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Balloon-Expandable Versus Self-Expanding Transcatheter Aortic Valve Replacement

A Propensity-Matched Comparison From the FRANCE-TAVI Registry

Editorial, see p 269

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BACKGROUND: No randomized study powered to compare balloon-expandable (BE) with selfexpanding (SE) transcatheter heart valves (THVs) on individual end points after transcatheter aortic valve replacement has been conducted to date.

METHODS: From January 2013 to December 2015, the FRANCE-TAVI nationwide registry (Registry of Aortic Valve Bioprostheses Established by Catheter) included 12 141 patients undergoing BE-THV (Edwards, n=8038) or SE-THV (Medtronic, n=4103) for treatment of native aortic stenosis. Longterm mortality status was available in all patients (median 20 months; interquartile range, 14 to 30). Patients treated with BE-THV (n=3910) were successfully matched 1:1 with 3910 patients treated with SE-THV by using propensity score (25 clinical, anatomical, and procedural variables) and by date of the procedure (within 3 months). The first coprimary outcome was ≥ moderate occurrence of paravalvular regurgitation or in-hospital mortality, or both. The second coprimary outcome was 2-year all-cause mortality.

RESULTS: In propensity–matched analyses, the incidence of the first coprimary outcome was higher with SE-THV (19.8%) compared with BE-THV (11.9%; relative risk, 1.68 [95% CI, 1.46–1.91]; *P*<0.0001). Each component of the outcome was also higher in patients receiving SE-THV: ≥ moderate paravalvular regurgitation (15.5% versus 8.3%; relative risk, 1.90 [95% CI, 1.63–2.22]; *P*<0.0001) and inhospital mortality (5.6% versus 4.2%; relative risk, 1.34 [95% CI, 1.07–1.66]; *P*=0.01). During followup, allcause mortality occurred in 899 patients treated with SE-THV (2-year mortality, 29.8%) and in 801 patients treated with BE-THV (2-year mortality, 26.6%; hazard ratio, 1.17 [95% CI, 1.06–1.29]; *P*=0.003). Similar results were found using inverse probability of treatment weighting using propensity score analysis.

CONCLUSION: The present study suggests that use of SE-THV was associated with a higher risk of paravalvular regurgitation and higher in-hospital and 2-year mortality compared with use of BE-THV. These data strongly support the need for a randomized trial sufficiently powered to compare the latest generation of SE-THV and BE-THV.

CLINICAL TRIAL REGISTRATION: URL: https://www.clinicaltrials.gov. Unique identifier: NCT01777828.

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The full author list is available on page 255.

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Sources of Funding, see page 255

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Clinical Perspective

What Is New?

- We compared the outcomes of balloon-expandable and self-expanding transcatheter heart valves (THVs) on a large nationwide registry (12 141 patients) after propensity matching on 25 major clinical and anatomical variables and on the time of the procedure (within 3 months).
- Self-expanding THV recipients had a higher risk of paravalvular regurgitation, mortality at 3 months, and mortality at 2 years.
- The risk of mortality remained higher than that of balloon-expandable THV after multivariable adjustment including paravalvular regurgitation severity and other periprocedural events.
- This study suggests that the 2 most widely used THV designs may not achieve the same clinical outcomes.

What Are the Clinical Implications?

- As transcatheter aortic valve replacement is moving to become the first-line treatment for patients with aortic stenosis, this study highlights the need (1) for a randomized clinical study sufficiently powered to compare individual end points on the efficacy of self-expanding and balloon-expandable THV and (2) to simplify and optimize the grading of paravalvular regurgitation and its long-term clinical effect.

Over the last decade, several randomized studies comparing transcatheter aortic valve replacement (TAVR) with surgical aortic valve replacement (SAVR) have established TAVR as a treatment option in patients with symptomatic aortic stenosis.[1–6]

Most available transcatheter heart valves (THVs) are designed on either a balloon-expandable (BE) or a self-expanding (SE) concept. Despite major differences, both designs are recommended to be used interchangeably in most clinical situations. Whether these 2 very different THV concepts are achieving similar or different clinical outcomes remains unclear, however. Although there is an urgent clinical need to clarify this issue in an exponentially growing therapeutic field, no large randomized study powered to compare the 2 THV designs on individual end points has been conducted or initiated.

The occurrence of paravalvular regurgitation (PVR), in particular moderate or severe PVR, has been associated with an increased longterm mortality risk.[7] Mild PVR has also been associated with higher mortality rate in some[8] but not all studies.[9] Small randomized studies[10] and large registries[11,12] have suggested that ≥ moderate PVR was more frequent with SE-THV than with BE-THV.

Recently, a large-scale registry suggested higher in-hospital mortality with the use of SE-THV as compared with BE-THV.[13] Whether this difference persists over time is unclear because the excess mortality was no longer statistically significant by 30 days and no long-term follow-up was conducted.[13] In addition, no information on PVR was available and no clear explanation was provided to elucidate the association observed in that study.

The FRANCE-TAVI nationwide registry (Registry of Aortic Valve Bioprostheses Established by Catheter) collects information on TAVR procedures performed in French TAVR centers and their follow-up.[12] The objective of this study was to evaluate the effect of THV design (SE versus BE) on the risk of PVR, intrahospital mortality, and 2-year mortality using a nationwide propensity score–matched comparison.

METHODS

FRANCE-TAVI Registry and Study Population

Because of the sensitive nature of the data collected for this study, reasonable requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding authors.

Since January 2013, FRANCE-TAVI has prospectively included data from all patients who have undergone TAVR in 48 out of 50 TAVR centers in France and who volunteered to participate. This registry was designed in continuity with the FRANCE-2 registry (French Aortic National CoreValve and Edwards)[12,14] and is an initiative of the French Society of Cardiology and the French Working Group of Interventional Cardiology with the participation of the French Society of Thoracic and Cardiovascular Surgery. All patients included in the registry provided written informed consent before the procedure including consent for anonymous processing of their data. The registry was approved by the institutional review board of the French Ministry of Higher Education and Research (Comité Consultatif sur le Traitement de l'Information en Matière de Recherche) and by the National Commission for Data Protection and Liberties (Commission Nationale de l'Informatique et des Libertés).

For the purposes of the present analysis, a database encompassing all patients (n=12 804) included in the FRANCE-TAVI registry from January 2, 2013, to December 31, 2015, was locked. Patients with a previous SAVR (n=559, including those referred for valve-in-valve procedures) and those treated with a different THV design (n=104; including Lotus THV, Boston Scientific; Direct Flow THV, Direct Flow Medical; and JenaValve THV, JenaValve Technology) were excluded from the analysis to achieve a total number of 12 141 patients treated with SE (Medtronic) or BE (Edwards Lifesciences) THV design (Figure 1).

Patient Selection and TAVR Procedure

The decision to perform TAVR, choices of vascular approach, and THV design were based on a heart team assessment at each participating center. Procedures and postprocedural management were performed in accordance with each site's routine protocol. Thirty-day follow-up was recommended

in the case report form and performed either on-site or by telephone contact with the patient and his or her physician depending on each site's protocol. Both commercially available valves were used: the BE-THV SAPIEN XT (January 2013 to last quarter 2014) or SAPIEN 3 (last quarter 2014 to December 2015) (Edwards Lifesciences) and the SE-THV CoreValve (Medtronic). For each device, 4 sizes were available (BE-THV: 20, 23, 26, and 29 mm; SE-THV: 23, 26, 29, and 31 mm).

Preprocedural sizing was performed using multidetector computed tomography imaging. The technical aspects of the TAVR procedure have been reported in detail.[14,15]

Evaluation of Aortic Regurgitation on Transthoracic Echocardiography

Preprocedural transthoracic echocardiography was performed in all patients and postprocedural transthoracic echocardiography was performed before hospital discharge (median, day 3; interquartile range, days 2 to 4).

Pre-TAVR native aortic regurgitation[16] and post-TAVR aortic regurgitation grading was reported by site and not centrally adjudicated. Aortic regurgitation grading was defined as mild, moderate, or severe, as described in FRANCE-2.[11] The analysis was based on a multiwindow, multiparameter approach integrating the data of semiquantitative and qualitative parameters, which include visual assessment of the number of jets, jet width, and circumferential extent of PVR and evaluation of regurgitant volume,[17] following the European and American Society of Echocardiography guidelines[16,18] and Valve Academic Research Consortium–2 recommendations.[19]

Follow-Up

Mortality data were acquired in all patients from an INSEE (Institut National de la Statistique et des Études Économiques) query on April 12, 2016, with dates of death available, with a median follow-up of 20 months (interquartile range, 14 to 30). Deaths were classified as cardiovascular unless a clear noncardiovascular cause was identified. Other follow-up adverse events, including rehospitalization, were reported by site and assessed according to the Valve Academic Research Consortium–2 classification.[19]

Clinical Outcome

Two coprimary outcomes were defined. The first coprimary outcome of the study was the assessment of PVR at discharge. Because PVR can only be evaluated in living patients, this was achieved by defining the occurrence of either ≥ moderate PVR on transthoracic echocardiography before discharge or in-hospital all-cause mortality as estimate of PVR. The second coprimary outcome of the study was 2-year all-cause mortality.

Secondary outcomes were as follows: (1) each individual component of the first coprimary outcome; (2) procedural and in-hospital events (requirement for a second THV, stroke, myocardial infarction, major or life-threatening bleeding, major vascular complication, permanent pacemaker); and (3) postprocedural transprosthetic gradient by echocardiography. Follow-up events including hospitalization for acute cardiac event or valve reintervention; stroke; cardiovascular mortality; and the composite of all-cause mortality, stroke, or acute cardiac event were also reported.

Data collection and management are detailed in the Appendix in the online-only Data Supplement.

Statistical Analysis

Full details are available in the Appendix in the online-only Data Supplement. We assessed the effect of THV design on short (PVR or intrahospital all-cause mortality, mean and high residual gradient) and 2-year follow-up (all-cause and cardiovascular follow-up mortality, hospitalization for acute cardiac event or valve reintervention) outcomes after taking into account the potential confounding factors by using prespecified propensity score methods.[20,21] As the primary analysis, propensity score was used to assemble well-balanced groups (propensity score–matched cohort) and, as a sensitivity analysis, propensity score was used to weight each subject by the inverse probability of treatment (stabilized inverse propensity score as weight) and generate an inverse probability treatment weighting (IPTW) cohort. Both analyses were performed to estimate the average treatment effect, namely the effect of treatment on the entire population eligible for TAVR. The propensity score was estimated using a nonparsimonious multivariable logistic regression model, with the THV design (SE versus BE) as the dependent variable and all of the baseline characteristics listed in Table 1 as the independent variables, because they were all considered potential confounders linked to clinical outcome. Patients treated with SE-THV were matched 1:1 to patients treated with BE-THV according to date of procedure and propensity score using the greedy nearest neighbor matching algorithm according to a caliper width of 0.2 SD of logit of propensity score and using the procedural date, which should be within 3 months of each other.[22,23] Because of missing baseline data (range, 0% to 14%), leading to 24.5% of the study sample with at least 1 missing value among confounders included in propensity score calculation, treatment effect sizes were estimated using the multiple imputation method.

In the propensity score–matched cohort, between-group comparisons (SE-THV versus BE-THV) were made using a generalized estimating equations model (binomial distribution, log function) with a compound symmetry working correlation structure for binary outcomes, a linear mixed model with the matched blocks as random effect for continuous outcomes, and Fine and Gray (by treating death as competing risk) and Cox regression models for long-term outcomes with a robust sandwich variance estimator to account for the matched design. In the IPTW cohort, comparisons were made using log-binomial (binary outcomes), linear mixed model (quantitative outcomes), Fine and Gray, and Cox regression models (long-term outcomes), using the stabilized inverse propensity score as weight, and including the year of intervention as covariate. Propensity score–matched and IPTW analyses were adjusted for center by including center as random effect in log-binomial and linear mixed models and as stratification factors in the Cox and Fine and Gray models. We assessed the proportional hazard assumption using Schoenfeld residuals plots[24]; because the proportional hazard assumption was violated for all-cause and cardiovascular mortalities, the treatment effect size was modeled using

Table 1. Baseline Characteristics According to SE-THV or BE-THV Design Before and After Matching

Characteristics	Before Matching*			After Matching*†		
	SE-THV (n=4103)	BE-THV (n=8038)	ASD, %	SE-THV (n=3910)	BE-THV (n=3910)	ASD, %
Clinical characteristics						
Age, y, mean±SD	83.5±7.0	83.5±7.1	0.4	83.5±7.1	83.5±9.0	0.5
Men	2027 (49.4)	3939 (49.0)	0.8	1922 (49.2)	1908 (48.8)	0.6
NYHA class						
I	210 (5.1)	325 (4.1)	7.8	189 (4.8)	161 (4.2)	7.5
II	1210 (29.5)	2232 (27.8)		1161 (29.7)	1099 (28.1)	
II	2257 (55.0)	4698 (58.4)		2152 (55.0)	2295 (58.7)	
IV	426 (10.4)	783 (9.7)		408 (10.4)	355 (9.1)	
Logistic EuroSCORE, median (IQR)	14.0 (9.0 to 22.5)	15.0 (9.6 to 23.0)	5.8‡	14.0 (9.0 to 22.6)	15.0 (9.6 to 22.2)	4.1‡
High operative risk	1509 (36.8)	3193 (39.7)	6.1	1451 (37.1)	1471 (37.6)	1.1
BMI, kg/m^2, mean±SD	26.5±5.4	26.5±5.3	0.6	26.5±5.4	26.5±6.6	0.5
Diabetes mellitus	1065 (25.9)	2106 (26.2)	0.6	1016 (26.0)	997 (25.5)	0.9
Hypertension	2722 (66.3)	5439 (67.8)	2.8	2604 (66.6)	2603 (66.6)	0.1
CAD	1830 (44.6)	3401 (42.3)	4.6	1724 (44.1)	1764 (45.1)	1.8
Previous stroke or TIA	467 (11.4)	873 (10.9)	1.6	444 (11.4)	441 (11.3)	0.1
PAD	965 (23.5)	1814 (22.6)	2.3	914 (23.4)	899 (23.0)	0.7
Atrial fibrillation	1016 (24.8)	1997 (24.8)	0.2	973 (24.9)	983 (25.2)	0.7
Permanent pacemaker	629 (15.3)	1093 (13.6)	4.9	586 (15.0)	607 (15.5)	1.3
Previous CABG	464 (11.3)	857 (10.7)	2.1	437 (11.2)	459 (11.8)	1.7
Respiratory insufficiency	871 (21.2)	1592 (19.8)	3.5	812 (20.8)	846 (21.6)	1.8
Renal insufficiency§	210 (5.1)	421 (5.2)	0.5	197 (5.1)	206 (5.3)	0.7
Preprocedural imaging						
Aortic annulus diameter, mm, mean ± SD	24.2±2.8	23.5±2.7	27.9	24.1±2.7	24.0±2.7	2.2
LVEF, %, mean±SD	54.7±13.7	55.5±13.7	5.6	54.9±14.0	54.7±15.3	1.9
<30%	186 (4.5)	334 (4.2)	4.6	170 (4.4)	185 (4.8)	1.9
30% to 49%	991 (24.1)	1805 (22.5)		926 (23.7)	931 (23.8)	
≥50%	2926 (71.3)	5898 (73.4)		2814 (72.0)	2794 (71.5)	
AVA, cm^2, median (IQR)	0.7 (0.5 to 0.8)	0.7 (0.5 to 0.8)	0.5‡	0.7 (0.5 to 0.8)	0.7 (0.5 to 0.8)	0.3‡
Transaortic gradient, mm Hg, mean±SD	47.1±16.0	47.6±16.0	2.8	47.3±16.1	47.2±18.0	0.5
AR grade ≥2	871 (21.2)	1442 (17.9)	8.3	798 (20.4)	825 (21.1)	1.6
MR grade ≥2	941 (22.9)	1776 (22.1)	2.0	888 (22.7)	884 (22.6)	0.3
Procedural characteristics						
Room of intervention						
Catheterization laboratory	1607 (39.2)	2681 (33.4)	13.7	1501 (38.4)	1472 (37.7)	2.9
Hybrid room	2343 (57.1)	4917 (61.2)		2260 (57.8)	2267 (58.0)	
Operating room	154 (3.7)	440 (5.5)		149 (3.8)	171 (4.4)	
General anesthesia	2166 (52.8)	4085 (50.8)	3.9	2037 (52.1)	2111 (54.0)	3.4
Transfemoral approach	3287 (80.1)	6754 (84.0)	10.2	3183 (81.4)	3130 (80.1)	3.1
Years of intervention						
January 2013 to December 2014	2619 (63.8)	4123 (51.3)	25.6	1470 (37.6)	1475 (37.8)	0.3
January 2015 to December 2015	1484 (36.2)	3915 (48.7)		2440 (62.4)	2435 (62.3)	

Values expressed as number (%) unless otherwise indicated. AR indicates aortic regurgitation; ASD, absolute standardized difference; AVA, aortic valve area; BE, balloon-expandable; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; IQR, interquartile range; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PAD, peripheral arterial disease; SE, self-expanding; THV, transcatheter heart valve; and TIA, transient ischemic attack.

*Calculated after handling missing data using multiple imputation procedure (m=10).

†Matching on propensity score and date of transcatheter aortic valve replacement procedure (±3 months).

‡Estimated using the rank-transformed data.

§Serum creatinine >200 μmol/L.

time-dependent coefficients.[25] We further investigated the heterogeneity in treatment effect size for the occurrence of ≥ moderate PVR (or in-hospital all-cause mortality) across key subgroups. Finally, predictors of all-cause and cardiovascular mortalities were assessed using univariable and multivariable Cox regression models. Falsification outcomes, including mortality owing to malignancy and infection (individual or combined criteria), were post hoc analyzed to acknowledge possible residuals confounding related to the nonrandomized, controlled design.

Statistical testing was conducted at the 2-tailed α level of 0.05. Data were analyzed using SAS software, version 9.3 (SAS Institute).

RESULTS

Population

From February 2013 to December 2015, a total of 12 141 patients with severe native aortic stenosis were treated by TAVR in 48 centers and received either a BE-THV (n=8038) or an SE-THV (n=4103; Figure 1).

Baseline characteristics according to THV design, before and after propensity score matching, and after handling missing values by multiple imputation are presented in Table 1. Baseline characteristics before matching and handling missing values are presented in Table I in the online-only Data Supplement. The distributions of propensity score according to THV design are reported in Figure I in the online-only Data Supplement. Before matching, most characteristics were already well-balanced (absolute standardized difference ≤10%), except that patients treated with a BE-THV had a lower mean aortic annulus diameter; were more often treated in a hybrid room, by femoral approach; and in the second study period (after January 2015) than patients treated by SE-THV (Figure 2). These differences were controlled after propensity score matching (Table 1 and Figure 2), where 3910 matched pairs could be found.

PVR and In-Hospital Mortality According to BE-THV or SE-THV

In the propensity score–matched cohort, postprocedural ≥ moderate PVR or in-hospital mortality occurred more frequently in patients treated with SE-THV (19.8%, n=776) than in patients treated with BE-THV (11.9%, n=466; matched relative risk [RR], 1.68 [95% CI, 1.47–1.91], Table 2). A similar difference was found in the IPTW cohort (RR, 1.74 [95% CI, 1.57–1.92], Table 2) as well as in the sensitivity analysis performed before handling missing outcome (ie, on patients with available data on PVR status by transthoracic echocardiography) with matched and IPTW RRs of 1.66 (95% CI, 1.46–1.88) and 1.73 (95% CI, 1.57–1.89), respectively.

Each component of the first coprimary outcome occurred more frequently in patients receiving the SE-THV. In the propensity score–matched cohort, ≥ moderate PVR was more frequent with SE-THV than BE-THV (15.5%, n=606, versus 8.3%, n=326; matched RR, 1.90 [95% CI, 1.63–2.22]; Table 2). In-hospital mortality was also higher in patients receiving an SE-THV than a BE-THV (5.6%, n=217, versus 4.2%, n=164; matched RR, 1.33 [95% CI, 1.06–1.165]; Table 2).

A similar difference was observed in the IPTW cohort (Table 2) as well as in sensitivity analysis performed before handling missing outcome with a matched and IPTW RR of 1.88 (95% CI, 1.16–2.20) and 2.04 (95% CI, 1.81–2.31), respectively.

A similar difference was observed when comparison was restricted to either older (before September 2014) or newer (after December 2014) THV iterations (Tables II and III in the online-only Data Supplement).

Among procedural and in-hospital events, implantation of a second THV during the procedure and need of a new pacemaker were more frequently observed in patients treated with an SE-THV than a BE-THV in the propensity score–matched and IPTW cohorts ($P<0.0001$ for both events, Table 2). Higher rates of stroke and myocardial infarction were also found in patients receiving an SE-THV in both propensity score–matched and IPTW cohorts, although the difference in stroke did not reach the significance level (Table 2). Conversely, mean transprosthetic gradient ($P<0.0001$ for propensity score–matched and IPTW cohorts) and rate of patients with a mean gradient >20 mm Hg ($P=0.17$ for the propensity score–matched cohort and $P=0.004$ for the IPTW cohort) were higher in patients receiving the BE-THV device.

Two-Year Clinical Outcome According to BE-THV or SE-THV Design

During follow-up (median duration 20 months; interquartile range, 14 to 30), 2390 patients died (including 1828 from cardiovascular death; see Table I in the online-only Data Supplement). In the propensity score–matched cohort, all-cause mortality occurred in 899 of 3910 patients treated by SE-THV (24-month Kaplan-Meier estimate, 29.8%) and in 801 of 3910 patients treated by BE-THV (24-month Kaplan-Meier estimate, 26.6%), corresponding to a matched hazard ratio of 1.17 (95% CI, 1.06–1.28; Figure 3A and Table 3; see Figure II in the online-only Data Supplement for the Kaplan-Meier event curve in the overall cohort before matching). However, proportional hazard assumption was not satisfied, because the excess mortality risk of SE-THV compared with that of BE-THV was only observed for the first 3-month period (hazard ratio, 1.37 [95% CI, 1.16–1.60]; Table 3). Similar results were found in the IPTW cohort, with a hazard ratio associated with SE-THV of 1.38 (95% CI, 1.21–1.58) for 3-month mortality.

Table 2. PVR, Intrahospital Mortality, and Other Procedural and In-Hospital Clinical Events According to SE-THV or BE-THV Design in Propensity Score–Matched and IPTW Cohorts

Outcomes	SE-THV (n=3910)	BE-THV (n=3910)	Effect Size (95% CI)	*P* Value
Propensity score–matched cohort				
≥ Moderate PVR or intrahospital mortality or both*	776 (19.8)	466 (11.9)	1.68 (1.47 to 1.91)†	<0.0001
≥ Moderate PVR	606 (15.5)	326 (8.3)	1.90 (1.63 to 2.22)†	<0.0001
Intrahospital mortality	217 (5.6)	164 (4.2)	1.33 (1.06 to 1.65)†	0.01
Other procedural and intrahospital events				
Second THV	143 (3.7)	38 (1.0)	3.79 (2.40 to 5.99)†	<0.0001
Stroke	96 (2.5)	70 (1.8)	1.38 (0.98 to 1.94)†	0.058
Myocardial infarction‡	14 (0.4)	7 (0.2)	2.07 (1.11 to 3.88)†	0.02
Major or life-threatening bleeding	398 (10.2)	356 (9.1)	1.03 (0.89 to 1.19)†	0.68
Major vascular complication	292 (7.5)	270 (6.9)	1.02 (0.85 to 1.22)†	0.81
Permanent pacemaker implantation	871 (22.3)	431 (11.0)	2.08 (1.83 to 2.35)†	<0.0001
Postprocedural transprosthetic echocardiography gradient				
Mean gradient	7 (5 to 10)	10 (7 o 13)	–0.21 (–0.24 to –0.19)§	<0.0001
Mean gradient >20 mm Hg	75 (1.9)	102 (2.6)	0.75 (0.48 to 1.16)§	0.17
IPTW cohort	N=4103	N=8038		
≥ Moderate PVR or intrahospital mortality or both*	817 (19.9)	871 (10.8)	1.74 (1.57 to 1.92)§	<0.0001
≥ Moderate PVR	640 (15.6)	605 (7.5)	2.05 (1.80 to 2.33)‖	<0.0001
Intrahospital mortality	229 (5.6)	307 (3.8)	1.33 (1.12 to 1.58)‖	0.001
Other procedural and intrahospital events				
Second THV implantation	151 (3.7)	66 (0.8)	4.26 (3.18 to 5.71)‖	<0.0001
Stroke	99 (2.4)	143 (1.8)	1.31 (0.99 to 1.71)‖	0.051
Myocardial infarction‡	15 (0.4)	11 (0.1)	2.51 (1.14 to 5.46)‖	0.02
Major or life-threatening bleeding	418 (10.2)	651 (8.1)	1.10 (0.97 to 1.24)‖	0.13
Vascular complications	299 (7.3)	518 (6.4)	0.98 (0.84 to 1.13)‖	0.74
Permanent pacemaker implantation	903 (22.0)	895 (11.1)	2.06 (1.88 to 2.25)‖	<0.0001
Postprocedural transprosthetic echocardiography gradient				
Mean gradient	7 (5 to 10)	10 (7 to 13)	–0.23 (–0.25 to –0.21)¶	<0.001
Mean gradient >20 mm Hg	79 (1.9)	245 (3.1)	0.65 (0.49 to 0.88)¶	0.004

Values are n (%) or median (interquartile range). Effect sizes are relative risk or mean difference ($\log_e$) in mean transprosthetic gradient calculated using BE-THV as reference group. BE indicates balloon-expandable; IPTW, inverse probability of treatment weighting; PVR, paravalvular regurgitation; SE, self-expanding; and THV, transcatheter heart valve.

*Prespecified as first coprimary outcome.

†Calculated using a generalized estimating equation model for binary data with a log link function to account for the matched sets and including center as random effect.

‡ST-segment–elevation myocardial infarction related to acute coronary obstruction.

§Calculated using a linear mixed model (on log-transformed data) including matched sets and center as random effects.

‖Calculated using a log-binomial regression model weighted by inverse probability of treatment using propensity score, including center as random effect and year of intervention as fixed effect.

¶Calculated using a linear mixed model (on log-transformed data) weighted by inverse probability of treatment using propensity score, including center as random effect and year of intervention as fixed effect. Values and effect sizes were calculated after handling missing values for variables included in the propensity score and outcomes by multiple imputation.

When only cardiovascular mortality was considered, SE-THV remained associated with higher short-term mortality both in matched and IPTW cohorts (Figure 3B and Table 3). The incidence of reported hospitalization for acute cardiac event or valve intervention was also higher in patients receiving SE-THV then in those receiving BE-THV (Table II in the online-only Data Supplement).

Differences in clinical outcome persisted when comparisons were restricted to either older (before September 2014) or newer (after December 2014) THV iterations (Tables II and III in the online-only Data Supplement; Figure 4).

Subgroup Analyses

In the propensity score–matched cohort, the relation between the occurrence of the primary outcome and THV design was consistent across key subgroups, except for delivery approach and study period, in which a significant interaction was observed (Figure 5A).

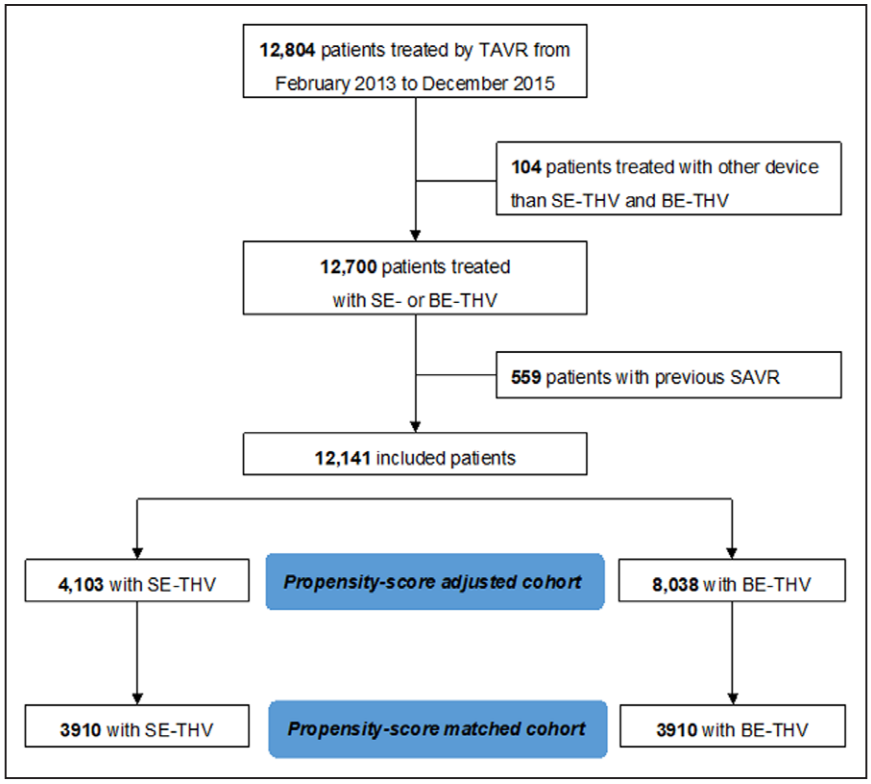

Figure 1. Study flow chart.
BE indicates balloon-expandable; SAVR, surgical aortic valve replacement; SE, self-expandable; TAVR, transcatheter aortic valve replacement; and THV, transcatheter heart valve.

The difference in the occurrence of the first coprimary outcome between SE-THV and BE-THV was stronger in patients treated by the femoral approach (RR, 1.82 [95% CI, 1.56–2.13]) than in those with nontransfemoral access (RR, 1.20 [95% CI, 0.94–1.53]; *P* for heterogeneity 0.004, Figure 5A). This was related to lower risk of events in patients treated by the femoral approach as compared with nontransfemoral treatment with a BE-THV (11.1% versus 15.1%), whereas the opposite was observed with an SE-THV (20.1% versus 17.6%).

The difference was also stronger in the second study period (before or on 1 January 2015; RR, 2.23 [95% CI, 1.71–2.94]) as compared with the first study period (after 1 January 2015; RR, 1.48 [95% CI, 1.28–1.72]; *P* for heterogeneity 0.006). This was related to a greater reduction of events between the first and second period in patients treated with BE-THV (14.3% versus 7.9%) than in patients treated with SE-THV (21.0% versus 18.0%). Similar heterogeneities were observed in the IPTW cohort (Figure 5B; *P* for heterogeneity <0.001 for both). A significant heterogeneity across sex was found (*P* for heterogeneity 0.02), with a stronger THV design difference in men (RR, 1.92 [95% CI, 1.68–2.19]) than in women (RR, 1.56 [95% CI, 1.36–1.79]). The same was true for the occurrence of ≥ moderate PVR considered alone (Figure III in the online-only Data Supplement).

PVR and 2-Year Mortality

As shown in Table V in the online-only Data Supplement, ≥ moderate PVR was associated with a higher rate of 2-year all-cause and cardiovascular mortality, in the overall study population and in each THV design. The other parameters associated with all-cause and cardiovascular mortalities by univariate analysis among baseline characteristics are presented in Table VI in the online-only Data Supplement. In multivariate analysis including univariate baseline predictors, both PVR severity and THV design were independently associated with a higher risk of all-cause and cardiovascular mortality (Table VII in the online-only Data Supplement).

Falsification Outcomes

Falsification outcomes (death from malignancy, death from infection, or the composite of both) were observed at similar frequencies in patients treated with SE-THV or BE-THV as observed in the propensity score–matched cohort and in the IPTW cohort (Table II in the online-only Data Supplement).

DISCUSSION

The present propensity score–matched comparison of 7820 patients with native aortic stenosis undergoing

Table 3. Follow-Up 2-Year Mortality According to the SE-THV Versus BE-THV Design in Propensity Score–Matched and IPTW Cohorts

Outcomes	SE-THV (n=3910)	BE-THV (n=3910)	HR (95% CI)	*P* Value
Propensity score–matched cohort				
Follow-up all-cause mortality	899 (29.8)	801 (26.6)	1.17 (1.06 to 1.28)*	0.002
0 to 3 months	381	286	1.37 (1.16 to 1.60)*	0.0001
3 to 6 months	104	92	1.23 (0.88 to 1.70)*	0.22
6 months to end of follow-up	414	423	1.00 (0.85 to 1.18)*	0.89
Follow-up cardiovascular mortality	675 (23.3)	612 (20.9)	1.18 (1.03 to 1.32)*	0.001
0 to 3 months	270	192	1.47 (1.19 to 1.82)*	0.0004
3 to 6 months	77	77	1.15 (0.80 to 1.65)*	0.44
6 months to end of follow-up	328	343	1.01 (0.82 to 1.20)*	0.86
IPTW cohort	N=4103	N=8038		
Follow-up all-cause mortality	958 (29.9)	1432 (25.7)	1.18 (1.08 to 1.29)†	<0.0001
0 to 3 months	402	541	1.38 (1.21 to 1.58)†	<0.0001
3 to 6 months	112	183	1.21 (0.93 to 1.56)†	0.19
6 months to end of follow-up	444	708	1.03 (0.90 to 1.17)†	0.66
Follow-up cardiovascular mortality	721 (23.4)	1107 (20.5)	1.19 (1.05 to 1.34)†	0.001
0 to 3 months	286	374	1.46 (1.24 to 1.73)†	<0.0001
3 to 6 months	84	155	1.14 (0.85 to 1.53)†	0.37
6 months to end of follow-up	351	578	1.00 (0.86 to 1.5)†	0.88

Values in parentheses in columns 2 and 3 are cumulative incidence at 2-year expressed as % (calculated using the Kalbfleisch and Prentice method for follow-up hospitalizations by treating death as competing risk or using Kaplan-Meier method for mortality). BE indicates balloon-expandable; HR, hazard ratio; IPTW, inverse probability of treatment weighting; SE, self-expanding; and THV, transcatheter heart valve.

*Calculated using a Fine and Gray or Cox regression model stratified by center with the robust sandwich variance estimate to account for the matched sets.

†Calculated using a Fine and Gray or Cox regression model stratified by center weighted by inverse probability of treatment using propensity score and including year of intervention as covariable. Number of events, cumulative incidence, and HRs were calculated after handling missing values for variables included in the propensity score by multiple imputation.

TAVR based on the nationwide FRANCE-TAVI registry is the largest observational study to date comparing SE-THV and BE-THV on PVR and 2-year clinical outcome including mortality. This study, in which patients were carefully matched on 25 major clinical and anatomical variables and on the time of the procedure (within 3 months), reports that use of SE-THV was associated with a higher risk of PVR or in-hospital mortality or both, and a higher risk of 2-year mortality as compared with use of BE-THV. The association of THV type with 2-year mortality remained after multivariable adjustment including PVR severity and other periprocedural events.

THV Design and PVR

This study, reporting on patients treated from 2013 through 2015, demonstrates a higher incidence of PVR with SE-THV as compared with BE-THV, irrespective of valve generation. Anatomical and procedural characteristics were included in the propensity score, in particular aortic annulus diameter as measured by multidetector computed tomography and the procedural route of delivery. The date of the procedure (within 3 months) was also incorporated in the matching process. As the study was running on a 3-year inclusion period, this allowed comparing each patient with a patient treated during the same time window (same valve generation, same level of expertise). Analyses restricted to the older period and to the newer period provided similar results with the main analysis (Tables III and IV in the online-only Data Supplement; Figure 4).

These results of the 2013 through 2015 period are in line with and confirm the observations made with the older generations of THV when optimal sizing using multidetector computed tomography was not routinely implemented, in particular in the 2010 through 2011 period in the FRANCE-2 registry[11] and in the 2012 through 2013 period in the CHOICE study (A Comparison of Transcatheter Heart Valves in High Risk Patients With Severe Aortic Stenosis: The CHOICE Trial).[10] The higher incidence of PVR with SE-THV was observed in all subgroups but the magnitude was stronger when the procedure was performed by femoral delivery (+88%), as observed previously,[11] and in those treated after January 2015 (+127%). The latter observation should be associated with the release during the last year of the study of the most recent generation of

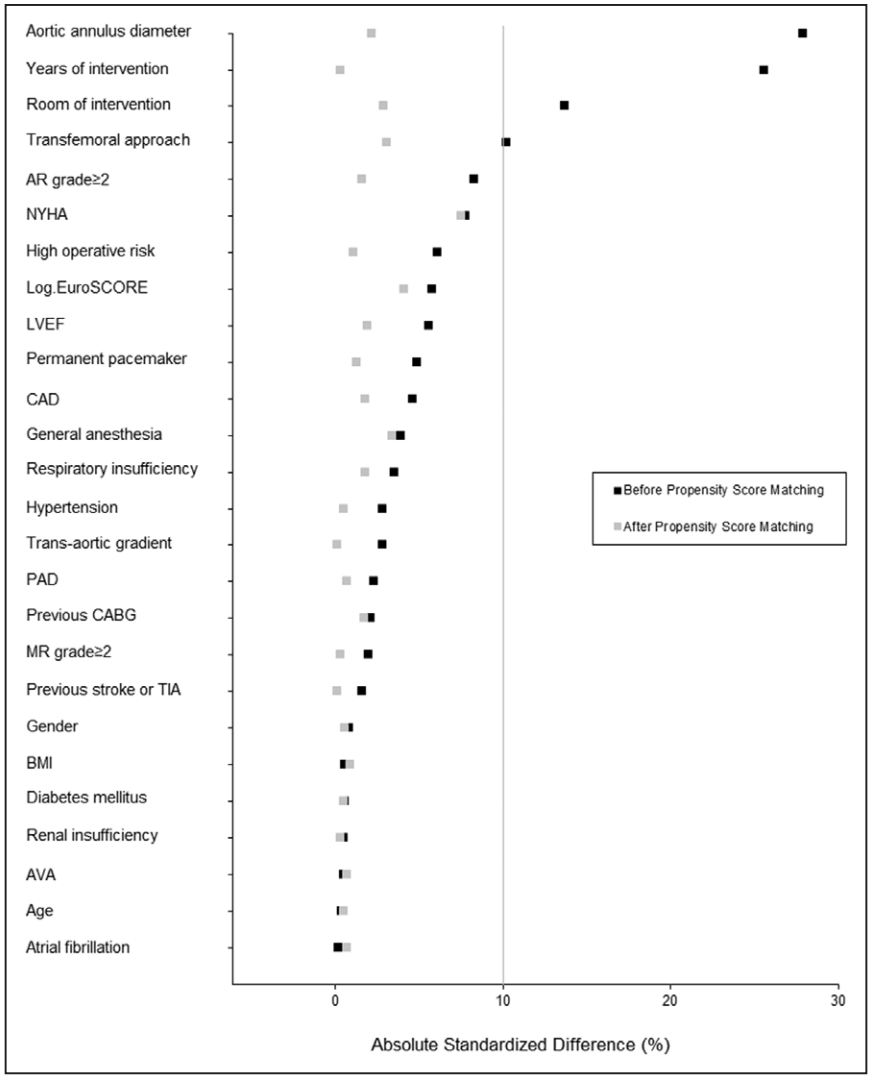

Figure 2. Absolute standardized differences between SE-THV and BE-THV treated patients before and after propensity score matching.
AR indicates aortic regurgitation; AVA, aortic valve area; BE, balloon-expandable; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; MR, mitral regurgitation; NYHA, New York Heart Association; PAD, peripheral arterial disease; SE, self-expandable; and THV, transcatheter heart valve.

BE-THV (SAPIEN 3), featuring an antileak skirt, and of the newer generation of SE-THV. Whereas the former allowed a decrease in the PVR rate from 9.2% to 6% compared with previous years, the latter was not associated with a major effect on PVR (15.9% to 14.8%). Whether the newer iteration of SE-THV (Evolut-Pro) featuring an outer pericardial wrap will mitigate this major difference is unknown. A recent small nonrandomized comparison did not show a significant difference in PVR rates between the 2 most recent iterations of SE-THV (Evolut versus Evolut-Pro).[26]

The remarkably low rate of PVR achieved in randomized clinical trials[3,9] was not replicated in an all-comers real-life registry irrespective of THV design (PVR rate >5%). This could be related to different characteristics of randomized clinical trials that cannot be replicated in everyday practice, such as the contribution of only high-volume expert centers, the use of centralized computed tomography core laboratory valve sizing, or the exclusion of patients when results are anticipated to be suboptimal.

PVR and Mortality

Moderate or > moderate PVR has been consistently associated with higher short-term and long-term mortality.[14,27] Although it has been suggested that the severity of PVR in SE-THV recipients could decrease over time or that PVR anatomy and grading differs between SE-THV and BE-THV, the present study confirms that a ≥ moderate PVR as measured at 3 days is associated with a similar 40% additional risk of death for both BE-THV and SE-THV, suggesting that if PVR can regress, it does so at a similar rate for both devices, or that the timing and the magnitude is not sufficient to affect mortality differently at 2 years, or both. Although there are discordant results regarding the role of mild or mild to

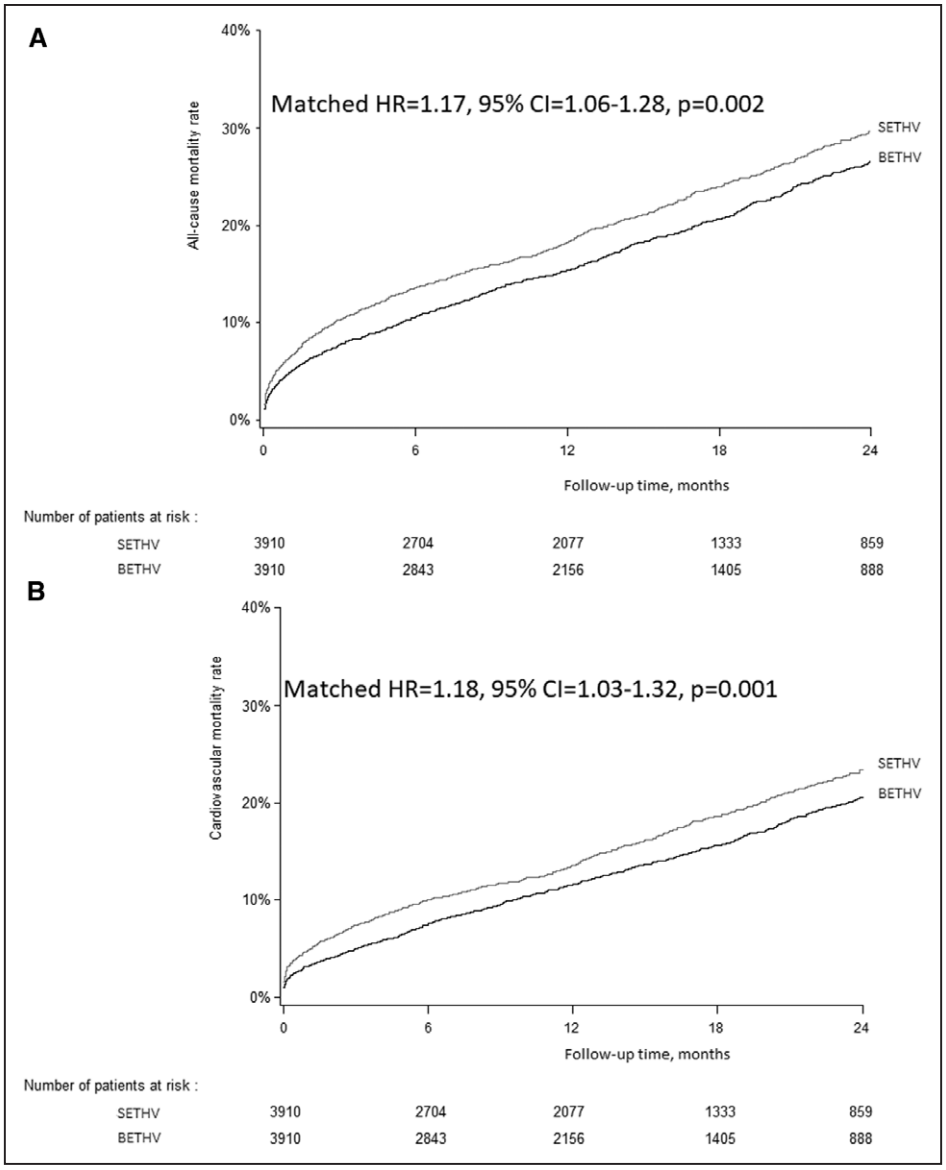

Figure 3. Kaplan-Meier curves.
Kaplan-Meier curves of (**A**) all-cause mortality and (**B**) cardiovascular mortality according to selfexpanding (SE) vs balloonexpandable (BE) transcatheter heart valves design in a propensity score–matched cohort. Kaplan-Meier estimates and number of patients at risk were calculated after handling missing values for variables included in the propensity score by multiple imputation (using a complementary log-log as normalizing transformation for survival probabilities).

moderate PVR on mortality,[27,28] we observed that mild PVR was also associated with an additional risk of death (+13% to 18%). The potential deleterious long-term effect of mild PVR, which is observed in more than 30% of "low-risk" cases,[5] will have to be elucidated further as the use of TAVR expands in this population.

THV Design and Mortality

In the absence of head-to-head sufficiently powered comparison, the equipoise between the 2 THV designs is hypothetical. The small CHOICE[10] and SOLVE-TAVI (Second-Generation Self-Expandable vs Balloon-Expandable Valves and General vs Local Anesthesia in TAVI) randomized noninferiority trials did not report mortality difference, but included only few hundreds of patients and were not powered to investigate mortality as a primary end point.

The present study demonstrates that the use of an SE-THV was associated with a 16% higher risk of death at 2 years compared with the use of a BE-THV. This is explained by a 36% higher risk of death during the first 3 months with the 2 mortality curves remaining parallel after that period. These findings confirm the recent observation by the CENTER collaboration initiative (Cerebrovascular Events in Patients Undergoing Transcatheter Aortic Valve Implantation) of higher in-hospital mortality with SE-THV compared with BE-THV.[13] However, in that study, in which the latest follow-up was at 30 days, the mortality difference was no longer present at that time (P=0.10), and the authors concluded that "there

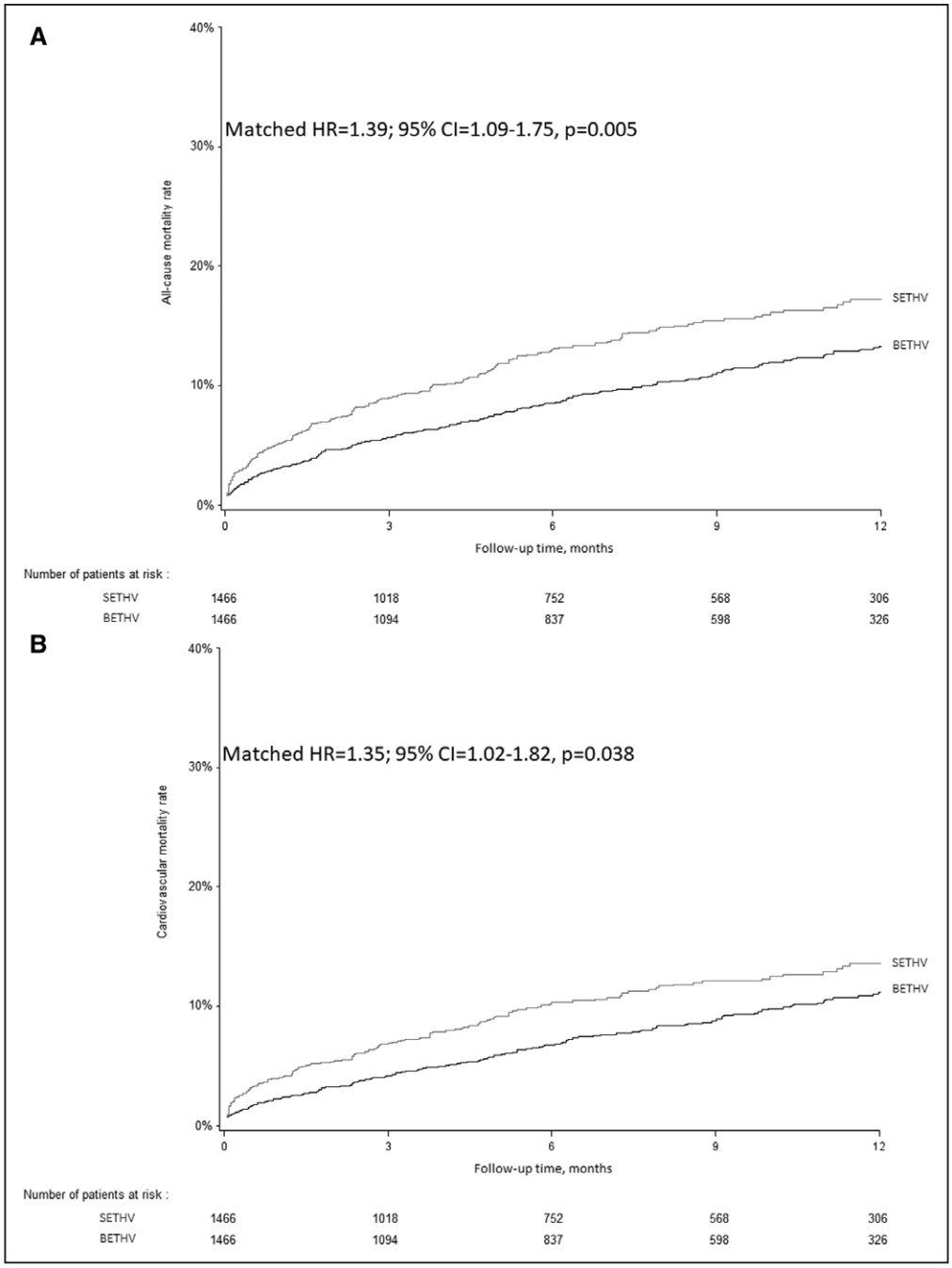

Figure 4. Kaplan-Meier curves of all-cause mortality (A) and cardiovascular mortality (B) according-transcatheter heart valve (THV) design in matched-propensity score cohort restricted to patients treated after January 1, 2015.
BE indicates balloon-expandable; and SE, self-expandable.

was no difference in 30-day mortality rates between both valve types." On the contrary, the present study, which provides a much longer follow-up, demonstrates that the mortality difference observed between the 2 THV designs remains significant at 2 years (*P*=0.003).

Other limitations of the study by Vlastra et al.[13] include a heterogeneous population originating from 10 different sources, lack of information on PVR, and lack of explanation for the "in-hospital mortality" finding that disappeared by 30 days.

Our study suggests that part of the additional risk of death observed with SE-THV may relate to a higher risk of PVR, and also to a higher risk of in-hospital events, including stroke, myocardial infarction, and pacemaker implantation. However, the additional mortality risk observed with SE-THV persists after adjustment on all baseline and procedural characteristics and all periprocedural complications, including PVR, which is highly suggestive of a direct and specific effect related to valve design. This observation, combined with the early

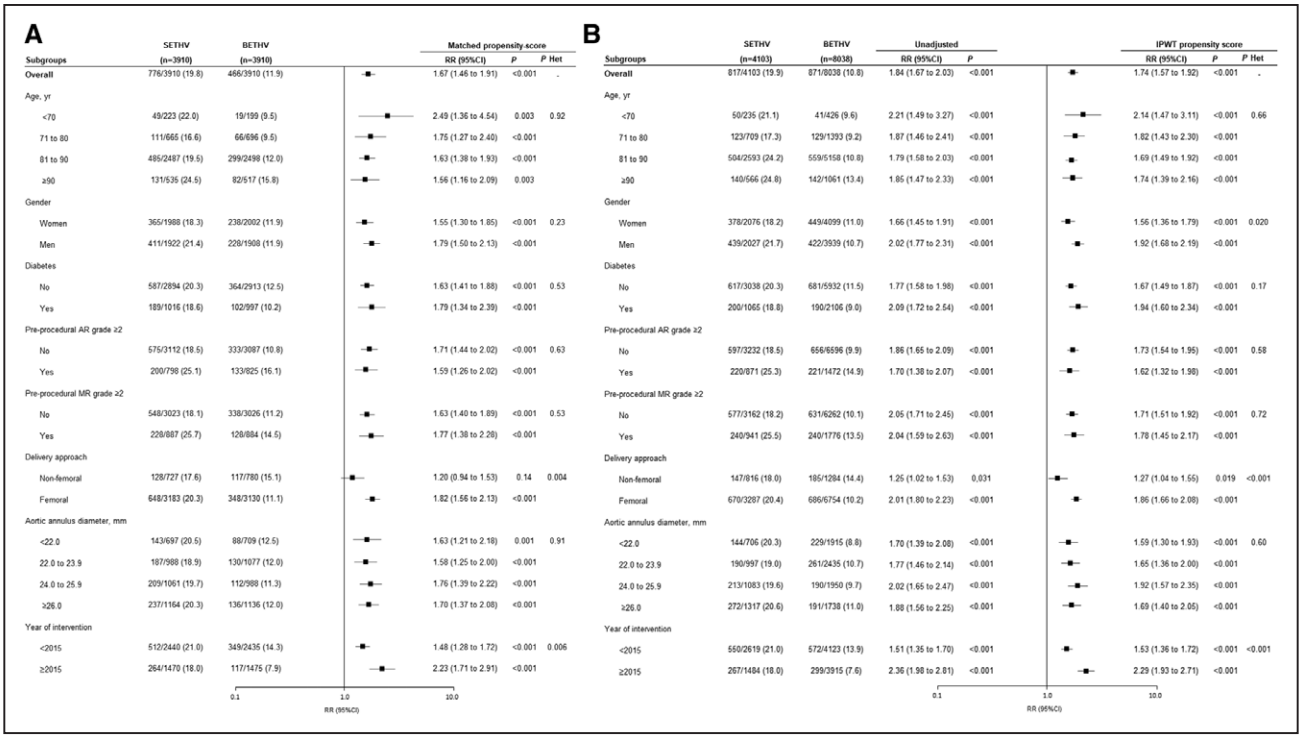

Figure 5. Comparisons of the occurrence of the first coprimary outcome (≥ moderate paravalvular regurgitation or in-hospital mortality, or both). Comparisons between selfexpanding (SE) and balloonexpandable (BE) transcatheter heart valve design according to key subgroups in (**A**) propensity score–matched and (**B**) inverse probability of treatment weighting (IPTW) cohorts. **A**, Relative risks (RRs) were calculated using a generalized estimating equation (GEE) model for binary data (with a log link function) to account for the matched sets and after adjustment for center (random effect). **B**, RRs were calculated using a binary log-binomial regression model before and after IPTW using propensity score, adjustment for center (random effect), and year of intervention (fixed effects). Number of events (%) and RRs were calculated after handling missing values for variables included in the propensity score by multiple imputation. AR indicates aortic regurgitation; MR, mitral regurgitation; *P* het, *P* value for heterogeneity; and RR, relative risk.

separation of survival curves, could also suggest that PVR is partly acting as a marker rather than being the main driver of the mortality difference between the 2 THV designs. More granular registry data are needed to identify the parameters associated with higher mortality risk, such as occurrence and type of conduction disorders, valve calcium score, prosthesis hemodynamics, left ventricular dimensions, valve thrombosis, and delayed coronary events.

Although designs and clinical end points may have been slightly different between the landmark trials evaluating BE-THV or SE-THV versus SAVR, transfemoral BE-THV was consistently superior to SAVR in high-risk,[2] intermediate-risk,[9] and low-risk[5] cases, whereas SE-THV only achieved superiority over SAVR in high-risk cases.[3,4,6] Our study sheds fresh light on these previous results and suggests that TAVR study findings should not be generalized as a class effect regardless of the SE-THV or BE-THV design.

Limitations

Observational registries are the only way to capture all-comers data on a national scale, but several limitations should be considered when interpreting the results. PVR grading is site-reported and was not analyzed in a core laboratory, which may have resulted in potential reporting bias and heterogeneity in PVR grading among centers. Clinical events, including rehospitalization, are site-reported and not adjudicated, therefore exposing the data to the risk of underreporting. Mortality data are complete, because they are obtained from an INSEE (Institut National de la Statistique et des Études Économiques) query. Furthermore, there is no reason to believe that underreporting by the sites of some clinical events would differ according to type of THV. In addition, the lack of difference in PVR severity among centers once adjusted to the type of THV does not support heterogeneity in PVR grading. This issue was further taken into account in multivariable analyses of predictors of PVR where adjustment for participating centers was done, which reinforced the interpretation of the main finding of this study.

This was not a randomized trial and potential differences in unmeasured variables might remain despite the risk adjustment matching process. Among others, the presence of extensive valve calcification, massively calcified aortic root, or small femoral vessel size were not measured and could be more frequent in patients receiving an SE-THV. Such residual confounders could

explain all or part of the mortality difference. However, the baseline clinical, anatomical, and procedural characteristics of this very large cohort were well-balanced between the 2 populations (Table 1). The propensity score matching process involving >25 variables was able to further balance the few variables that were not well-balanced, in particular aortic annulus diameter and delivery approach. Furthermore, the analysis of falsification end points found no signs of a hidden bias exaggerating the mortality difference observed between the 2 THV groups. A similar methodology using registry data and propensity score analysis has previously been highly predictive of the results of randomized studies, as in the study by Thourani et al.[29] accurately predicting the results of the PARTNER IIA study (Placement of Aortic Transcatheter Valves–PIIA),[9] or in the study by Makkar et al.[30] investigating the use of TAVR in patients with bicuspid versus tricuspid aortic stenosis.

It remains to be demonstrated whether the differences observed in the present study would still stand when comparing the newer SE-THV (Evolut-Pro) with the SAPIEN 3. Although the Evolut-Pro does not appear to be associated with a significantly lower risk of PVR compared with previous iterations of SE-THV,[25] on multivariable analysis the significant difference between BE-THV and SE-THV with respect to mortality persisted despite comprehensive adjustment for several factors, including PVR (Table VII in the online-only Data Supplement). The 4 THV iterations (CoreValve, Evolut, SAPIEN XT, SAPIEN 3) investigated in the present study are also used in randomized studies investigating the benefit of TAVR versus SAVR, including the most recent studies. In particular, the SAPIEN 3 was the BE-THV used in all patients undergoing TAVR in the PARTNER 3 study,[5] whereas the CoreValve and Evolut were used in the majority of patients (80%) undergoing TAVR in the Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients study,[6] with the other 20% receiving the Evolut-Pro.

Conclusion

The present study suggests important differences in clinical outcome according to THV design, as use of SE-THV was associated with a higher risk of all-cause mortality at 2 years as compared with BE-THV. However, because the propensity score matching approach cannot rule out residual confounders, and because some of the most recent THV iterations were not part of the investigation, there is an urgent need to conduct a randomized trial sufficiently powered to compare the latest generation of SE-THV and BE-THV on all-cause mortality. The present results also demonstrate the need to refine the identification and grading of PVR and its long-term clinical effect.[31,32]

ARTICLE INFORMATION

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APPENDIX

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CHU de Clermont-Ferrand	Interventional cardiologists: Nicolas Combaret, Geraud Souteyrand Cardiac surgeons: Nicolas D'Ostrevy, Andréa Innorta Noninterventional cardiologists: Guillaume Clerfond, Charles Vorilhon
CHU de Rennes	Interventional cardiologists: Vincent Auffret, Marc Bedossa, Dominique Boulmier, Hervé Le Breton, Guillaume Leurent Cardiac surgeons: Amedeo Anselmi, Majid Harmouche, Jean-Philippe Verhoye Noninterventional cardiologists: Erwan Donal
Hôpital Saint Joseph-Marseille	Interventional cardiologists: Jacques Bille, Patrick Joly, Cardiac surgeon: Rémi Houel Noninterventional cardiologists: Bertrand Vilette
CHU d'Angers	Interventional cardiologists: Wissam Abi Khalil, Stéphane Delepine Cardiac surgeons: Olivier Fouquet, Frédéric Pinaud Noninterventional cardiologist: Frédéric Rouleau
CHU Bichat, Paris	Interventional cardiologists: Jérémie Abtan, Dominique Himbert, Marina Urena Cardiac surgeons: Soleiman Alkhoder, Walid Ghodbane Noninterventional cardiologists: Dimitri Arangalage, Eric Brochet, Coppelia Goublaire
CHU La Pitié Salpêtrière, Paris	Interventional cardiologists: Olivier Barthelemy, Rémi Choussat, Jean-Philippe Collet Cardiac surgeons: Guillaume Lebreton, Pascal Leprince, Chiro Mastrioanni Noninterventional cardiologist: Richard Isnard
CHU Louis Pradel, Lyon	Interventional cardiologists: Raphael Dauphin, Olivier Dubreuil, Guy Durand De Gevigney, Gérard Finet, Brahim Harbaoui, Sylvain Ranc, Gilles Rioufol Cardiac surgeons: Fadi Farhat, Olivier Jegaden, Jean-François Obadia, Matteo Pozzi
Centre Cardiologique Marie Lannelongue, Le Plessis Robinson	Interventional cardiologists: Saïd Ghostine, Philippe Brenot, Sahbi Fradi Cardiac surgeons: Alexandre Azmoun, Philippe Deleuze Noninterventional cardiologists: Martin Kloeckner

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APPENDIX Continued

Centers	Investigators
Clinique Saint-Gatien, Tours	Interventional cardiologists: Olivier Bar, Didier Blanchard, Christophe Barbey, Stephan Chassaing Cardiac surgeons: Didier Chatel, Olivier Le Page, Arnaud Tauran Noninterventional cardiologists: Didier Bruere, Laurent Bodson, Yvon Meurisse, Aurélien Seemann
Institut Mutualiste Montsouris, Paris	Interventional cardiologists: Nicolas Amabile, Christophe Caussin, Alain Dibie, Simon Elhaddad, Luc Drieu, Alice Ohanessian François Philippe, Aurélie Veugeois Cardiac surgeons: Matthieu Debauchez, Konstantinos Zannis Noninterventional cardiologists: Daniel Czitrom, Chrystelle Diakov, François Raoux
Clinique du Tonkin, Lyon	Interventional cardiologists: Didier Champagnac, Yves Lienhart, Patrick Staat, Oualid Zouaghi Cardiac surgeons: Vincent Doisy, Jean Philippe Frieh, Fabrice Wautot Noninterventional cardiologists: Julie Dementhon, Olivier Garrier, Fadi Jamal, Pierre Yves Leroux
CHU de Bordeaux	Interventional cardiologists: Lionel Leroux, Benjamin Seguy, Frédéric Casassus Cardiac surgeons: Laurent Barandon, Louis Labrousse, Julien Peltan Noninterventional cardiologists: Claire Cornolle, Marina Dijos, Stéphane Lafitte
Hôpital Privé Clairval, Marseille	Interventional cardiologists: Gilles Bayet, Claude Charmasson, Frédéric Collet Cardiac surgeons: Alain Vaillant, Jacques Vicat Noninterventional cardiologist: Marie Paule Giacomoni
CHU Mondor, Créteil	Interventional cardiologist: Emmanuel Teiger Cardiac surgeon: Eric Bergoend Noninterventional cardiologist: Céline Zerbib
Clinique Saint-Augustin, Bordeaux	Interventional cardiologists: Olivier Darremont, Jean Louis Leymarie Cardiac surgeons: Philippe Clerc, Emmanuel Choukroun, Nicolas Elia, Jean-Philippe Grimaud, Jean-Philippe Guibaud, Stéphane Wroblewski Noninterventional cardiologists: Eric Abergel, Emmanuel Bogino, Christophe Chauvel, Patrick Dehant, Marc Simon
CHU de Nancy	Interventional cardiologists: Michel Angioi, Julien Lemoine, Simon Lemoine, Batric Popovic Cardiac surgeons: Thierry Folliguet, Pablo Maureira Noninterventional cardiologists: Olivier Huttin, Christine Selton Suty
CHU de Montpellier-Nîmes	Interventional cardiologists: Guillaume Cayla, Delphine Delseny, Florence Leclercq, Gilles Levy, Jean Christophe Macia, Eric Maupas, Christophe Piot, François Rivalland, Gabriel Robert, Laurent Schmutz, Frédéric Targosz, Mariama Akodad Cardiac surgeons: Bernard Albat, Arnaud Dubar, Nicolas Durrleman, Thomas Gandet, Emmanuel Munos Noninterventional cardiologists: Stéphane Cade, Frédéric Cransac
CHU de Toulouse	Interventional cardiologists: Frédéric Bouisset, Thibault Lhermusier Cardiac surgeons: Etienne Grunenwald, Bertrand Marcheix Noninterventional cardiologist: Pauline Fournier
CHU de Strasbourg	Interventional cardiologists: Olivier Morel, Patrick Ohlmann Cardiac surgeons: Michel Kindo, Minh Tam Hoang Noninterventional cardiologists: Hélène Petit, Hafida Samet, Anne Trinh
Hôpital Privé Saint Martin-Caen	Interventional cardiologists: Bruno Huret, Guillaume Lecoq, Jean François Morelle, Pascal Richard Cardiac surgeons: Thierry Derieux, Emmanuel Monier Noninterventional cardiologist: Cédric Joret
CHU de Dijon	Interventional cardiologist: Luc Lorgis Cardiac surgeon: Olivier Bouchot Noninterventional cardiologist: Jean Christophe Eicher
Institut Arnaud Tzanck, Saint Laurent du Var	Interventional cardiologists: Laurent Drogoul, Pierre Meyer Cardiac surgeons: Stéphane Lopez, Michel Tapia, Jacques Teboul Noninterventional cardiologists: Jean-Pierre Elbeze, Alain Mihoubi
CHU de Grenoble	Interventional cardiologists: Bernard Bertrand, Gérald Vanzetto, Olivier Wittenberg Cardiac surgeons: Vincent Bach, Cécile Martin Noninterventional cardiologists: Carole Sauier, Charlotte Casset
CHU de Brest	Interventional cardiologists: Philippe Castellant, Martine Gilard Cardiac surgeons: Eric Bezon, Jean-Noel Choplain, Ahmed Kallifa, Bahaa Nasr Noninterventional cardiologists: Yannick Jobic
Hôpital Européen Georges Pompidou, Paris	Interventional cardiologists: Didier Blanchard, Antoine Lafont, Jean-Yves Pagny, Christian Spaulding Cardiac surgeons: Ramzi Abi Akar, Jean-Noël Fabiani, Rachid Zegdi Noninterventional cardiologists: Alain Berrebi, Tania Puscas
CHU de Tours	Interventional cardiologists: Bernard Desveaux, Fabrice Ivanes, Laurent Quilliet, Christophe Saint Etienne Cardiac surgeon: Thierry Bourguignon Noninterventional cardiologists: Blandine Aupy, Romain Perault
CHU La Timone, Marseille	Interventional cardiologists: Jean-Louis Bonnet, Thomas Cuisset, Marc Lambert Cardiac surgeons: Dominique Grisoli, Nicolas Jaussaud Noninterventional cardiologist: Erwan Salaun

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APPENDIX Continued

Centers	Investigators
Polyclinique du Bois, Lille	Interventional cardiologist: Maxence Delomez Cardiac surgeon: Amine Laghzaoui Noninterventional cardiologist: Christine Savoye
CHU de Caen	Interventional cardiologists: Farzin Beygui, Mathieu Bignon, Vincent Roule, Rémy Sabatier Cardiac surgeons: Calin Ivascau, Vladimir Saplacan Noninterventional cardiologists: Eric Saloux
Infirmerie Protestante, Lyon	Interventional cardiologists: Damien Bouchayer, Jean-Philippe Claudel, Guillaume Tremeau Cardiac surgeons: Camille Diab, Joel Lapeze, Franck Pelissier, Thomas Sassard Noninterventional cardiologists: Catherine Matz, Nicolas Monsarrat
Clinique de la Sauvegarde, Lyon	Interventional cardiologists: Ivan Carel, Alain Hepp, Franck Sibellas Cardiac surgeon: Alain Curtil
Hôpital Privé Parly 2, Le Chesnay	Interventional cardiologists: Grégoire Dambrin, Xavier Favereau, Arnaud Jegou Cardiac surgeons: Gabriel Ghorayeb, Laurent Guesnier, Wassim Khoury, Christophe Kucharski, Bruno Pouzet, Claude Vaislic Noninterventional cardiologists: Riadh Cheikh-Khelifa, Loïc Hilpert, Philippe Maribas
Hôpital Privé de Bois-Bernard-CH Lens-Bois-Bernard, Lens	Interventional cardiologists: Antoine Gommeaux, Gery Hannebicque, Philippe Hochart, Marc Paris, Max Pecheux, Matthieu Bic Cardiac surgeons: Olivier Fabre, Laurent Guesnier
CHU d'Amiens	Interventional cardiologists: Laurent Leborgne, Anfani Mirode, Marcel Peltier, Faouzi Trojette Cardiac surgeon: Doron Carmi Noninterventional cardiologist: Christophe Tribouilloy
CHU de Poitiers	Interventional cardiologists: Luc Christiaens, Jean Mergy Cardiac surgeon: Pierre Corbi Noninterventional cardiologist: Pascale Raud Raynier
Hôpital Clinique Claude Bernard, Metz	Interventional cardiologists: Sylvain Carillo, Charles Christophe, Arnaud Hueber, Fédéric Moulin Cardiac surgeon: Georges Pinelli
CHU de Limoges	Interventional cardiologists: Claude Cassat, Nicole Darodes Cardiac surgeon: Francis Pesteil
CHU de Reims	Interventional cardiologist: Damien Metz Cardiac surgeon: Chadi Aludaat Noninterventional cardiologist: Frédéric Torossian
CH d'Annecy	Interventional cardiologists: Loïc Belle, Lionel Mangin Cardiac surgeon: Nicolas Chavanis Noninterventional cardiologist: Chrystelle Akret
CHU de Saint Etienne	Interventional cardiologists: Alexis Cerisier, Karl Isaaz Cardiac surgeons: Jean Pierre Favre, Jean François Fuzellier Noninterventional cardiologist: Romain Pierrard
CH de Mulhouse	Interventional cardiologists: Laurent Jacquemin, Olivier Roth, Jean Yves Wiedemann Cardiac surgeons: Nicolas Bischoff, Georghe Gavra Noninterventional cardiologist: Nicolas Bourrely
Centre Cardiologique du Nord, Saint Denis	Interventional cardiologists: Franck Digne, Philippe Guyon, Mohammed Najjari, Victor Stratiev Cardiac surgeons: Nicolas Bonnet, Patrick Mesnildrey Noninterventional cardiologists: David Attias, Julien Dreyfus, Daniel Karila Cohen, Thierry Laperche, Julien Nahum, Aliocha Scheuble
Clinique Sainte Clotilde, Saint Denis de La Réunion	Interventional cardiologists: Christophe Pouillot, Geoffrey Rambaud Cardiac surgeon: Eric Brauberger Noninterventional cardiologist: Michel Ah Hot
Clinique Ambroise Paré, Neuilly sur Seine	Interventional cardiologists: Philippe Allouch, Fabrice Beverelli, Serge Makowski, Julien Rosencher Cardiac surgeons: Stéphane Aubert, Jean Michel Grinda, Thierry Waldman
CHU de Besançon	Interventional cardiologists: Nicolas Meneveau, François Schiel, Romain Chopard, Marion Chatot Cardiac surgeons: Enrica Derigo et Djamel Kaili

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