] Hypothetically, the shallow implantation technique can minimize the risk of NOP-LBBB, and it can be beneficial especially for patients with pre-TAVI LVEF <40%. Biventricular synchronization therapy has been widely used to improve LBBB-induced intracardiac dyssynchrony.[29,30] Given most patients with pre-TAVI LVEF <40% remained in the range of moderately reduced LVEF 6 to 12 months after TAVI, the benefit of cardiac resynchronization therapy needs to be investigated, especially in this patient group.

This is a retrospective observational study, and the sampling bias cannot be excluded. Because of the limited sample size, especially for patients with pre-TAVI LVEF <40%, chronological LVEF changes and the causal relation between the development of NOP-LBBB and clinical outcomes were not fully investigated in this present study. There was no centralized core laboratory to evaluate the used cardiovascular imaging and no central committee to verify the reported clinical events in this study. However, it reflects the real-world experience of high-volume TAVI centers carrying internal databases. All of the participated hospitals are large TAVI-referral centers, and some patients were mainly followed by outside healthcare systems after TAVI. Therefore, there is a possibility of missing some longitudinal follow-up results.

In conclusion, this multicenter international study demonstrated the development of NOP-LBBB was significantly associated with worse outcomes without cofounding effects from the presence of pre-TAVI and post-TAVI PPM implantation. The worst outcomes were observed in

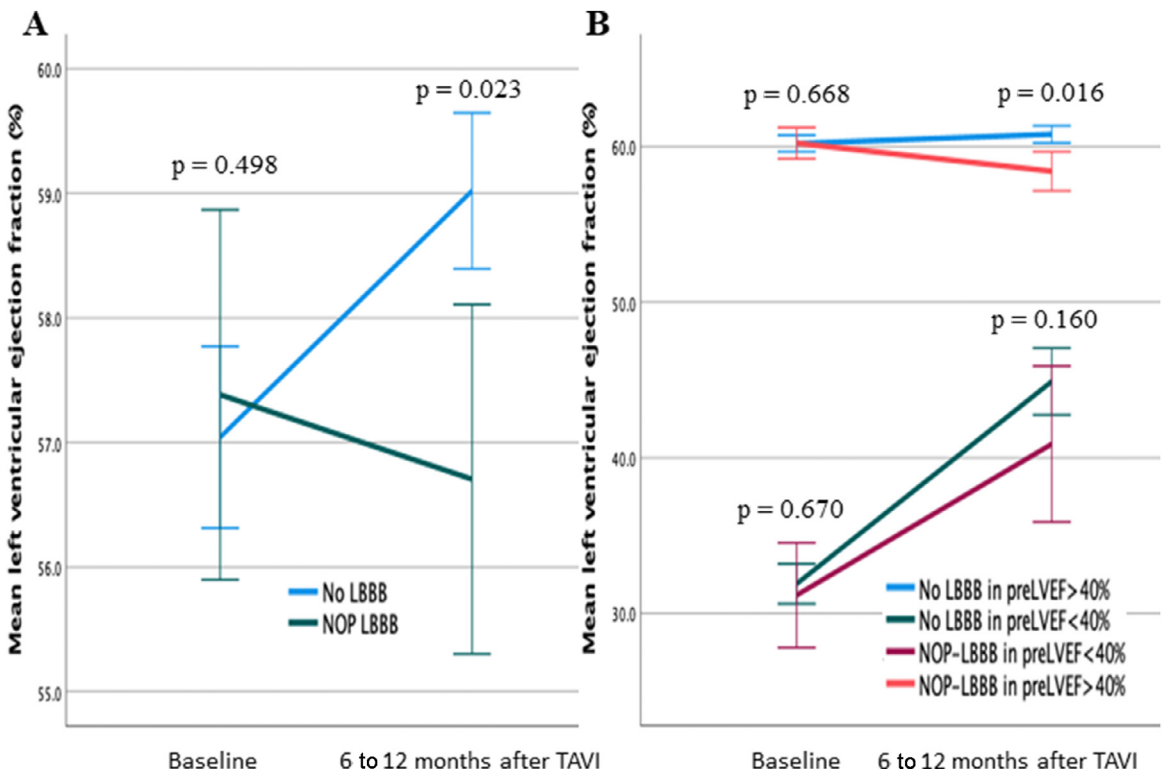

Figure 3. Chronologic change on LVEF 6 to 12 months after TAVI. Chronologic changes of left ventricular systolic function after TAVI between NOP-LBBB and No-LBBB (*A*) and in newly stratified patient groups (*B*). No-LBBB = no new-onset persistent left bundle branch block.

Table 3
Chronological changes of post-TAVR LVEF

	LVEF (%)			
	Pre-TAVR	6-12 months	Δ LVEF	p-Value*
NOP-LBBB (n=225)	57.4 ± 11.3	56.7 ± 10.7	- 0.7 ± 10.6†	<0.001
No-LBBB (n=1047)	57.0 ± 12.0	59.0 ± 10.3	+ 2.0 ± 9.4†	0.300
Newly classified group				
NOP-LBBB in pre-TAVR LVEF >40% (n=203)	60.2 ± 7.3	58.4 ± 9.1	- 1.8 ± 9.7‡	0.018
No-LBBB in pre-TAVR LVEF >40% (n=930)	60.2 ± 8.2	60.8 ± 8.6	+ 0.6 ± 8.1‡	0.006
NOP-LBBB in pre-TAVR LVEF <40% (n=22)	31.1 ± 7.6	40.9 ± 11.3	+ 9.7 ± 13.6§	0.005
No-LBBB in pre-TAVR LVEF <40% (n=117)	31.9 ± 7.0	44.9 ± 11.7	+ 13.0 ± 11.7§	<0.001

*LVEF between pre-TAVR and 6-12 months were compared with Wilcoxon signed rank test.

† Δ LVEF between all patients with NOP-LBBB and No-LBBB were compared with Wilcoxon signed rank test (p <0.001).

‡ In patients with pre-TAVR LVEF more than 40%, Δ LVEF between patients with NOP-LBBB and No-LBBB were compared with Wilcoxon signed rank test (p=0.003).

§ In patients with pre-TAVR LVEF less than 40%, Δ LVEF between patients with NOP-LBBB and No-LBBB were compared with Wilcoxon signed rank test (p=0.157).

Δ LVEF = delta left ventricular ejection fraction; LVEF = left ventricular ejection fraction; NOP-LBBB = new-onset persistent left bundle branch block; No-LBBB = no new-onset persistent left bundle branch block; TAVR = transcatheter aortic valve replacement.

patients who developed NOP-LBBB in the setting of pre-TAVI LVEF <40%. This high-risk population will need a multidisciplinary approach to advanced HF management after TAVI.

Disclosures

Dr. Attizzani is a consultant and is on the advisory board of Medtronic. Dr. Mackall has received consulting honoraria from Abbott. Dr. Ohno is a consultant and is on the advisory board of Medtronic. Dr. Kaneko is a consultant/speaker for Edwards Lifesciences, Medtronic, Abbott, Baylis, Cook Medical, 4C medical, and CardioMech. Dr. Barbanti is a consultant for Edwards Lifesciences and an advisory board member for Medtronic. The remaining authors have no conflicts of interest to declare.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2022.03.053.

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