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CLINICAL RESEARCH

Long-term outcomes of new-onset conduction abnormalities following transcatheter aortic valve implantation

Résultats à long terme des anomalies de conduction d'apparition récente après 2 implantations de valve aortique transcatheter

Daijiro Tomii[a,1], **Taishi Okuno**[a,1], **Dik Heg**[b], **Thomas Pilgrim**[a], **Stephan Windecker**[a,*]

[a] *Department of Cardiology, Inselspital, University of Bern, 3010 Bern, Switzerland*
[b] *CTU Bern, University of Bern, 3012 Bern, Switzerland*

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Conduction abnormalities ;
Left bundle branch block ;
Permanent pacemaker ;
Transcatheter aortic valve implantation

Summary
Background. — Previous studies provided conflicting data on the impact of new conduction abnormalities (CA), including new left bundle branch block (LBBB) and permanent pacemaker (PPM) implantation, on patient outcomes after transcatheter aortic valve implantation (TAVI).
Aims. — To investigate the effect of new-onset CA after TAVI on long-term clinical outcomes and the impact of new CA depending on patient baseline profile.
Methods. — Using data from a prospective TAVI registry (NCT01368250), patients without pre-existing LBBB or PPM were included in this study, and were stratified into three groups: no CA, new LBBB and new PPM after TAVI.
Results. — Among 2370 eligible patients, 1533 (64.7%) had no CA, 336 (14.2%) had new LBBB and 501 (21.1%) had new PPM after TAVI. At 5 years, patients with new LBBB had an increased risk of all-cause death (adjusted hazard ratio [$HR_{adjusted}$] 1.41, 95% confidence interval [CI] 1.04—1.92; $P = 0.026$), whereas patients with new PPM had a numerically increased risk of

Abbreviations: AS, aortic stenosis ; CA, conduction abnormalities ; CI, confidence interval ; HR, hazard ratio ; LBBB, left bundle branch block ; NYHA, New York Heart Association ; PPM, permanent pacemaker ; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality ; TAVI, transcatheter aortic valve implantation.

* Corresponding author. Department of Cardiology, Inselspital, Bern University Hospital, Freiburgstrasse 18, 3010 Bern, Switzerland.
Adresse e-mail : stephan.windecker@insel.ch (S. Windecker).

[1] Drs Tomii and Okuno contributed equally to this work and are joint first authors.

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mortality ($HR_{adjusted}$ 1.26, 95% CI 0.99—1.60; $P = 0.065$) compared to patients without CA. There was no significant difference in cardiovascular mortality between groups ($HR_{adjusted}$ for new LBBB 1.33, 95% CI 0.91—1.97; $P = 0.15$; $HR_{adjusted}$ for new PPM 1.25, 95% CI 0.93—1.68; $P = 0.13$]). The adverse effects of new CA were consistent across all subgroups except for the impact of new PPM stratified by balloon-expandable versus self-expanding or mechanically expanding valves ($P_{interaction} = 0.004$).
Conclusions. — New-onset LBBB after TAVI was associated with an increased risk of 5-year all-cause mortality, while new PPM implantation conferred a non-significant trend.

Résumé
Contexte. — Des études antérieures ont fourni des données contradictoires sur l'impact de nouvelles anomalies de conduction de conduction (CA), y compris les nouveaux blocs de branche gauche (LBBB) et l'implantation d'un stimulateur cardiaque permanent (PPM) sur les résultats des patients après l'implantation d'une valve aortique transcathéter (TAVI).
Objectifs. — Étudier l'effet de l'apparition d'un nouveau CA après un TAVI sur les résultats cliniques à long terme et l'impact du nouveau CA en fonction des patients.
Méthodes. — En utilisant les données d'un registre prospectif de TAVI (NCT01368250), les patients sans BBG ou PPM préexistant ont été inclus dans cette étude et ont été stratifiés en trois groups: pas de CA, nouveau LBBB et nouveau PPM après TAVI.
Résultats. — Parmi les 2370 patients éligibles, 1533 (64,7 %) n'avaient pas de CA, 336 (14,2 %) avaient un nouveau LBBB et 501 (21,1 %) avaient un nouveau PPM après le TAVI. Après 5 ans, les patients présentant un nouveau LBBB avaient un risque accru de décès toutes causes confondues (rapport de risque ajusté [$HR_{adjusted}$] 1,41, intervalle de confiance à 95 % [IC] 1,04—1,92; P = 0,026), tandis que les patients présentant un nouveau PPM avaient un risque numériquement accru de mortalité (HR ajusté 1,26, IC 95 % 0,99—1,60; $P = 0,065$) par rapport aux patients sans CA. Il n'y avait pas de différence significative en matière de mortalité cardiovasculaire entre les groupes (HR ajusté pour un nouveau LBBB 1,33, IC à 95 % 0,91—1,97; $P = 0,15$; HR ajusté pour le nouveau PPM 1,25, IC à 95 % 0,93—1,68; $P = 0,13$]). Les effets indésirables du nouvel CA étaient cohérents dans tous les sous-groupes, à l'exception de l'impact de la nouvelle PPM stratifiée selon qu'il s'agit d'une prothèse expansible par ballonnet ou d'une prothèse auto-expansible ou mécanique ($P_{interaction} = 0,004$).
Conclusions. — L'apparition d'un LBBB après un TAVI est associée à un risque accru de mortalité à 5 ans, toutes causes confondues, tandis que l'implantation d'une nouvelle PPM a conféré une tendance non significative.

Introduction

Despite recent advancements in device technology and implantation techniques, the occurrence of new conduction abnormalities (CA), including left bundle branch block (LBBB) and advanced high-degree atrioventricular block requiring new permanent pacemaker (PPM) implantation, remains a limitation of transcatheter aortic valve implantation (TAVI) [1—3]. With the rapid expansion of TAVI to younger and lower-risk populations, the long-term effects of new CA are becoming increasingly important. However, recent observational studies provided conflicting data on the impact of new CA on long-term patient outcomes, possibly due to differences in methodologies, follow-up duration and populations studied. Therefore, we aimed to investigate the effect of new CA after TAVI on long-term clinical outcomes in a prospective TAVI registry. Furthermore, we assessed whether there is a difference in the impact of new CA across patient baseline profiles, such as age, sex, surgical risk and cardiac function.

Methods

Study design and population

The Bern TAVI registry is a prospective study enrolling consecutive patients undergoing TAVI at Bern University Hospital, Switzerland, which forms part of the nationwide SwissTAVI registry (registered at clinicaltrials.gov with NCT01368250) [4]. For the present study, patients that underwent TAVI for pure aortic regurgitation, those with pre-existing PPM implantation or LBBB, those with incomplete electrocardiographic data pre- or post-TAVI, and those who died within

30 days of TAVI were excluded. The registry is approved by the Bern cantonal ethics committee, and patients provided written informed consent to participate. The study was conducted in compliance with the Declaration of Helsinki.

Electrocardiographic assessment

Twelve-lead electrocardiograms were recorded at baseline, immediately after the procedure, at hospital discharge, at 30 days and at 1 year and 5 years after TAVI. PPM implantations after TAVI were performed according to guideline indications for complete heart block, advanced high-degree atrioventricular block, LBBB with progressive QRS widening after TAVI, or in the presence of sinus node dysfunction and documented symptomatic bradycardia, as previously described [5,6]. No electrophysiological studies were performed to assess indications for new PPM following TAVI at our institution.

For this study, we stratified patients into three groups based on 12-lead electrocardiogram at 30 days after TAVI: no CA (patients without new-onset LBBB and new PPM implantation within 30 days after TAVI), new LBBB (patients with new-onset LBBB but no new PPM implantation within 30 days after TAVI) and new PPM implantation (patients who underwent new PPM implantation within 30 days after TAVI).

Data collection and clinical endpoints

Baseline clinical, procedural and follow-up data were prospectively recorded in a web-based database, held at the Clinical Trials Unit of the University of Bern, Switzerland. Echocardiographic measurements were re-evaluated by dedicated imaging specialists in accordance with echocardiographic guidelines [7] and integrated into the database. Right ventricular function was assessed as previously described, and right ventricular dysfunction was documented in the presence of at least two of the following parameters: tricuspid annular plane systolic excursion < 1.7 cm, S' < 9.5 cm/s and fractional area change < 35% [8]. Severe pulmonary hypertension was defined as pulmonary artery systolic pressure $\geq$ 60 mmHg [9–11]. Clinical follow-up data at 30 days, at 1 year and 5 years were obtained by standardized interviews, documentation from referring physicians and hospital discharge summaries. All adverse events were systematically collected and adjudicated by a dedicated clinical event committee based on the Valve Academic Research Consortium definitions applicable at the time of the procedure [12,13]. The outcomes of interest in this study included all-cause and cardiovascular death, New York Heart Association (NYHA) functional class III or IV, and new PPI at 1 and 5 years after TAVI.

Statistical analysis

Categorical variables are presented as frequencies and percentages, and the differences between groups were evaluated with the chi-square test or Fisher's exact test. Continuous variables are presented as mean values $\pm$ standard deviation (SD) and compared between groups using the F test from an ANOVA. Rate ratios with 95% confidence intervals (CI) from Poisson regressions were provided where appropriate. Cumulative incidence curves were constructed using the Kaplan-Meier method. Univariable and multivariable Cox proportional hazards models were used to calculate crude or adjusted hazard ratios (HR) and 95% CIs. Multivariable adjustment was performed with predefined baseline variables potentially related to clinical outcomes including age, sex, Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), diabetes, chronic kidney disease, peripheral artery disease, atrial fibrillation, left ventricular ejection

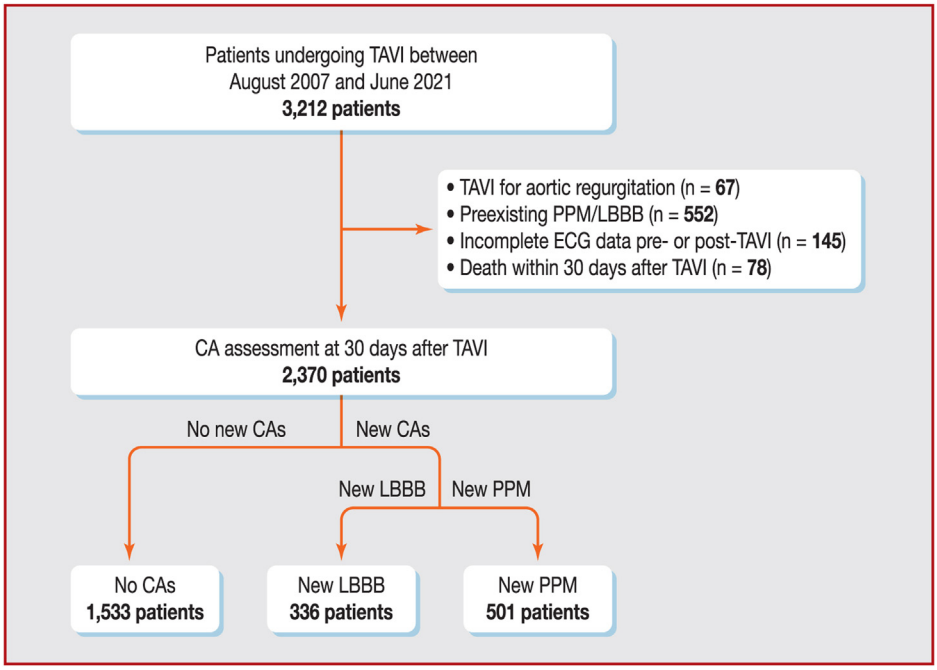

Figure 1. Study flow chart. CA: conduction abnormalitiy; ECG: electrocardiogram; LBBB: left bundle branch block; PPM: permanent pacemaker; TAVI: transcatheter aortic valve implantation.

Table 1 Baseline and procedural characteristics according to new CA after TAVI.

	All patients ($n = 2370$)	No CA ($n = 1533$)	New LBBB ($n = 336$)	New PPM ($n = 501$)	*P*
Age (years)	81.6 ± 6.2	81.5 ± 6.4	81.1 ± 5.9	82.4 ± 5.9	0.005
Female sex (%)	1187 (50.1)	781 (50.9)	192 (57.1)	214 (42.7)	<0.001
Body mass index (kg/m^2)	26.8 ± 5.3	26.6 ± 5.2	26.8 ± 5.9	27.2 ± 5.3	0.13
Body surface area (m^2—Haycock)	1.85 ± 0.24	1.84 ± 0.24	1.84 ± 0.26	1.88 ± 0.24	0.007
STS-PROM (%)	4.83 ± 3.69	4.70 ± 3.55	4.75 ± 3.87	5.28 ± 3.95	0.008
NYHA III or IV (%)	1504 (63.5)	957 (62.5)	212 (63.1)	335 (66.9)	0.21
Concomitant diseases (%)					
Hypertension	2070 (87.3)	1338 (87.3)	291 (86.6)	441 (88.0)	0.83
Diabetes mellitus	650 (27.4)	410 (26.7)	75 (22.3)	165 (32.9)	0.002
Renal failure (eGFR < 60 mL/min/1.73 m^2)	1511 (63.8)	955 (62.4)	215 (64.0)	341 (68.1)	0.07
Coronary artery disease	1355 (57.2)	847 (55.3)	203 (60.4)	305 (60.9)	0.038
Atrial fibrillation	742 (31.3)	462 (30.1)	105 (31.3)	175 (34.9)	0.13
Peripheral artery disease	300 (12.7)	184 (12.0)	51 (15.2)	65 (13.0)	0.28
Right bundle branch block	255 (11.1)	110 (7.3)	4 (1.3)	141 (29.6)	<0.001
Echocardiography					
Indexed aortic valve area (cm^2/m^2)	0.24 ± 0.08	0.24 ± 0.08	0.24 ± 0.09	0.24 ± 0.08	0.94
Mean aortic valve gradient (mmHg)	40.6 ± 17.0	40.6 ± 16.4	41.1 ± 20.3	40.3 ± 16.2	0.83
Low gradient aortic stenosis (%)	1168 (50.7)	757 (50.8)	174 (53.2)	237 (48.8)	0.46
Left ventricular ejection fraction (%)	56.9 ± 13.4	57.6 ± 12.9	55.2 ± 14.6	55.7 ± 13.9	0.001
Left ventricular mass index (g/m^2)	132.0 ± 42.1	129.0 ± 39.7	135.0 ± 45.0	139.9 ± 46.4	0.003
Right ventricular dysfunction (%)	916 (77.5)	575 (78.2)	131 (80.4)	210 (73.9)	0.22
Severe pulmonary hypertension (%)	376 (15.9)	234 (15.3)	56 (16.7)	86 (17.2)	0.55
Moderate/severe aortic regurgitation (%)	190 (9.5)	134 (10.4)	20 (7.2)	36 (8.4)	0.17
Moderate/severe mitral regurgitation (%)	378 (17.9)	236 (17.4)	53 (18.0)	89 (19.4)	0.60
Moderate/severe tricuspid regurgitation (%)	205 (10.6)	128 (10.1)	34 (12.3)	43 (11.1)	0.52
Procedure					
General anaesthesia (%)	422 (17.8)	272 (17.8)	60 (17.9)	90 (18.0)	0.99
Femoral main access site (%)	2178 (91.9)	1404 (91.6)	309 (92.0)	465 (92.8)	0.68
Valve type (%)					<0.001
Balloon-expandable	1266 (53.5)	884 (57.8)	167 (49.7)	215 (42.9)	<0.001
Self-expandable	992 (41.9)	599 (39.2)	151 (44.9)	242 (48.3)	0.001
Mechanically expandable	109 (4.6)	47 (3.1)	18 (5.4)	44 (8.8)	<0.001
Valve size (mm)	26.4 ± 2.2	26.1 ± 2.2	26.6 ± 2.3	27.1 ± 2.2	<0.001
Predilations (%)	61 (2.6)	31 (2.0)	8 (2.4)	22 (4.4)	0.014
Postdilations (%)	58 (2.4)	35 (2.3)	6 (1.8)	17 (3.4)	0.26

Values are mean ± SD or n (%). CA: conduction abnormalities; eGFR: estimated glomerular filtration rate; LBBB: left bundle branch block; NYHA: New York Heart Association; PPM: permanent pacemaker; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI: transcatheter aortic valve implantation.

fraction < 50%, moderate or severe mitral regurgitation, moderate or severe tricuspid regurgitation, severe pulmonary hypertension and right ventricular dysfunction. All statistical tests were two-sided and *P*-values of < 0.05 were considered significant. Statistical analyses were performed using Stata 15.1 (StataCorp, College Station, TX, USA).

Results

Study population and baseline characteristics

Among 3212 patients who underwent TAVI between August 2007 and June 2021, 2370 patients were eligible for this analysis. Of these, 1533 patients (64.7%) had no CA, 336 (14.2%) had new LBBB and 501 (21.1%) had new PPM implantation at 30 days after TAVI (Fig. 1). The occurrence of new CA stratified by the year of the procedure is shown in Supplementary Table 1. Details on the type of PPM device are presented in Supplementary Table 2.

Baseline and procedural characteristics according to new CA are shown in Table 1. Overall, the mean age was 81.6 ± 6.2 years and 50.1% were female. Patients with no CA had a lower surgical risk (STS-PROM 4.70 ± 3.55 vs 4.75 ± 3.87 vs 5.28 ± 3.95; $P = 0.008$) and lower prevalence of coronary artery disease (55.3% vs 60.4% vs 60.9%; $P = 0.038$) compared to patients with new LBBB and PPM implantation. Diabetes mellitus (26.7% vs 22.3% vs 32.9%; $P = 0.002$) and right bundle branch block (7.3% vs 1.3% vs 29.6%; $P < 0.001$) were more frequently observed in patients with new PPM implantation compared to patients with new LBBB or with no CA.

Patients with no CA had a higher left ventricular ejection fraction (57.6% ± 12.9% vs 55.2% ± 14.6% vs 55.7 ± 13.9%; $P = 0.001$) and lower LV mass index (129.0 ± 39.7 g/m^2 vs 135.0 ± 45.0 g/m^2 vs 139.9 ± 46.4 g/m^2; $P = 0.003$) than those with new LBBB and PPM implantation. There were no significant differences between groups in the severity of AS, prevalence of concomitant valve disease, right ventricular dysfunction and severe pulmonary hypertension.

TAVI was performed by transfemoral access in 91.9% of patients, without significant differences between groups. Patients with new CA were more likely to have self- or mechanically expanding valves compared with balloon-expandable valves, and larger valve sizes (26.1 ± 2.2 mm vs 26.6 ± 2.3 mm vs 27.1 ± 2.2 mm; $P < 0.001$) (Table 1).

Clinical outcomes at 1 and 5 years according to new conduction abnormalities after TAVI

At a median follow-up of 1095 (interquartile range 394—1825) days, 656 patients (27.7%) had died. Clinical outcomes 1 and 5 years after TAVI are shown in Table 2.

At 5 years, all-cause death had occurred in 41.0% of patients with no CA, in 45.3% of those with new LBBB and in 50.7% of those with new PPM implantation (Fig. 2). After multivariable adjustment, patients with new LBBB had an increased risk of all-cause mortality ($HR_{adjusted}$ 1.41, 95% CI 1.04—1.92; $P = 0.026$), whereas patients with new PPM implantation had a non-significantly increased risk of all-cause mortality ($HR_{adjusted}$ 1.26, 95% CI 0.99—1.60; $P = 0.065$) compared to patients with no new CA. Cardiovascular death had more frequently occurred in patients with new LBBB (34.7% vs 30.3%; $P = 0.013$) and in those with new PPM implantation (39.3% vs 30.3%; $P < 0.001$) than in those with no CA. However, after multivariable adjustment, the differences in cardiovascular death according to CA were no longer significant ($HR_{adjusted}$ for new LBBB 1.33, 95% CI 0.91—1.97; $P = 0.15$; $HR_{adjusted}$ for new PPM 1.25, 95% CI 0.93—1.68; $P = 0.13$). There was no significant difference in heart failure symptoms (NYHA functional class III or IV) between groups. Late PPM implantation occurred more frequently in patients with new LBBB compared to those with no CA (4.0% vs 1.3%; $HR_{adjusted}$ 3.43, 95% CI 1.92—6.12; $P < 0.001$).

Subgroup analysis investigating the impact of new LBBB and new PPM implantation on 5-year mortality stratified by patient clinical, procedural and echocardiographic parameters are shown in Figs. 3 and 4. The adverse effect of new LBBB on 5-year all-cause mortality was consistent across the subgroups examined. There were no significant interactions between the effect of new PPM implantation on 5-year mortality and the examined subgroups except for the type of implanted transcatheter heart valve. The adverse crude effect of new PPM implantation on 5-year mortality was more pronounced in patients treated with self- or mechanically expanding valves than those with balloon-expandable valves ($P_{interaction} = 0.004$).

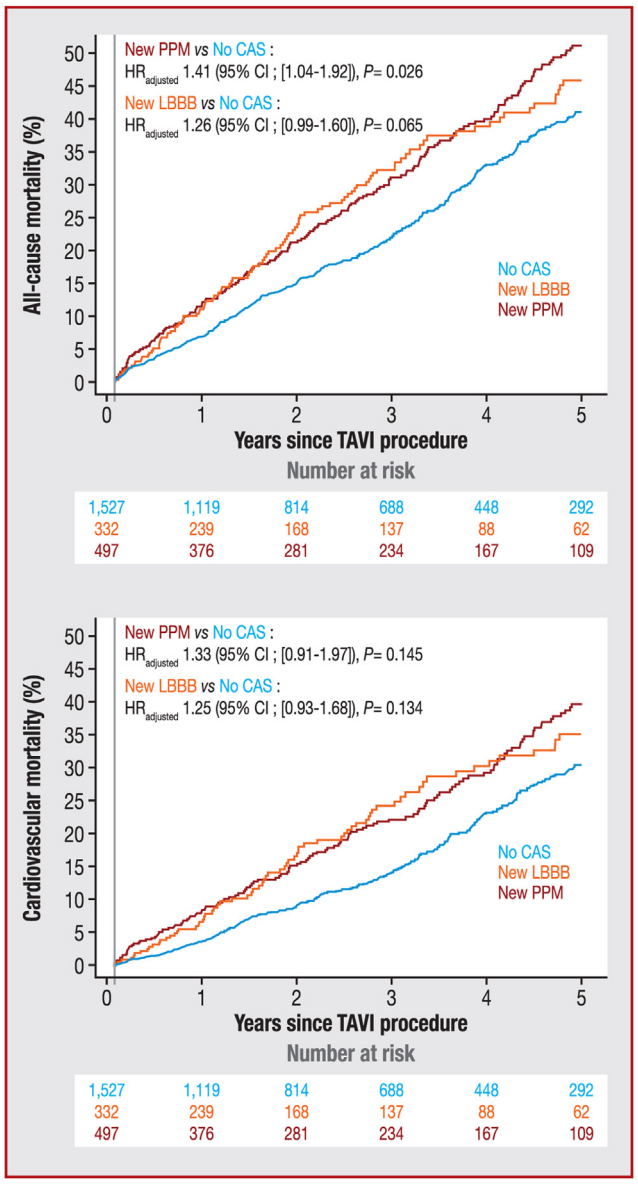

Figure 2. Kaplan-Meier curves according to new CA. Kaplan-Meier cumulative event curves for all-cause (left) and cardiovascular (right) death. Hazard ratios and *P*-values were calculated with the use of Cox proportional hazards models. CA: conduction abnormalities; CI: confidence interval; HR: hazard ratio; LBBB: left bundle branch block; PPM: permanent pacemaker; TAVI: transcatheter aortic valve implantation.

Discussion

In this registry-based study including more than 2000 patients undergoing TAVI, patients with new LBBB had an increased risk of all-cause mortality, whereas patients with new PPM implantation had a non-significant trend for increased all-cause mortality up to 5 years following TAVI.

Data on the impact of new CA on patient outcomes following TAVI remain conflicting. A recent nationwide cohort study from Sweden suggested that there was no significant difference in long-term survival up to 10 years between patients with and without new PPM implantation (HR 1.03, 95% CI 0.88—1.22; $P = 0.692$) [14]. Similarly, in a multicentre study including 1020 patients undergoing TAVI, new LBBB was not associated with increased mortality after a median follow-up of 3 years [15]. Similar findings were reported by several other studies and some meta-analyses [16—18]. In

Table 2 Clinical outcomes according to CA after TAVI.

	New CA at 30 days after TAVI			New LBBB[a]				New PPM[a]			
	No CA ($n = 1533$)	New LBBB ($n = 336$)	New PPM ($n = 501$)	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	$P_{adjusted}$	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	$P_{adjusted}$
At 1 year											
All-cause death, n (%)	98 (6.9% [5.7—8.3])	34 (10.9% [7.9—15.0])	56 (11.8% [9.2—15.1])	1.61 (1.09-2.37)	0.017	1.79 (0.97—3.29)	0.06	1.75 (1.26—2.43)	<0.001	1.38 (0.83—2.30)	0.22
Cardiovascular death, n (%)	51 (3.7% [2.8—4.8])	20 (6.6% [4.3—10.0])	38 (8.2% [6.0—11.0])	1.82 (1.08—3.05)	0.023	2.07 (0.83—5.16)	0.12	2.29 (1.50—3.48)	<0.001	1.76 (0.87—3.58)	0.12
PPM implantation, n (%)	18 (1.3% [0.8—2.1])	12 (4.0% [2.3—6.9])	—	3.12 (1.50—6.49)	0.002	3.16 (1.16—8.63)	0.025	—	—	—	—
NYHA III or IV, n (%)[b]	129/1289 (10.0%)	27/268 (10.1%)	56/401 (14.0%)	1.01 (0.68—1.49)	0.97	1.07 (0.64—1.77)	0.81	1.40 (1.04—1.87)	0.026	1.41 (0.94—2.10)	0.09
At 5 years											
All-cause death, n (%)	374 (41.0% [37.6—44.5])	101 (45.3% [38.5—52.6])	181 (50.7% [45.3—56.3])	1.30 (1.05—1.62)	0.018	1.41 (1.04—1.92)	0.026	1.39 (1.17—1.67)	<0.001	1.26 (0.99—1.60)	0.065
Cardiovascular death, n (%)	242 (30.3% [27.0—33.8])	70 (34.7% [28.1—42.3])	126 (39.3% [33.8—45.2])	1.40 (1.07—1.83)	0.013	1.33 (0.91—1.97)	0.15	1.49 (1.21—1.85)	<0.001	1.25 (0.93—1.68)	0.13
PPM implantation, n (%)	49 (5.7% [4.2—7.7])	30 (16.8% [11.5—24.1])	—	3.07 (1.95—4.84)	<0.001	3.43 (1.92—6.12)	<0.001	—	—	—	—
NYHA III or IV, n (%)[b]	57/380 (15.0%)	15/79 (19.0%)	16/133 (12.0%)	1.27 (0.76—2.12)	0.37	1.18 (0.63—2.21)	0.60	0.80 (0.48—1.35)	0.40	1.01 (0.55—1.84)	0.99

Values are n (% [95% CI]), unless otherwise indicated. Adjusted HR for death and robust adjusted Poisson regressions for NYHA with 95% CI, using $n = 1000$ patients with complete data, adjusted for age, sex, STS-PROM, diabetes mellitus, renal failure (eGFR < 60 mL/min/1.73 m^2), peripheral artery disease, atrial fibrillation, left ventricular ejection fraction, moderate or severe mitral regurgitation, moderate or severe tricuspid regurgitation, severe pulmonary hypertension, and right ventricular dysfunction. Patient who died before 30 days are not included. Number of events and in brackets: cumulative incidences from Kaplan-Meier estimate for death and PPM implantation; percentages for NYHA. CA: conduction abnormalities; CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; LBBB: left bundle branch block; NYHA: New York Heart Association; PPM: permanent pacemaker implantation; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI: transcatheter aortic valve implantation.

[a] Compared with the reference group (no CA).

[b] Described risk ratios (95% CI) from robust Poisson regression are reported, with corresponding *P* values.

	No CAs N = 1,533	New LBBB N = 336	Hazard Ratio (95% CI)	P value	Interaction p-value
Age					0.805
Age ≥75	336/1316	91/286	1.29 (1.02-1.62)	0.033	
Age <75	38/217	10/50	1.43 (0.71-2.88)	0.311	
Sex					0.361
Male	191/752	41/144	1.17 (0.83-1.64)	0.366	
Female	183/781	60/192	1.44 (1.07-1.93)	0.015	
STS-PROM					0.358
STS-PROM >8%	85/192	19/36	1.52 (0.92-2.50)	0.103	
STS-PROM 4-8%	158/517	50/121	1.54 (1.12-2.12)	0.008	
STS-PROM <4%	131/824	32/179	1.08 (0.74-1.60)	0.682	
Atrial fibrillation					0.311
Yes	157/462	47/105	1.49 (1.07-2.06)	0.017	
No	217/1071	54/231	1.19 (0.88-1.60)	0.259	
THV type					0.335
BEV	172/646	62/169	1.41 (1.05-1.88)	0.021	
SEV/MEV	202/884	39/167	1.13 (0.80-1.60)	0.472	
LV systolic function					0.134
Baseline LVEF <50%	96/288	36/82	1.66 (1.13-2.43)	0.010	
Baseline LVEF ≥50%	268/1188	61/240	1.16 (0.87-1.53)	0.309	
Low gradient AS					0.163
Mean gradient ≥40 mmHg	195/757	59/174	1.49 (1.11-1.99)	0.008	
Mean gradient <40 mmHg	167/733	39/153	1.08 (0.76-1.53)	0.657	
LV hypertrophy					0.109
Yes	204/619	53/143	1.24 (0.92-1.68)	0.158	
No	47/230	16/41	2.10 (1.19-3.70)	0.010	
Aortic regurgitation					0.780
Moderate or severe	47/134	6/20	1.19 (0.51-2.79)	0.686	
None or mild	285/1152	81/259	1.34 (1.05-1.72)	0.019	
Mitral regurgitation					0.453
Moderate or severe	72/236	21/53	1.48 (0.91-2.41)	0.115	
None or mild	274/1124	68/241	1.22 (0.94-1.60)	0.136	
Tricuspid regurgitation					0.824
Moderate or severe	49/128	16/34	1.21 (0.69-2.14)	0.500	
None or mild	267/1139	68/242	1.33 (1.02-1.73)	0.037	
Severe PH					0.996
Yes	104/234	28/56	1.30 (0.86-1.98)	0.217	
No	270/1299	73/280	1.31 (1.01-1.69)	0.043	
RV dysfunction					0.283
Yes	68/160	17/32	1.65 (0.97-2.81)	0.064	
Normal	182/575	46/131	1.18 (0.85-1.63)	0.318	
RBBB					0.959
Yes	27/110	1/4	1.40 (0.19-10.36)	0.740	
No	339/1388	95/314	1.33 (1.06-1.67)	0.014	
Year of TAVI					0.872
2007-2011	327/1417	91/314	1.31 (1.04-1.66)	0.022	
2012-2021	47/116	10/22	1.22 (0.62-2.41)	0.570	

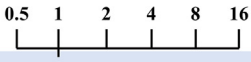

Figure 3. Subgroup analyses of the effect of new LBBB on five-year mortality. LBBB: left bundle branch block; BEV: balloon-expandable valves; LVEF: left ventricular ejection fraction; MEV: mechanically-expandable valves; PH: pulmonary hypertension; RBBB: right bundle branch block; RV: right ventricular; SEV: self-expanding valves; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve.

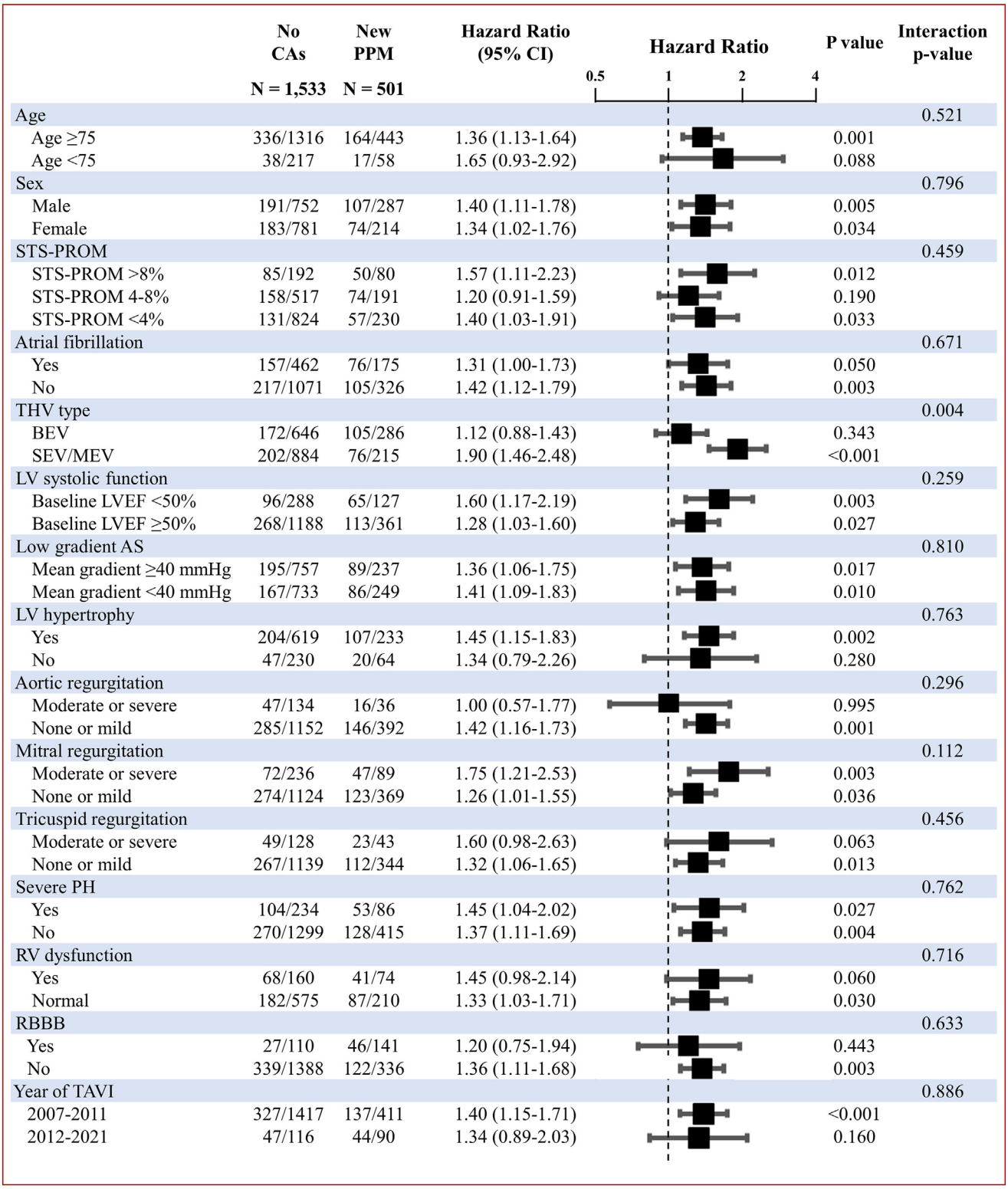

Figure 4. Subgroup analyses of the effect of new PPM implantation on five-year mortality. PPM: permanent pacemaker. LBBB: left bundle branch block; BEV: balloon-expandable valves; CA: conduction abnormalities; CI: confidence interval; LVEF: left ventricular ejection fraction; MEV: mechanically expandable valves; PH: pulmonary hypertension; RBBB: right bundle branch block; RV: right ventricular; SEV: self-expanding valve; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve.

contrast, a recent Danish single-centre study showed higher 5-year mortality in patients with new bundle branch block (48.4%; HR 1.79, 95% CI 1.24—2.59) and those with new PPM implantation (46.7%; HR 1.58, 95% CI 1.01—2.46) than those without new CA [19]. These findings were also corroborated by some recent meta-analyses [20,21].

In the Danish study, the authors argued that the inclusion of known/new LBBB (or known/new PPM implantation) in the comparator group may have diluted the potential impact of new CA in most previous studies. In the present study, we conducted the analysis using a similar design as the Danish study and observed similar outcomes for the impact of new LBBB and new PPM implantation on all-cause mortality in crude analysis. However, after multivariable adjustment, the impact on all-cause mortality was statistically significant for new LBBB, whereas the association did not reach the conventional level of statistical significance for new PPM implantation.

It is reasonable to assume that new CA may adversely affect patient outcomes following TAVI, given available knowledge of adverse effects of LBBB and right ventricular pacing in non-AS populations: both right ventricular apical pacing and LBBB cause atrioventricular and inter/intraventricular dyssynchrony [22,23], which has been shown to result in adverse LV remodelling, but may be prevented by biventricular pacing [24]. The association between new LBBB/new PPM and adverse LV remodelling has also been suggested in TAVI populations [15,18,19]. Furthermore, right ventricular pacing lead may interact with the tricuspid valve and cause or worsen tricuspid regurgitation, impairing patient prognosis [25]. His-bundle or physiological pacing may decrease dyssynchronous ventricular pacing and attenuate the adverse effect of PPM implantation after TAVI [26,27].

It has been argued that the high-risk nature and the advanced age of patients undergoing TAVI have masked the potential adverse effects of new CA on long-term patient outcomes. To assess whether there is any difference in the impact of new CA depending on patient baseline profile, we performed subgroup analyses, which showed no significant interactions between the effect of new CA and patient baseline profiles, including age, surgical risk, baseline LV/right ventricular function or presence/absence of tricuspid regurgitation. However, it needs to be emphasized that most of the procedures in this study were performed before recent updates in European guidelines on the management of valvular heart disease; therefore, young or low-risk patients were less prevalent in this study. Thus, the impact of new CA on young and low-risk patients with a longer life expectancy, who could be treated with surgical aortic valve replacement, may have not been adequately addressed in the present study. Indeed, in a recent large cohort study of 24,983 patients undergoing surgical aortic valve replacement with a mean age of 70 years, all-cause mortality was significantly higher in patients with new PPM implantation than those without (HR 1.14, 95% CI 1.01—1.29; $P = 0.03$) after inverse propensity score weighting [28]. Further studies are needed on whether the higher incidence of new CA following TAVI can adversely affect long-term patient prognosis in young or low-risk populations where both TAVI and surgical aortic valve replacement can be reasonable treatment options.

An interesting finding from the subgroup analysis is that the crude adverse effect of new PPM implantation on 5-year mortality was only observed in patients treated with self- or mechanically expanding valves and not in those treated with balloon-expandable valves. Although pacemaker dependency could not be evaluated in our registry, a possible explanation would be that patients treated with balloon-expandable valves were less likely to be pacemaker dependent because new CA were transient only, due to indirect injury such as acute tissue inflammation and oedema [29].

With the increased expansion of TAVI to younger and lower-risk patients with a longer life expectancy, the long-term consequences of new CA following TAVI are becoming increasingly important. It should be noted that current literature on this subject was largely limited to studies conducted in elderly or surgically increased risk populations [30]. As discussed above, the data on the clinical impact of new CA were conflicting even between meta-analyses and not conclusive at this stage. However, given the negative effects of right ventricular pacing on left ventricular remodelling and tricuspid regurgitation as well as longer hospital stays and increased costs related to the occurrence of new CA, every effort should be made to avoid new CA following TAVI [31,32]. Known risk factors for new CA following TAVI, such as right bundle branch block and short membranous septum length, should be meticulously assessed and considered in the decision-making process [30]. The cusp overlap technique has recently been introduced to facilitate high valve deployment and reduce the risk of new CA following TAVI with self-expanding valves; however, surgical aortic valve replacement may remain a preferred option for patients at high risk of new CA as it remains uncertain whether TAVI with these techniques can result in a comparable risk of new CA than surgical aortic valve replacement. Furthermore, the technique of high implantation of transcatheter heart valves within the annulus may impair coronary access and increase the risk of coronary obstruction during future valve-in-valve procedures; thus, the optimal implantation height of the device remains a matter of debate [33—37].

Study limitations

The findings of our study should be interpreted in light of several limitations. First, this was a single-centre observational study based on a prospective registry. Thus, the findings may have been confounded by unmeasured or unrecognized variables despite the use of sophisticated statistical methods. In turn, we provide comprehensive data on more than 2000 patients evaluated for CA following TAVI from a large prospective registry adhering to high standards of data quality with rigorous data collection, standardized follow-up and independent event adjudication. Second, although clinical event and functional outcome data were systematically collected, hospitalization for heart failure, a potentially relevant outcome, was not captured and could not be assessed in the present study. Third, pacemaker dependency during follow-up, which could significantly affect patient outcomes, was not evaluated in our study. Finally, follow-up echocardiography was not systematically performed in the registry; thereby, the impact of new CA on

LV function or tricuspid regurgitation could not be evaluated.

Conclusions

In this prospective TAVI registry, new LBBB was significantly associated with a 1.4-fold increased risk of mortality at 5 years, while new PPM implantation conferred a non-significant trend. The findings warrant further investigations particularly in younger and lower-risk populations with a longer life expectancy.

Sources of funding

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://doi.dx.org/10.1016/j.acvd.2022.02.008.

Disclosure of interest

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