Pacemaker Implantation After Balloon-or Self-Expandable Transcatheter Aortic Valve Replacement in Patients With Aortic Stenosis

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BRIEF COMMUNICATION

Pacemaker Implantation After Balloon- or Self-Expandable Transcatheter Aortic Valve Replacement in Patients With Aortic Stenosis

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BACKGROUND: The incidence of conduction abnormalities requiring permanent pacemaker implantation (PPI) after transcatheter aortic valve replacement (TAVR) with early and later generation prostheses remains debated.

METHODS AND RESULTS: Based on the administrative hospital-discharge database, we collected information for all patients treated with TAVR between 2010 and 2019 in France. We compared the incidence of PPI after TAVR according to the type and generation of valve implanted. A total of 49 201 patients with aortic stenosis treated with TAVR using the balloon-expandable (BE) Edwards SAPIEN valve (early Sapien XT and latest Sapien 3) or the self-expanding (SE) Medtronic CoreValve (early CoreValve and latest Evolut R) were found in the database. Mean (SD) follow-up was 1.2 (1.5 years) (median [interquartile range] 0.6 [0.1–2.0] years). PPI after the procedure was reported in 13 289 patients, among whom 11 010 (22.4%) had implantation during the first 30 days. In multivariable analysis, using early BE TAVR as reference, adjusted odds ratio (95% CI) for PPI during the first 30 days was 0.88 (0.81–0.95) for latest BE TAVR, 1.40 (1.27–1.55) for early SE TAVR, and 1.17 (1.07–1.27) for latest SE TAVR. Compared with early BE TAVR, the adjusted hazard ratio for PPI during the whole follow-up was 1.01 (0.95–1.08) for latest BE TAVR, 1.30 (1.21–1.40) for early SE TAVR, and 1.25 (1.18–1.34) for latest SE TAVR.

CONCLUSIONS: In patients with aortic stenosis treated with TAVR, our systematic analysis at a nationwide level found higher rates of PPI than previously reported. BE technology was independently associated with lower incidence rates of PPI both at the acute and chronic phases than SE technology. Recent generations of TAVR were not independently associated with different rates of PPI than early generations during the overall follow-up.

Key Words: aortic stenosis ■ pacemaker ■ transcatheter aortic valve implantation

See Editorial by Huang and Mansour

The number of transcatheter aortic valve replacement (TAVR) procedures has risen worldwide in recent years for treating patients with aortic stenosis, and is expected to continue growing.[1] The incidence of conduction abnormalities requiring permanent pacemaker implantation (PPI) after TAVR with different devices available in recent years remains a matter of debate. So far in France, 2 different technologies are available: the balloon-expandable (BE) Edwards SAPIEN valve (Edwards lifesciences Inc., Irvine, CA) and the self-expanding (SE) Medtronic CoreValve (Medtronic Inc., Minneapolis, MN). In France

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in 2018, the latest available generations of each valve (Edwards Sapien 3 and Medtronic CoreValve Evolut R) were widely introduced in 2014 and 2015, respectively, with the aim to reduce the incidence of paravalvular leak. A patient-tailored transcatheter heart valve therapy would need to be evaluated, and specific recommendations for implantation of each prosthesis taking into consideration some clinical characteristics may be needed to reduce the risk of PPI. We compared the incidence of PPI after TAVR according to the type and generation of valve implanted.

METHODS

The data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Because this study used data from human subjects, the data and everything pertaining to the data are governed by the French Health Agencies and cannot be made available to other researchers.

This retrospective cohort study was based on the national hospitalization database covering hospital care from the entire French population. The data for all patients admitted with aortic stenosis in France from January 2010 to June 2019 were collected from the national administrative Programme de Médicalisation des Systèmes d'Information (PMSI) database. Through this program, medical activity is recorded in a database and rendered anonymous. It includes >98% of the French population (67 million people) from birth (or immigration) to death (or emigration), even if a person changes occupation or retires. This process allows the determination of each hospital's budget, in the 1546 French healthcare facilities for both public and private hospitals. Each hospitalization is encoded in a standardized data set, which includes information about the patient (age and sex), hospital, stay (date of admission, date of discharge, and mode of discharge), pathologies, and procedures. Routinely collected medical information includes the principal diagnosis and secondary diagnoses. In the PMSI system, identified diagnoses are coded according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*). All medical procedures are recorded according to the national nomenclature, Classification Commune des Actes Medicaux. The PMSI contains individual pseudoanymized information on each hospitalization that are linked to create a longitudinal record of hospital stays and diagnoses for each patient. The reliability of PMSI data has already been assessed, and this database has previously been used to study patients with cardiovascular conditions, including those with aortic stenosis treated with TAVR.[1,2]

The study was conducted retrospectively and, as patients were not involved in its conduct, there was no impact on their care. Ethical approval was not required, because all data were anonymized. The French Data Protection Authority granted access to the PMSI data. Procedures for data collection and management were approved by the Commission Nationale de l'Informatique et des Libertés, the independent National Ethical Committee protecting human rights in France, which ensures that all information is kept confidential and anonymous, in compliance with the Declaration of Helsinki (authorization number 1897139).

Study Population

From January 1, 2010 to June 30, 2019, 520 662 adults (age ≥18 years) were hospitalized with a diagnosis of aortic stenosis (I350, I352, I060, and I062 using *ICD-10* codes) as the principal diagnosis (ie, the health problem that justified admission to hospital), the related diagnosis (ie, potential chronic disease or health state during the hospital stay), or a significantly associated diagnosis (ie, comorbidity or associated complication). For the analysis of TAVR procedures, we included all adults with a single percutaneous procedure (Classification Commune des Actes Medicaux code: DBLF001). Early and more recent generation balloon-expandable (BE) and self-expandable (SE) TAVR were differentiated using their codes used for pricing. Patient information (demographics, comorbidities, medical history, and events during hospitalization or follow-up) was described using data collected in the hospital records. For each hospital stay, combined diagnoses at discharge were obtained. Each variable was identified using *ICD-10* codes. Based on the database, we were able to estimate a proxy of the EuroSCORE II (Data S1 and Figure S1). We also used the Charlson Comorbidity Index and the Claims-based Frailty Indicator to assess patient clinical status. Exclusion criteria were age <18 years.

Statistical Analysis

Qualitative variables are described as frequency and percentages and quantitative variable as means (SDs). Comparisons were made using χ^2 tests for categorical variables and the Student *t* test or nonparametric Kruskal–Wallis test, as appropriate, for continuous variables.

For the analysis in the cohort, PPI was identified using its several specific codes from the Classification Commune des Actes Medicaux and we report outcomes at 30 days and during whole follow-up. The logistic regression model was used for the specific outcome of pacemaker implantation at 30 days and odds ratios are reported. The cut-off at 30 days has been used in many reference analyses.[3–5] The evaluation during a "hospital phase" may be less standardized

because the duration and pathway across several departments (or hospitals) during the initial hospital phase may markedly differ in different patients treated with TAVR. For longer-term follow-up, the incidence rates for outcomes (%/y) in each group were estimated. Analyses were performed using a Cox regression model and the hazard ratios are reported. Multivariable analysis included all parameters listed in Table 1. All comparisons

Table 1. Characteristics and Outcomes of Patients Treated With TAVR

	Early BE TAVR	Latest BE TAVR	Early SE TAVR	Latest SE TAVR
	(n=4262)	(n=25 174)	(n=5319)	(n=14 446)
Age, y	82.9±7.1 (84, 8)	82.4±6.9 (84, 8)	82.8±6.8 (84, 7)	82.7±6.8 (84, 7)
EuroSCORE II	3.8±1.0 (3.7, 1.3)	3.7±1.0 (3.5, 1.3)	3.9±1.0 (3.8, 1.4)	3.8±1.0 (3.6, 1.4)
Charlson comorbidity index	4.8±2.8 (5, 4)	4.0±2.9 (3, 4)	4.9±2.9 (5, 4)	3.8±2.8 (3, 3)
Frailty index	11.3±9.3 (9, 12)	8.7±8.7 (6.1, 10.5)	11.6±9.5 (9.5, 12.9)	8.7±8.7 (6.1, 10.4)
Sex (male)	2014 (47.3)	13 413 (53.3)	2800 (52.6)	5866 (40.6)
Hypertension	3709 (87.0)	21 312 (84.7)	4643 (87.3)	12 214 (84.5)
Diabetes mellitus	1394 (32.7)	7831 (31.1)	1727 (32.5)	4370 (30.3)
Heart failure	2722 (63.9)	13 697 (54.4)	3435 (64.6)	7574 (52.4)
Coronary artery disease	2867 (67.3)	16 218 (64.4)	3677 (69.1)	9098 (63.0)
Previous myocardial infarction	554 (13.0)	3518 (14.0)	905 (17.0)	1985 (13.7)
Previous PCI	1074 (25.2)	7539 (29.9)	1500 (28.2)	4194 (29.0)
Previous CABG	0.1±0.3	0.1±0.3	0.1±0.3	0.1±0.3
Vascular disease	1473 (34.6)	9144 (36.3)	2137 (40.2)	5150 (35.7)
Mitral regurgitation	813 (19.1)	4767 (18.9)	1052 (19.8)	2787 (19.3)
Aortic regurgitation	619 (14.5)	2544 (10.1)	742 (13.9)	1890 (13.1)
Tricuspid regurgitation	138 (3.2)	1110 (4.4)	185 (3.5)	719 (5.0)
Atrial fibrillation	2028 (47.6)	11 359 (45.1)	2480 (46.6)	6345 (43.9)
Left bundle branch block	512 (12.0)	4379 (17.4)	883 (16.6)	2895 (20.0)
Right bundle branch block	285 (6.7)	1968 (7.8)	395 (7.4)	1142 (7.9)
Previous pacemaker or defibrillator	833 (19.5)	4766 (18.9)	1408 (26.5)	3012 (20.9)
Ischemic stroke	176 (4.1)	1370 (5.4)	300 (5.6)	893 (6.2)
Smoker	345 (8.1)	2390 (9.5)	493 (9.3)	1293 (9.0)
Dyslipidemia	2225 (52.2)	12 636 (50.2)	2765 (52.0)	7323 (50.7)
Obesity	1247 (29.3)	7327 (29.1)	1452 (27.3)	3946 (27.3)
Alcohol-related diagnoses	224 (5.3)	1395 (5.5)	322 (6.1)	652 (4.5)
Abnormal renal function	757 (17.8)	4242 (16.9)	1066 (20.0)	2473 (17.1)
Lung disease	1128 (26.5)	5668 (22.5)	1529 (28.7)	3192 (22.1)
Sleep apnea syndrome	292 (6.9)	2403 (9.5)	437 (8.2)	1315 (9.1)
Liver disease	189 (4.4)	1257 (5.0)	298 (5.6)	689 (4.8)
Thyroid diseases	564 (13.2)	3340 (13.3)	657 (12.4)	2285 (15.8)
Anemia	1130 (26.5)	6802 (27.0)	1485 (27.9)	4191 (29.0)
Previous cancer	634 (14.9)	5095 (20.2)	916 (17.2)	2627 (18.2)
Outcomes				
Death during follow-up	1525 (35.8)	3486 (13.8)	1807 (34.0)	1666 (11.5)
Death at day 30	233 (5.5)	621 (2.5)	312 (5.9)	453 (3.1)
Death beyond day 30*	1292 (11.1)	2865 (11.5)	1495 (11.8)	1213 (10.1)
Pacemaker implantation during follow-up	1267 (29.7)	6191 (24.6)	1739 (32.7)	4092 (28.3)
Pacemaker implantation at day 30	934 (21.9)	5203 (20.7)	1359 (25.5)	3514 (24.3)
Pacemaker implantation beyond day 30*	333 (3.9)	988 (5.2)	380 (4.2)	578 (6.3)

Values are mean±SD (median, interquartile range) for continuous variables, N (%) for categorical variables. BE indicates balloon-expandable; CABG, coronary artery bypass graft; Early BE, Edwards Sapien XT; Early SE, Medtronic Corevalve; Latest BE, Edwards Sapien 3; Latest SE, Medtronic Evolut; PCI, percutaneous coronary intervention; SE, self-expandable; and TAVR, transcatheter aortic valve replacement.

*% are yearly incidence.

with $P<0.05$ were considered statistically significant. All analyses were performed using Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC), USA and STATA version 12.0 (Stata Corp, College Station, TX).

RESULTS

Among 49 201 patients, patients treated with early BE and SE valves had higher Charlson comorbidity and frailty indexes than those treated with second generation, and slightly higher EuroSCORE II. Patients treated with SE valves had higher rates of previous pacemaker or defibrillator than those treated with BE valves (Table 1). Mean (SD) follow-up was 1.2 (1.5 years) (median [interquartile range] 0.6 [0.1–2.0] years).

PPI at the time of or after the procedure was reported in 13 289 patients, among whom 11 010 had implantation in during the first 30 days (ranging from 20.7% for latest BE to 25.5% for early SE TAVR) (Table 1) (Figure).

In multivariable analysis, using early BE TAVR as reference, adjusted odds ratios (95% CI) for PPI during the first 30 days was 0.88 (0.81–0.95) for latest BE TAVR, 1.40 (1.27–1.55) for early SE TAVR, and 1.17 (1.07–1.27) for latest SE TAVR. Other independent predictors of PPI during the first 30 days were older age, male sex, history of hypertension, obesity, diabetes mellitus, myocardial infarction, history of pulmonary edema, atrial fibrillation, left bundle branch block, right bundle branch block, and abnormal renal function (Table 2).

Compared with early BE TAVR, adjusted hazard ratio for PPI during the whole follow-up was 1.01 (0.95–1.08) for latest BE TAVR, 1.30 (1.21–1.40) for early SE TAVR, and 1.25 (1.18–1.34) for latest SE TAVR (Table 2). Other independent predictors of PPI during the whole follow-up as well as predictors for PPI for the specific period beyond the 30th day post TAVR are in Table 2.

While latest BE TAVR was associated with a lower risk of PPI than early BE TAVR during the first 30 days, it was associated with a higher risk of PPI than early BE TAVR in the subsequent period beyond the 30th day (adjusted hazard ratio 1.35 [1.18–1.53]). Similarly, latest SE TAVR was associated with a lower risk of PPI than early SE TAVR during the first 30 days, but was associated with a higher risk of PPI than early SE TAVR on the subsequent period beyond the 30th day.

DISCUSSION

Our large adjusted analysis showed that BE TAVR technology was associated with lower incidence rates of PPI compared with SE TAVR. Latest generations of

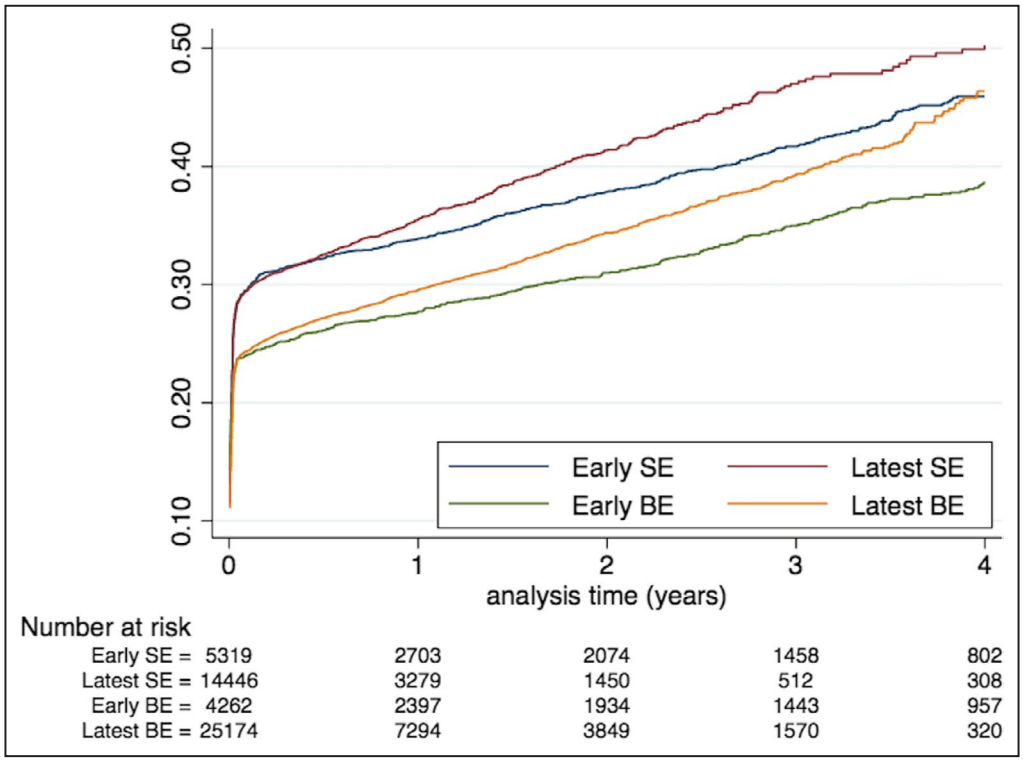

Figure. Incidence of permanent pacemaker implantation in patients treated with TAVR, according to type and generation of device.
BE indicates balloon-expandable; Early BE, Edwards Sapien XT; Early SE, Medtronic Corevalve; Latest BE, Edwards Sapien 3; Latest SE, Medtronic Evolut; SE, self-expandable; and TAVR, transcatheter aortic valve replacement.

Table 2. Independent predictors of PPI During the First 30 Days and During the Whole Follow-Up in Patients Treated With TAVR

	Whole Follow-Up		First 30 Days		Beyond 30 Days	
	HR, 95% CI	*P* Value	OR, 95% CI	*P* Value	HR, 95% CI	*P* Value
Age, per 10 y	1.09 (1.06–1.12)	<0.0001	1.14 (1.10–1.18)	<0.0001	0.97 (0.90–1.04)	0.34
EuroSCORE II	1.02 (0.99–1.04)	0.28	1.01 (0.98–1.05)	0.45	1.04 (0.98–1.11)	0.23
Charlson comorbidity index	0.98 (0.97–0.99)	0.001	0.98 (0.95–1.01)	0.40	0.98 (0.96–1.01)	0.14
Frailty index, per 10 units	0.99 (0.97–1.01)	0.35	0.98 (0.95–1.00)	0.18	1.13 (1.08–1.18)	<0.0001
Sex (male)	1.24 (1.20–1.29)	<0.0001	1.29 (1.23–1.36)	<0.0001	1.45 (1.33–1.59)	<0.0001
Hypertension	1.09 (1.04–1.14)	<0.0001	1.16 (1.09–1.23)	<0.0001	0.95 (0.85–1.06)	0.35
Diabetes mellitus	1.09 (1.05–1.14)	<0.0001	1.08 (1.02–1.14)	0.01	1.17 (1.06–1.30)	0.002
Heart failure	1.03 (0.99–1.08)	0.12	1.01 (0.96–1.07)	0.75	1.15 (1.05–1.27)	0.004
History of pulmonary edema	1.12 (1.03–1.21)	0.01	1.13 (1.01–1.27)	0.03	1.03 (0.84–1.27)	0.76
Aortic regurgitation	1.06 (1.00–1.12)	0.04	1.07 (1.00–1.15)	0.06	1.05 (0.93–1.19)	0.45
Mitral regurgitation	0.91 (0.87–0.96)	<0.0001	0.87 (0.82–0.92)	<0.0001	1.00 (0.90–1.12)	0.94
Coronary artery disease	0.96 (0.92–1.00)	0.06	0.93 (0.88–0.99)	0.01	1.01 (0.91–1.12)	0.90
Previous myocardial infarction	1.13 (1.06–1.20)	<0.0001	1.15 (1.06–1.24)	0.001	1.16 (1.01–1.34)	0.04
Previous PCI	1.01 (0.97–1.06)	0.54	1.04 (0.98–1.01)	0.25	0.95 (0.86–1.06)	0.38
Previous CABG	0.92 (0.86–0.99)	0.04	0.92 (0.83–1.01)	0.09	0.90 (0.77–1.05)	0.17
Vascular disease	0.90 (0.86–0.94)	<0.0001	0.85 (0.80–0.90)	<0.0001	1.01 (0.91–1.13)	0.81
Atrial fibrillation	1.06 (1.02–1.10)	0.003	1.05 (1.01–1.11)	0.03	1.26 (1.16–1.37)	<0.0001
Left bundle branch block	1.29 (1.23–1.34)	<0.0001	1.35 (1.27–1.42)	<0.0001	1.75 (1.58–1.93)	<0.0001
Right bundle branch block	1.71 (1.61–1.81)	<0.0001	2.21 (2.03–2.40)	<0.0001	1.34 (1.14–1.58)	<0.0001
Ischemic stroke	1.01 (0.94–1.09)	0.82	0.98 (0.89–1.09)	0.73	1.07 (0.89–1.28)	0.50
Smoker	1.01 (0.94–1.07)	0.89	1.01 (0.92–1.10)	0.87	1.03 (0.89–1.20)	0.68
Dyslipidemia	1.01 (0.98–1.05)	0.45	1.03 (0.98–1.08)	0.33	0.98 (0.90–1.07)	0.69
Obesity	1.16 (1.11–1.21)	<0.0001	1.24 (1.17–1.31)	<0.0001	1.00 (0.90–1.11)	0.95
Alcohol-related diagnoses	1.02 (0.93–1.12)	0.72	1.10 (0.97–1.24)	0.14	0.74 (0.58–0.93)	0.009
Abnormal renal function	1.07 (1.02–1.12)	0.009	1.09 (1.02–1.17)	0.01	0.99 (0.87–1.11)	0.81
Lung disease	0.95 (0.91–0.99)	0.03	0.95 (0.90–1.01)	0.08	0.89 (0.81–0.99)	0.03
Sleep apnea syndrome	0.99 (0.93–1.05)	0.72	0.96 (0.88–1.05)	0.35	1.12 (0.97–1.30)	0.13
Liver disease	0.97 (0.88–1.06)	0.47	0.91 (0.81–1.09)	0.12	1.07 (0.87–1.32)	0.53
Thyroid diseases	1.01 (0.96–1.07)	0.63	1.02 (0.95–1.09)	0.63	1.02 (0.90–1.16)	0.75
Inflammatory disease	1.02 (0.96–1.08)	0.60	1.03 (0.95–1.11)	0.49	0.99 (0.86–1.14)	0.89
Anemia	0.96 (0.93–1.00)	0.07	0.96 (0.91–1.02)	0.17	0.95 (0.86–1.05)	0.33
Previous cancer	1.02 (0.97–1.07)	0.54	0.99 (0.93–1.06)	0.71	1.06 (0.95–1.19)	0.31
Edwards Sapien XT	1.00	···	1.00	···	1.00	···
Edwards Sapien 3	1.01 (0.95–1.08)	0.75	0.88 (0.81–0.95)	0.002	1.35 (1.18–1.53)	<0.0001
Medtronic Corevalve	1.30 (1.21–1.40)	<0.0001	1.40 (1.27–1.55)	<0.0001	1.27 (1.10–1.48)	0.001
Medtronic Evolut	1.25 (1.17–1.34)	<0.0001	1.16 (1.07–1.27)	0.001	1.59 (1.38–1.83)	<0.0001

BE indicates balloon-expandable; CABG, coronary artery bypass graft; Early BE, Edwards Sapien XT; Early SE, Medtronic Corevalve; HR, hazard ratio; Latest BE, Edwards Sapien 3; Latest SE, Medtronic Evolut; PCI, percutaneous coronary intervention; PPI, permanent pacemaker implantation; SE, self-expandable; and TAVR, transcatheter aortic valve replacement.

TAVR had slightly lower adjusted odds ratio for PPI at day 30, but higher adjusted hazard ratios for PPI on a longer-term follow-up, resulting in a similar rate of PPI for the overall follow-up.

Since TAVR was introduced, the BE Sapien technology has evolved from Sapien XT to Sapien 3 (in 2012) and the SE CoreValve technology, which has evolved to the Evolut R system (in 2013). International guidelines recommend that severe aortic stenosis be treated with TAVR in eligible patients without recommendation regarding the type of TAVR technology. There is considerable heterogeneity in the average PPI rates in the literature, ranging from 5.9% to 20.7% for BE-bioprosthesis.[6] A higher rate of 30-day PPI has been reported with SE valves.[7] Our analysis at a nationwide level has the main advantage of being

exhaustive, avoiding selection and reporting biases for a reliable picture of PPI after TAVR. We also found a higher rate of 30-day pacemaker implantation with SE valves, although the difference was less marked than in the CENTER (Cerebrovascular Events in Patients Undergoing Transcatheter Aortic Valve Implantation) analysis.[7] This difference persisted in the longer term. The second-generation BE prosthesis has an outer skirt to minimize paravalvular leakage and has been associated with higher rates of PPI,[8] which was not clearly seen in our study (similar for overall follow-up, being lower in the early phase and higher on a longer term in the multivariable analysis). Our "real life" incidences of pacemaker implantation at 30 days are slightly higher than in the randomized SOLVE TAVR (Comparison of Second-Generation Self-Expandable vs. Balloon-Expandable Valves and General vs. Local Anaesthesia in Transcatheter Aortic Valve Implantation) trial.[9] They were also higher than in an earlier French observational study, considering the hospital phase (16–18%) and using a declarative method that may underestimate the true rates of PPI.[10] Higher rates of in-hospital PPI (up to 22%) were, however, reported in the most recent findings from this declarative registry.[11] This contrasts in part with the findings at day 30 in our systematic analysis at a nationwide level from a mandatory administrative database, including centers where patients may be transferred after the TAVR procedure.

This overall suggests that, in daily practice, physicians may have a relatively aggressive approach towards pacemaker implantation for patients treated with TAVR, regardless of the type of valve implanted. Targeting shorter hospital stay may play a role in these results, favoring more frequent and earlier PPI, and avoiding a too long ECG monitoring.[12–14] It has also been reported that delayed atrioventricular block may be an underappreciated complication of TAVR among patients without preprocedure pacing devices,[15] and this may lead to a more aggressive approach at a nationwide level. Predictors for PPI at the acute phase post TAVR and on a longer term were broadly similar to those previously reported by others in far smaller series, particularly for older age and right bundle branch block.[15–17] Our results also suggest that the best strategy for PPI in these patients, including the appropriate role of electrophysiological study, may need to be more properly defined. A few randomized studies are ongoing, 2 of them comparing incidences of PPI with 2 different TAVR devices and 1 comparing an electrophysiology-based algorithmic approach to standard clinical follow-up with clinical events at the 12th month.[18]

Limitations

A main limitation of our work is inherent to the retrospective, observational nature of the study and its potential biases. Furthermore, the study was based on administrative data, with limitations inherent to such methodology. The PMSI database contains diagnoses coded using *ICD-10*, which are obtained at hospital discharge and are the physician's responsibility. Data were not systematically externally checked, and this could have caused information bias. However, the large scale of the database is likely to partly compensate this bias and, as coding of complications is linked to reimbursement and is regularly controlled, it is expected to be of good quality.

Our large population of patients treated with the TAVR procedure likely represents a heterogeneous group of patients admitted with various kinds of illnesses and severities. The nonrandomized design of the analysis leaves a risk of residual confounding factors. We have been able to estimate the EuroSCORE II, which in our cohort showed a satisfying correlation with early clinical outcomes. Moreover, the Charlson comorbidity index and Frailty index were used as risk predictors of all-cause death over a longer term. Our analysis was restricted to the variables present in the database, which meant that characteristics such as mean gradient, valve area, calcifications, and paravalvular leak were not available for analysis. We had information for diagnoses of left or right bundle branch block or atrioventricular block on *ICD-10* codes, but precise QRS durations in ms on surface ECG and results obtained during electrophysiological study were not available. Left anterior fascicular block was not included in our analysis because it is generally not reliably indicated in administrative medical records. Definite conclusions for comparisons between groups may not be fully appropriate, as multivariable analysis cannot fully eradicate the possible confounding related to some of these (or other) variables between these groups. There were multiple independent risk factors (>10) predictive for PPI outside of TAVI type, but it should be acknowledged that this could be a result of the large study size because the effect size of many independent variables was relatively small. Finally, the latest generation of Sapien BE valve is the Sapien Ultra. However, despite CE (European Conformity) mark in November 2018, this valve was not available in France during the study and still has not been launched in 2019.

CONCLUSIONS

In patients with aortic stenosis treated with TAVR, our systematic analysis at a nationwide level found higher rates of PPI than previously reported. BE technology was independently associated with lower incidence rates of PPI both at the acute and chronic phases than

SE technology. However, this was less apparent than previously reported in this large analysis of unselected patients seen in "real life" practice. Recent generations of TAVR were not independently associated with a different rate of PPI than early generations.

ARTICLE INFORMATION

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Supplementary Materials

Data S1
Figure S1
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Supplemental Material

Data S1.

Supplemental Methods

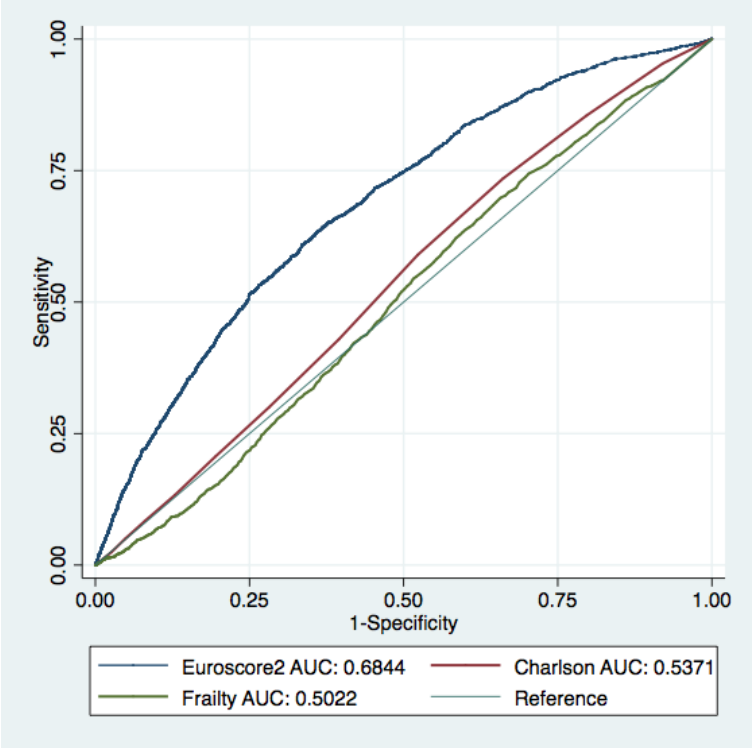
Estimated EuroSCORE II

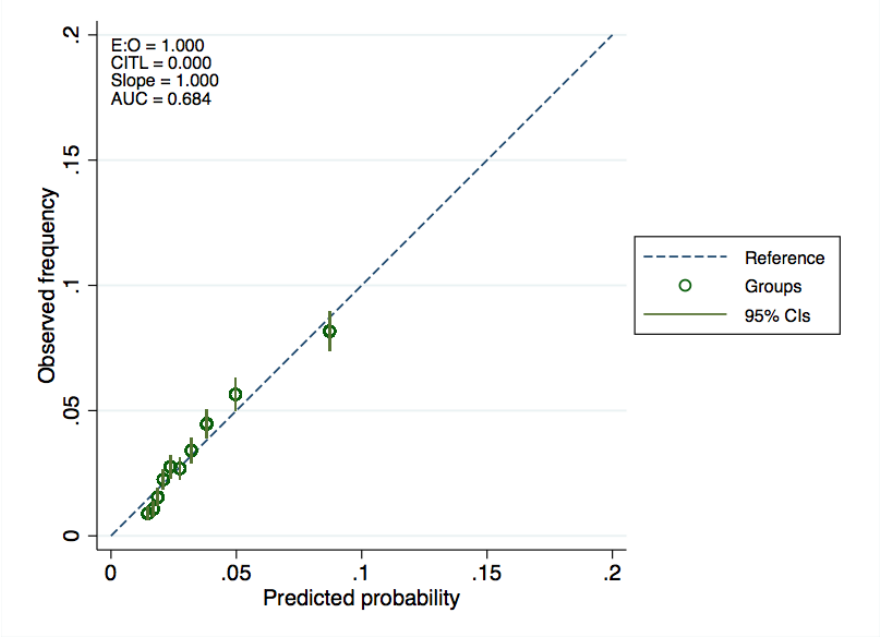
For each patient, the EuroSCORE II was estimated using the formulas available at the EuroSCORE website (www.euroscore.org) (19, 20).

Age, sex, extracardiac arteriopathy, poor mobility, previous cardiac surgery, chronic lung disease, active endocarditis, diabetes on insulin, recent MI are items available in the PMSI database using the ICD-10 or CCAM codes. For renal impairment, dialysis regardless of creatine clearance (CC) is an available item in the database and patients with history of abnormal renal function were considered as having CC <50 ml/min. NYHA class was considered to be at least II in these patients with severe aortic stenosis needing intervention, III in case of previous hospitalization with heart failure, and IV in case of history of pulmonary oedema. None of the patients were considered as having CCS class 4 angina (angina at rest). Patients with history of cardiomyopathy (whether ischemic or non-ischemic) were considered as having poor LVEF. Pulmonary hypertension was considered moderate in patients with previous hospitalization with heart failure and severe in case of history of pulmonary oedema. The item 'critical preoperative state' was considered present for patients with recent ventricular tachycardia, ventricular fibrillation, aborted cardiac arrest or acute renal failure. Patients with pulmonary oedema cardiogenic shock were considered as needing urgent intervention and those with cardiac arrest as needing emergency intervention. All patients were considered as having single non-CABG for weight of the intervention and no surgery on thoracic aorta.

In the full cohort of patients with TAVR, mean estimated EuroSCORE II was 3.7±1.0 while all-cause death at day 30 was 3.3%. The area under the curve (AUC) of the estimated EuroSCORE II for predicting the risk of all-cause death at day 30 was 0.684 (95%CI 0.672-0.697). This score outperformed Charlson comorbidity index (AUC 0.537, 95%CI 0.524-0.550, p<0.0001 for DeLong test) and frailty index (AUC 0.502, 95%CI 0.489-0.516, p<0.0001 for DeLong test) for identifying the risk of all-cause death at day 30 (Figure S1). The observed versus predicted risks of all-cause death at day 30 post-TAVR within risk deciles are shown in Figure S1.

Figure S1. Top panel: Receiver operating curves of the derivation model for the estimated EuroSCORE II, Charlson comorbidity index and frailty index for identifying death at day 30 after intervention. Lower panel: Calibration plots of the estimated EuroSCORE II for the overall cohort.





The diagonal line represents perfect calibration. Calibration of the futility prediction score is satisfying across the 10 deciles and a predicted 30-day mortality rate of approximately 10%. Vertical bars represent 95% CIs.