Valvular Heart Disease

Postprocedural Aortic Regurgitation in Balloon-Expandable and Self-Expandable Transcatheter Aortic Valve Replacement Procedures

Analysis of Predictors and Impact on Long-Term Mortality: Insights From the FRANCE2 Registry

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Background—Significant postprocedural aortic regurgitation (AR) is observed in 10% to 20% of cases after transcatheter aortic valve replacement (TA VR). The prognostic value and the predictors of such a complication in balloon-expandable (BE) and self-expandable (SE) TA VR remain unclear.

Methods and Results—TA VR was performed in 3195 consecutive patients at 34 hospitals. Postprocedural transthoracic echocardiography was performed in 2769 (92%) patients of the eligible population, and these patients constituted the study group. Median follow-up was 306 days (Q1–Q3=178–490). BE and SE devices were implanted in 67.6% (n=1872) and 32.4% (n=897). Delivery was femoral (75.3%) or nonfemoral (24.7%). A postprocedural AR≥grade 2 was observed in 15.8% and was more frequent in SE (21.5%) than in BE-TA VR (13.0%, P=0.0001). Extensive multivariable analysis confirmed that the use of a SE device was one of the most powerful independent predictors of postprocedural AR≥grade 2. For BE-TA VR, 8 independent predictors of postprocedural AR≥grade 2 were identified including femoral delivery (P=0.04), larger aortic annulus (P=0.0004), and smaller prosthesis diameter (P=0.0001). For SE-TA VR, 2 independent predictors were identified including femoral delivery (P=0.0001). Aortic annulus and prosthesis diameter were not predictors of postprocedural AR for SE-TA VR. A postprocedural AR≥grade 2, but not a postprocedural AR=grade 1, was a strong independent predictor of 1-year mortality for BE (hazard ratio=2.50; P=0.0001) and SE-TA VR (hazard ratio=2.11; P=0.0001). Although postprocedural AR≥grade 2 was well tolerated in patients with AR≥grade 2 at baseline (1-year mortality=7%), it was associated with a very high mortality in other subgroups: renal failure (43%), AR<grade 2 at baseline (31%), low transaortic gradient (35%), or nonfemoral delivery (45%).

Conclusions—Postprocedural AR≥grade 2 was observed in 15.8% of successful TA VR and was the strongest independent predictor of 1-year mortality. The use of the SE device was a powerful independent predictor of postprocedural AR≥grade 2. (Circulation. 2014;129:1415-1427.)

Key Words: aortic valve ■ aortic valve insufficiency ■ aortic valve stenosis

Transcatheter aortic valve replacement (TA VR) is a technique to treat patients with symptomatic aortic stenosis and contraindications or at high risk for conventional surgical valve replacement.1 Two revalving devices based on different technical concepts, self-expandable (SE) or balloon-expandable (BE), have been developed and are currently available.1,2

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Clinical Perspective on p 1427

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In ≈10% to 20% of cases, TAVR procedures are associated with the occurrence of a significant postprocedural aortic regurgitation (AR). Three recent registries, each including between 600 and 900 patients and mainly focusing on patients treated with a SE device (77%), have suggested that the occurrence of a grade 2 AR as documented by angiography at the end of the procedure is associated with an increased mid- and long-term mortality. Although this issue is of potential clinical importance, it remains unclear whether the occurrence of such AR, as documented by echocardiography after an otherwise successful procedure, is also an independent predictor of mortality. Although such a relationship was observed in the Placement of Aortic Transcatheter Valve (PARTNER) trial including 348 patients who underwent TAVR with a BE device, this needs to be confirmed in larger studies, and in patients treated with a SE device, as well. It is also unclear whether the clinical impact of AR is similar in all groups or whether there are patients with particular comorbidities in which the presence AR specifically may or may not be more deleterious. Among the subgroups of interest, the type of device used during the procedure (BE versus SE) is of a specific importance, because it has been suggested that the severity of AR could regress over time after the implantation of a SE device and have less impact on outcome. In addition, although some small studies have attempted to elucidate the predictors of AR after TAVR, there is no comprehensive analysis available, and the predictors of such complications remain largely unclear. In particular, the parameters associated with postprocedural AR for each device technology are largely unknown.

In 2010, a national TAVR coordination and prospective monitoring program was set to analyze patient characteristics and clinical outcome in all centers performing TAVR in France (France 2 Registry). This extensive registry program included all consecutive patients (n=3195) from January 2010 to October 2011. As part of the registry, baseline clinical and echocardiography characteristics, postprocedural echocardiography, and follow-up were prospectively recorded. It is to-date the largest registry available and the only large-scale TAVR registry that includes all consecutive patients treated in a defined geographical territory during a given period of time.

The present study was designed to (1) describe the rate of postprocedural total and paravalvular ARs in a large series of consecutive patients successfully treated with both BE- and SE-device technology, (2) analyze the predictors of such ARs in the overall population and for each device technology, and (3) analyze the impact of those ARs on long-term on clinical outcome in the overall population and in various subgroups.

### Methods

#### Patient Selection

At each of the 34 centers, a multidisciplinary team identified symptomatic patients requiring TAVR for severe aortic stenosis who were at very high risk and ineligible for conventional surgical replacement owing to comorbidities. All eligible patients meeting these criteria were prospectively included. No exclusion criteria were applied. All patients gave written informed consent before the procedure and agreed to anonymous processing of their data. The registry was approved by the institutional review board of the French Ministry of Health. Additional information is provided in Methods in the online-only Data Supplement.

In total, TAVR was performed on 3195 patients from January 2010 to October 2011. Of these patients, 3025 had a successful procedure and were alive at day 2. These patients were eligible for postprocedural transthoracic echocardiography (TTE). Postprocedural TTE was performed in 2769 (92%) patients of the eligible population; these patients constituted the study group.

#### Transcatheter Aortic Valve Replacement Procedure

The technical aspects of the TAVR procedure for the 2 devices have been previously reported in detail. Both commercially available valves were used: the BE prosthesis known as the Edwards SAPIEN or SAPIEN XT valve (Edwards Lifesciences, Irvine, CA) and the SE prosthesis known as the Medtronic CoreValve Revalving System (Medtronic, Minneapolis, MN). For each device, 3 sizes were available (BE, 23, 26, and 29 mm; and SE, 26, 29, and 31 mm). The 29-BE device required a transapical approach. More details are provided in Methods in the online-only Data Supplement.

#### Transthoracic Echocardiography

TTE was performed before TAVR in all patients. Postprocedural TTE was intended to be performed at day 2 after the procedure and was performed, at the latest, before hospital discharge. The median day for postprocedural TTE was day 3 (Q1–Q3=2–4).

A complete echocardiographic study was performed for each patient in a standard fashion and details are provided in the online-only Data Supplement.

Mitral and aortic regurgitation were assessed by using a color-flow Doppler signal and graded in 5 groups as none or trivial (0/4), mild (1/4), mild-to-moderate (2/4), moderate-to-severe (3/4), or severe (4/4).

Native and post-TAVR ARs were evaluated according to the European Association of Echocardiography guidelines and the American Society of Echocardiography recommendations by the use of a multiparametric and integrative approach rather than a single measurement. In case of post-TAVR ARs, because they are often paravalvular, the evaluation relied more heavily on the circumferential extent of the paravalvular jet(s) as evaluated just below the bioprosthesis on the short-axis view, than on the other parameters. Mild, moderate, and severe post-TAVR ARs were defined according to American Society of Echocardiography guidelines with the following adaptation that, similar to the European Association of Echocardiography proposal for the evaluation of ARs of the native valves, ARs were subdivided in mild-to-moderate and moderate-to-severe ARs. When several AR jets were present, AR was expressed as an overall grade unless otherwise stated. A valvular regurgitation ≥2 was considered significant.

The Prosthesis Annulus Cover Index was defined as 100×(prosthesis diameter [as provided by the manufacturer] minus annulus diameter-by-TTE)/prosthesis diameter (as provided by the manufacturer).

#### Clinical Follow-Up

Clinical follow-up was obtained in all patients at a median of 306 days (Q1–Q3=178–490). All adverse events were assessed according to the Valve Academic Research Consortium classification. Mortality was adjudicated by an independent clinical events committee. Causes of death were classified as noncardiovascular or cardiovascular. Deaths of unknown cause and sudden deaths were classified as cardiovascular deaths.

#### Statistical Analysis

Continuous variables are expressed as mean±standard deviation. Discrete variables are presented as absolute numbers and percentages. The association between the severity of postprocedural AR (grade 0, 1, 2) or the type of device used (BE versus SE) and baseline and procedural characteristics was evaluated with the use of a
(ordinal or binomial) logistic regression analysis (with or without adjustment for sex). Multivariable binomial logistic regression models were used to calculate odds ratios (ORs) for covariates of post-procedural AR ≥ grade 2 in the overall population, for each type of device (BE or SE) and to test for interactions. Cumulative mortality rates were estimated with the Kaplan-Meier method, and differences were tested with a log-rank test. Hazard ratios (HRs) were calculated by using simple (univariable) and multiple (multivariable) Cox proportional hazard models. Multivariable analyses were performed by using variables with $P$ values of $<0.10$ in the univariable analysis and all potential confounders, as well. Temporal analyses were performed (online-only Data Supplement). A systematic adjustment on participating centers was performed.

All hypotheses were 2-tailed with a 0.05 type I error rate. Analyses were conducted by using SPSS 17.0 (Chicago, IL) and the SAS system (SAS v8; SAS-Institute, Cary, NC).

**Results**

**Frequency of Postprocedural AR and Patient Characteristics**

The baseline and procedural characteristics of the population eligible for postprocedural TTE but in whom it was not done (n=256) and of the study population in whom TTE was actually performed (n=2769) are presented in Tables 1 and 2. No significant difference was observed between the 2 populations. Half of the population was female (48.9%), the mean age was 83±7 years, 3/4 were New York Heart Association 3 or 4, and the mean logistic EuroSCORE was 21.5±13.8. The procedure was performed with a BE device in 2/3 of the cases (67.6%) and through a transfemoral approach in 75.3% of the cases.

Postprocedural AR grade=0 to 1, grade=2, and grade=3 to 4 were observed in 84.2%, 14.7%, and 11.1% of the cases, respectively. Paravalvular AR grade=0 to 1, grade=2, and grade=3 to 4 were observed in 85.2%, 14.0%, and 0.8% of the cases, respectively. Intravalvular AR grade=0 to 1, grade=2, and grade=3 to 4 was observed in 98.8%, 0.9%, and 0.3% of the cases, respectively. A postprocedural AR grade=2 was observed in 15.8% of the cases, including 14.6% paravalvular, 1.0% intravalvular, and 0.2% mixed.

Correlates of the severity of postprocedural AR as a function of baseline patient characteristics by univariable analysis and after adjustment on sex are presented in Table 1. Correlates of the severity of postprocedural AR as a function of procedural characteristics are presented in Table 2.

The occurrence of postprocedural AR ≥ grade 2 was not significantly modified by the temporal increased experience of each center (Table 1). Although postprocedural AR ≥ grade 2 was more frequent in patients receiving the SE (21.5%) than the BE device (13.0%; $P=0.0001$, Table 2), some differences in baseline characteristics were also observed between patients treated with a BE or SE device (Table 1). In particular, patients treated with a BE device were more likely to be female (35.3% versus 39.1%, $P=0.0001$), to be older (82.9±7.2 versus 82.3±7.0, $P=0.04$), to have a lower body mass index (26.0±4.8 versus 26.5±5.1, $P=0.01$), and to have a smaller aortic annulus diameter by TTE (21.8±1.9 versus 22.8±2.3, $P=0.01$). However, after adjustment for sex, most of these differences, including the one observed on aortic annulus diameter, disappeared (Table 1). Conversely, adjustment for sex revealed that patients treated with BE devices were more likely to have peripheral arterial disease ($P=0.003$), coronary artery disease ($P=0.005$), or a history of myocardial infarction ($P=0.005$). These differences were observed because, in comparison with patients without peripheral arterial disease, those with peripheral arterial disease were more likely to be treated through a nonfemoral approach (54% versus 17%, $P<0.0001$); the nonfemoral approach used a BE device more frequently than a SE device (75.9% versus 24.1%, $P<0.0001$).

**Predictors of Postprocedural AR**

To verify the role of the type of device on postprocedural AR ≥ grade 2, a multivariable logistic analysis, including all potential confounding parameters as identified by univariable analysis, was conducted. It confirmed that the use of a SE device (OR=2.03 [1.46–2.83], $P<0.0001$), but also the use of a femoral delivery approach (OR=1.72 [1.28–32.31], $P=0.0003$) were independent correlates of postprocedural AR ≥ grade 2 (Figure 1A). The respective roles of the type of endoprosthesis and of the delivery approach are illustrated in Figure 2. These results were not significantly modified after exclusion of the patients in whom a 29-mm BE device was used (Figure I in the online-only Data Supplement) nor were they significantly modified while centers were gaining experience (Results and Figure II in the online-only Data Supplement).

Other independent correlates of postprocedural AR ≥ grade 2 are male sex (OR=1.80 [1.38–2.38], $P<0.0001$), diabetes mellitus (OR=0.74 [0.57–0.97], $P=0.03$), the presence of mitral regurgitation ≥ grade 2 at baseline (OR=1.29 [1.02–1.64], $P=0.03$), the presence of AR ≥ grade 2 at baseline (OR=1.35 [1.05–1.73], $P=0.02$), a higher (1-mm increase) aortic annulus diameter by TTE (OR=1.09 [1.02–1.16], $P=0.01$), and the use of a larger (3-mm increase) endoprosthesis (OR=0.67 [0.50–0.89], $P=0.006$; Figure 1A).

Although no statistical interaction was observed between the type of device (BE versus SE) and most of the predictors of postprocedural AR ≥ grade 2, a significant interaction was observed between the type of device and aortic annulus diameter ($P=0.04$) and between the type of device and prosthesis diameter ($P=0.003$).

**Predictors of Postprocedural AR by Type of Device**

Because of these interactions, a separate analysis of the predictors of postprocedural AR ≥ grade 2 was conducted for each type of device.

Among patients treated with a BE device (Figure 1B), correlates of postprocedural AR ≥ grade 2 are male sex (OR=2.08 [1.45–2.98], $P=0.0001$), the presence of atrial fibrillation at baseline (OR=1.35 [1.01–1.83], $P=0.04$), the presence of mitral regurgitation ≥ grade 2 at baseline (OR=1.54 [1.14–2.09], $P=0.005$), a higher (1-mm increase) aortic annulus diameter by TTE (OR=1.18 [1.07–1.30], $P=0.001$), use of a femoral delivery approach (OR=1.45 [1.02–2.07], $P=0.04$), and the use of a larger (3-mm increase) endoprosthesis diameter (OR=0.43 [0.29–0.63], $P<0.0001$). The positive relationship between postprocedural AR ≥ grade 2 and aortic annulus diameter and the inverse relationship between postprocedural AR ≥ grade 2 and endoprosthesis diameter translated into a strong inverse relationship between the Prosthesis Annulus Cover Index and the risk of postprocedural AR ≥ grade 2 (Figure 3).
### Table 1. Baseline Patient Characteristics According to Device and Postprocedural Aortic Regurgitation

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>Eligible Patients Not in the Study</th>
<th>Study Population</th>
<th>Postprocedural AR</th>
<th>Device</th>
<th>P</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>256</td>
<td>2769</td>
<td>964 (34.8)</td>
<td>1369 (49.4)</td>
<td>436 (15.8)</td>
<td>1872 (67.6)</td>
</tr>
<tr>
<td>Sex</td>
<td>125 (48.8)</td>
<td>1353 (48.9)</td>
<td>543 (40.1)</td>
<td>648 (47.9)</td>
<td>162 (12.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.9±4.8</td>
<td>26.1±4.9</td>
<td>26.4±5.0</td>
<td>26.1±4.9</td>
<td>25.6±4.8</td>
<td>0.009</td>
</tr>
<tr>
<td>NYHA class</td>
<td>17 (5.7)</td>
<td>166 (5.9)</td>
<td>64 (49.0)</td>
<td>51 (39.7)</td>
<td>9 (6.3)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Female</td>
<td>159 (62.1)</td>
<td>1733 (62.6)</td>
<td>605 (41.0)</td>
<td>691 (50.9)</td>
<td>30 (22.8)</td>
<td>0.49</td>
</tr>
<tr>
<td>CAD</td>
<td>186 (72.1)</td>
<td>2033 (74.9)</td>
<td>692 (47.7)</td>
<td>737 (56.1)</td>
<td>35 (25.8)</td>
<td>0.12</td>
</tr>
<tr>
<td>Previous MI</td>
<td>35 (19.5)</td>
<td>403 (16.7)</td>
<td>56 (37.0)</td>
<td>51 (39.7)</td>
<td>8 (6.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>Previous CAGB</td>
<td>215 (83.9)</td>
<td>2267 (81.9)</td>
<td>772 (34.1)</td>
<td>1127 (49.7)</td>
<td>372 (16.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>PAD</td>
<td>49 (19.2)</td>
<td>559 (23.2)</td>
<td>225 (40.3)</td>
<td>265 (47.4)</td>
<td>69 (12.3)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>30 (11.6)</td>
<td>262 (9.5)</td>
<td>95 (36.3)</td>
<td>117 (44.7)</td>
<td>43 (16.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>65 (25.4)</td>
<td>711 (25.7)</td>
<td>190 (26.7)</td>
<td>378 (53.2)</td>
<td>143 (20.1)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Permanent pacemaker</td>
<td>29 (11.3)</td>
<td>398 (14.4)</td>
<td>140 (35.2)</td>
<td>195 (48.9)</td>
<td>64 (16.1)</td>
<td>0.88</td>
</tr>
<tr>
<td>COPD</td>
<td>67 (26.1)</td>
<td>646 (23.3)</td>
<td>242 (37.5)</td>
<td>313 (48.5)</td>
<td>91 (14.1)</td>
<td>0.16</td>
</tr>
<tr>
<td>Renal insufficiency†</td>
<td>30 (11.7)</td>
<td>233 (8.4)</td>
<td>69 (29.6)</td>
<td>119 (51.1)</td>
<td>45 (19.3)</td>
<td>0.16</td>
</tr>
<tr>
<td>Preprocedural TTE</td>
<td>22.1±2.4</td>
<td>22.1±2.1</td>
<td>21.9±2.1</td>
<td>22.1±2.1</td>
<td>22.6±2.2</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Table 1. Continued

<table>
<thead>
<tr>
<th>AR grade ≥ 2</th>
<th>Postprocedural AR</th>
<th>Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF &lt; 30%</td>
<td>27 (10.3)</td>
<td>119 (60.4)</td>
</tr>
<tr>
<td>LVEF 30%–49%</td>
<td>75 (29.4)</td>
<td>589 (67.4)</td>
</tr>
<tr>
<td>LVEF ≥ 50%</td>
<td>154 (60.3)</td>
<td>1164 (68.7)</td>
</tr>
<tr>
<td>AVA, cm²</td>
<td>0.67±0.23</td>
<td>0.67±0.17</td>
</tr>
<tr>
<td>Mean aortic grade, mm Hg</td>
<td>47.1±17.4</td>
<td>48.8±16.2</td>
</tr>
<tr>
<td>AR grade ≥ 2</td>
<td>Present: 44 (17.1)</td>
<td>292 (62.5)</td>
</tr>
<tr>
<td></td>
<td>Absent: 212 (82.9)</td>
<td>1580 (68.6)</td>
</tr>
<tr>
<td>MR grade ≥ 2</td>
<td>Present: 48 (18.8)</td>
<td>416 (71.7)</td>
</tr>
<tr>
<td></td>
<td>Absent: 208 (61.2)</td>
<td>1456 (66.5)</td>
</tr>
<tr>
<td>PAP, mm Hg</td>
<td>45.7±13.3</td>
<td>45.8±13.9</td>
</tr>
<tr>
<td>Experience at each center</td>
<td>Early (tirel 1)</td>
<td>464 (69.3)</td>
</tr>
<tr>
<td></td>
<td>Mid (tirel 2)</td>
<td>635 (68.5)</td>
</tr>
<tr>
<td></td>
<td>Late (tirel 3)</td>
<td>593 (64.9)</td>
</tr>
<tr>
<td>Participating center</td>
<td>NA</td>
<td>285 (30.7)</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>292 (31.5)</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>320 (35.1)</td>
</tr>
</tbody>
</table>

Values are given in numbers (%) or mean±SD. AR indicates aortic regurgitation; AVA, aortic valve area; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NA, not applicable; NYHA, New York Heart Association; PAD, peripheral arterial disease; SD, standard deviation; and TTE, transthoracic echocardiography.

*P adjusted for sex.
†Serum creatinine is >200 μmol/L.

Among patients treated with a SE device (Figure 1C), besides the presence of AR ≥ grade 2 at baseline (OR=1.45 [1.01–2.07], P=0.04), the use of a femoral delivery approach (OR=2.25 [1.30–3.91], P=0.003) was the only independent correlate of postprocedural AR ≥ grade 2. Importantly, aortic annulus diameter and device diameter were not associated with the risk of postprocedural AR (Figure 1C). The lack of relationship between postprocedural AR ≥ grade 2 and aortic annulus diameter or endoprosthesis diameter translated into a lack of relationship between the Prosthesis Annulus Cover Index and the risk of postprocedural AR ≥ grade 2 (Figure 3).

Impact of AR on Mortality

During the follow-up period, 312 patients died, including 175 from cardiovascular death.

In comparison with patients without AR (AR=grade 0), a postprocedural AR ≥ grade 2 was associated with a higher mortality (unadjusted \( \chi^2=44.1, HR=2.33 [1.82–2.99], P<0.0001; \) Figure 4) and a higher cardiovascular mortality (unadjusted \( \chi^2=25.9, HR=2.36 [1.70–3.29], P<0.0001 \)) during the follow-up period. No association was found between postprocedural AR = grade 1 and total or cardiovascular mortality.

The association between postprocedural AR ≥ grade 2 and mortality was not modified by the gain of experience at each center (Results and Figure III in the online-only Data Supplement).

Other baseline characteristics associated with all-cause mortality by univariable analysis (P<0.05) were age, male sex, a lower body mass index, logistic EuroSCORE, New York Heart Association class, renal failure, atrial fibrillation, a lower left ventricular ejection fraction, a lower transaortic gradient, and a higher pulmonary pressure.

Multivariable analysis showed that a postprocedural AR ≥ grade 2 was associated with total mortality (\( \chi^2=38.2, HR=2.43 [1.83–3.25], P<0.0001; \) Figure 5) and with cardiovascular mortality (\( \chi^2=26.3, HR=2.53 [1.78–3.61], P<0.0001 \)). Eight other parameters were also associated with total mortality: atrial fibrillation (HR=1.74 [1.36–2.23], P=0.005), renal failure (HR=1.75 [1.24–2.48], P=0.0005), New York Heart Association class (HR=1.32 [1.08–1.60], P=0.007), a lower (10 mm Hg) transaortic gradient at baseline (HR=1.10 [1.02–1.20], P=0.01), the absence of AR at baseline (HR=1.49 [1.04–2.11], P=0.02), use of a nonfemoral delivery approach (HR=1.28 [1.02–1.60], P=0.03), male sex (HR=1.31 [1.02–1.70], P=0.04), and a lower (1 kg/m²) body mass index (HR=1.03 [1.01–1.06], P=0.04; Figure 5).

No statistical interaction was observed between the type of device (BE versus SE) and the predictors of mortality.

The impact of postprocedural AR ≥ grade 2 on mortality according to key clinical or procedural characteristics are presented in Figure 6. It is important to notice that, although no statistical interaction was observed between the occurrence...
of postprocedural AR$\geq$ grade 2 and most of the other predictors of mortality, a strong interaction was found with the presence of AR at baseline ($P=0.0006$; Figure 6C) and with the delivery approach ($P=0.04$; Figure 6F). Indeed, although among patients with an AR$\geq$ grade 2 at baseline, the occurrence of a postprocedural AR$\geq$ grade 2 was not associated with an increased mortality at 1 year (HR=0.60 [0.25–1.41]), it was associated with a 3-fold increase in mortality in patients without an AR$\geq$ grade 2 at baseline (HR=2.94 [2.25–3.82]; Figure 6C). Similarly, although, in patients in whom a postprocedural AR$\geq$ grade 2 did occur, the use of a nonfemoral delivery approach was associated with a 2-fold increase in mortality (HR=1.98 [1.21–3.24]), it was not the case in patients without a postprocedural AR$\geq$ grade 2 (HR=1.12 [0.84–1.51]; Figure 6F).

It is also interesting to notice that in patients combining no atrial fibrillation at baseline and no postprocedural AR$\geq$ grade 2, the 1-year mortality rate was <10% (Figure 6A). At the other end of the spectrum, the combination of renal failure and postprocedural AR$\geq$ grade 2 was associated with a 1-year mortality rate close to 50% (Figure 6B). Similarly, although the impact of a low transaortic gradient(<40 mm Hg) on mortality was relatively minimal in patients without a postprocedural AR$\geq$ grade 2 (HR=1.21 [1.02–1.66]), it was very detrimental in patients in whom a postprocedural AR$\geq$ grade 2 was observed (HR=1.77 [1.15–2.74]; Figure 6D). Finally, the impact of postprocedural AR$\geq$ grade 2 on mortality was of the same magnitude in patients treated with BE (HR=2.50 [1.82–3.43]) or SE (HR=2.11 [1.40–3.18]) devices (Figure 6E).

### Discussion

This study, based on the largest nationwide registry available, demonstrates that after a successful TAVR procedure (paravalvular) AR$\geq$ grade 2 by echocardiography is observed in $\approx$ 16% of cases and is the most powerful predictor of mortality at 1 year. It shows that, although such postprocedural AR$\geq$ grade 2 cases are more frequently observed after implantation of a SE than a BE device, the impact on mortality is not device dependent. The results further demonstrate that, although delivery through a nonfemoral approach is associated with a lower risk of AR for the 2 devices, annulus and endoprosthesis diameters are important predictors of ARs for BE, but not for the SE device. Finally, subgroups could be identified as having either a very poor clinical tolerance (renal failure, low aortic gradient, nonfemoral delivery), or, in contrast, a very good tolerance (AR$\geq$ grade 2 at baseline) for postprocedural AR$\geq$ grade 2.

### Incidence and Predictive Value of AR on One-Year Mortality

A summary of the main studies investigating the incidence and the predictive value of postprocedural AR, also reported in the meta-analysis by Athappan et al.,13 is presented in Table 3.1–4,14–17 The present study has important characteristics overcoming their limitations and allowing for a robust multivariable
adjustment and subgroup analyses that were not touched on in those previous studies. First, the present study used the only large-scale TAVR registry investigating this issue, including all consecutive patients treated in a defined geographical territory during a given period, thus eliminating the risk of selection bias present in previous studies and in the recent meta-analysis. It is also by far the largest multicenter registry available, including nearly 4 times more patients and analyzing nearly 2 times more events than the largest study available until now and allowing extensive multivariable adjustment. A recent meta-analysis also included a large number of patients. However, because individual patients’ data were not available, no multivariable adjustment could be made. Third, although most previous studies focused primarily on patients treated with 1 type of device, the present study included

Figure 1. Correlates of postprocedural aortic regurgitation grade 2 by multivariable logistic regression in the overall population (A), in patients treated with a BE device (B), and in patients treated with a SE device (C). Other parameters in the 3 models are all individual components of the logistic EuroSCORE, BMI, CAD, participating centers, and tertiles of experience at each center. AR indicates aortic regurgitation; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; MR, mitral regurgitation; and TTE, transthoracic echocardiography.

Figure 2. Occurrence of aortic regurgitation grade 2 according to the type of device (BE vs SE) and to the type of delivery approach (femoral versus nonfemoral). AR indicates aortic regurgitation; BE, balloon-expandable; and SE, self-expandable.

Figure 3. A significant inverse relationship was observed between aortic regurgitation grade 2 and Prosthesis Annulus Cover Index with BE devices (P<0.0001) but not with SE devices (P=0.89). Analyses were performed by using logistic regression with Prosthesis Annulus Cover Index as an independent quantitative variable and adjustment on the same covariates than in Figure 1B (BE) and Figure 1C (SE). AR indicates aortic regurgitation; BE, balloon-expandable; and SE, self-expandable.
a large number of patients treated with either of the 2 devices available. Fourth, although the schemes of evaluation of AR of the studies presented in the meta-analysis were very different from 1 study to another—including in the nature of the evaluation, angiography versus transesophageal echocardiography versus TTE; in the timing of the evaluation; in the catheterization laboratory versus after the procedure; and in the grading systems, as well—the present study provides information on the rate of AR as evaluated by a standardized methodology based on a TTE performed at day 3 (2–4) postprocedure and a single grading system. Finally, this study is also one of the few to investigate the impact of postprocedural AR severity on both total and cardiovascular mortality.

Although previous studies have reported rates of postprocedural AR≥grade 2 ranging from 8% to nearly 40%, and the meta-analysis reported a rate of 11.7%; in the present study, it was observed in ≈16% of cases. As can be seen in Table 3, these apparent differences are mainly related to differences in the method of AR evaluation (angiography versus echocardiography) and in the proportion of patients treated with the SE or the BE device in each study. The meta-analysis, and studies purely based on angiography, as well, could not provide information on the mechanisms of AR; in addition, previous studies based on echocardiography evaluation reported that paravalvular AR could represent 82% or 100% of the total number of ARs. In the present series, the AR was confirmed to be paravalvular in 94% of cases.

With the use of extensive multivariable adjustment (24 variables), the present study confirmed that the presence of AR≥grade 2 is the strongest predictor and an independent predictor of total mortality at 1 year and further demonstrated that it is also the strongest independent predictor of cardiovascular mortality. At the difference with the PARTNER study and the meta-analysis of previous studies, the occurrence of a mild (grade=1) AR was not associated with a significant increase in total or cardiovascular mortality.

Although to date there is little available information on the role of postprocedural AR≥grade 2 in specific subgroups (Table 3), the present study identified important groups of interest. The results demonstrate that the occurrence of postprocedural AR in patients with chronic renal failure is particularly dreadful with a 1-year mortality rate close to 50%. Similarly, the occurrence of AR in patients with a low transaortic gradient at baseline is associated with a mortality rate of 35% at 1 year.

It is interesting to note that 1 group of patients appeared to be protected from the deleterious effect of the occurrence of a postprocedural AR. Indeed, in patients in whom a significant AR was already present before the procedure, the occurrence of a postprocedural AR≥grade 2 did not significantly impact 1-year survival. This may suggest that the left ventricle of patients with preexisting AR is already adapted to volume overload and can thus better tolerate postprocedural AR. Although, in patients without preexisting AR, the pronounced concentrically remodeled and small left ventricular cavity, with reduced compliance and impaired filling, will poorly tolerate postprocedural AR.

Because maneuvers that have been shown to reduce the severity of postprocedural ARs have their own induced morbidity, identification of subgroups with poor or good tolerance to ARs is of clinical importance.

Role of Prosthesis Type (BE Versus SE) on the Risk of AR

Higher rates of postprocedural AR have previously been reported in patients treated with a SE device than in those treated with the BE device (Table 3). However, with the exception of an elegant case-match study including 82 patients, no direct comparison was made in those individual studies.
The results of these studies have also been reported in a meta-analysis by Athappan et al.13 The authors, however, could neither control for selection and publication biases, nor for the heterogeneity of the populations and of the schemes of evaluation of ARs. In addition, because they did not have access to individual patient data, they could not verify whether the apparent higher rate of AR observed with SE devices in comparison with BE devices was still observed after multivariable adjustment. Because of these limitations, no definitive conclusion could be made.
The present study is the first to do such a comparison in a single large population, with the use of a common methodology of evaluation for the 2 devices, and to demonstrate that the use of a SE device is an independent predictor of postprocedural AR. The actual rates of AR ≥ grade 2 as observed by echocardiography for each device (SE=21.5% and BE=13.0%) in the present study are in line with the rates of AR ≥ grade 2 observed in previous studies for each device (Table 3). The present study is also the first to demonstrate on a large scale that, for each device, the mechanism of postprocedural AR is paravalvular in >92% of the cases (Table 3).13

Regarding the difference in the rate of AR between the SE and the BE device, it is important to note that the figure is more striking when a femoral approach (21.9% versus 13.9%) rather than a nonfemoral approach (10.7% versus 8%) is used. Although this finding was never identified before in any individual study or in the meta-analysis,13 it may suggest that catheter control during delivery, which is typically more difficult during a femoral than a nonfemoral procedure, is important for minimizing the risk of AR with the SE device. This observation, combined with the trapezoidal shape of the lower end of the SE device, may also suggest that femoral delivery, because it makes the depth of implantation more difficult to control, creates additional uncertainty regarding the true diameter of the prosthesis at the level of the aortic annulus, and thus increases the risk of AR. This further suggests that, to reduce the risk of AR with SE devices, future directions might include a modified shape and a repositionable ability.

Finally, although it has been suggested that the rate of postprocedural ARs could decrease during the first days following implantation of the SE device, the predictive value of an AR ≥ grade 2 as observed by echocardiography 2 days after the procedure showed no differences between the BE (HR=2.50) and the SE (HR=2.11) device.

### Role of Annulus Dimension and Prosthesis Diameter on the Risk of Postprocedural AR

The present study is the first to allow the analysis of predictors of AR for each device separately and to demonstrate the distinctive role of annulus and prosthesis dimensions.

Annulus dimension and prosthesis diameter, as well as the resulting Prosthesis Annulus Cover Index, are major predictors of postprocedural AR for the BE device. These results confirm the initial observation of Detaint et al14 and identify 2 clear directions of improvement to reduce the risk of postprocedural AR with the BE device. First, it is key to obtain a

### Table 3. Previous Studies Investigating the Relationship Between Postprocedural AR and Mortality

<table>
<thead>
<tr>
<th>Device Type</th>
<th>Authors</th>
<th>Multicenter</th>
<th>Population, n</th>
<th>AR≥Grade 2, %</th>
<th>Timing of Evaluation of AR</th>
<th>Method of Evaluation of AR</th>
<th>Mechanism of AR</th>
<th>Total Number of Deaths*</th>
<th>Relation With Mortality Multivariable</th>
<th>Relation With CV Mortality</th>
<th>Subgroup Analysis</th>
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<tr>
<td>Self-expandable device</td>
<td>Tamburino et al2</td>
<td>Yes</td>
<td>663</td>
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<td>Cathlab</td>
<td>Angio.</td>
<td>NA</td>
<td>114</td>
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<td>17.9</td>
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<td>Angio.</td>
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<td>56</td>
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<td>NA</td>
<td>NA</td>
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<td></td>
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<td>452</td>
<td>17.3</td>
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<td>Gotzmann et al14</td>
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<td>198</td>
<td>14.1</td>
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<td></td>
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<td>No</td>
<td>97</td>
<td>18.6</td>
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<td>39.6</td>
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<td>PV=100%</td>
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<td>Nombela-Franco et al17</td>
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<td>Postprocedure</td>
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<td>PV=92%</td>
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<td>Yes</td>
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<td>13.9</td>
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<td>410</td>
<td>9.6</td>
<td>Cathlab</td>
<td>Angio.</td>
<td>NA</td>
<td>186</td>
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<td>321</td>
<td>10.6</td>
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<td>PV=86%</td>
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<td>Postprocedure</td>
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<td>PV=100%</td>
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<td>22</td>
<td>Postprocedure</td>
<td>TTE</td>
<td>PV=100%</td>
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<td>Present study</td>
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<td>Postprocedure</td>
<td>TTE</td>
<td>PV=95%</td>
<td>312</td>
<td>Yes</td>
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</tr>
</tbody>
</table>

Angio. indicates angiography; AR, aortic regurgitation; Cathlab, catheterization laboratory; CV, cardiovascular; NA, not available; PV, paravalvular; and TTE, transthoracic echocardiography.

*Number of deaths in the entire cohort.
proper evaluation of aortic annulus dimension, which is best done by transesophageal echocardiogram or computed tomography scan. Second, it also suggests that a broader choice of prosthesis diameters would help to best match the annulus dimension and reduce the risk of postprocedural AR without increasing the risk of aortic annulus rupture.

For the SE device, however, annulus dimension and prosthesis diameter are not predictors of postprocedural AR. This lack of relationship, which was not identified previously, may be related to some specific characteristics of this device. First, because of its SE nature, and as illustrated by the high mean Prosthesis Annulus Cover Index of 17.6%, the diameter of the prosthesis is usually much larger than the annulus diameter. Therefore, the use of a smaller prosthesis would remain associated with a significant oversizing of the annulus. Second, because of its the shape, the prosthesis diameter will only be reached at the very distal end of the frame, whereas the true prosthesis diameter at the level of contact with the aortic annulus will be significantly smaller and depend on implantation’s depth. Finally, it has also been reported that the control of the depth of implantation of a SE device is more difficult as the diameter of the device increases, thus minimizing the potential benefit of using a larger prosthesis.

Other Parameters Associated With Postprocedural AR
Among other parameters associated with a higher risk of postprocedural AR, patients with an AR≥grade 2, an mitral regurgitation≥grade 2, or an atrial fibrillation before the procedure, were more likely to have a postprocedural AR≥grade 2. These clinical conditions are potential surrogate markers for aortic and mitral annulus calcification that have previously been reported to be associated with a higher risk of postprocedural AR.

Diabetic patients were identified as having a lower risk of postprocedural AR. This could potentially reflect a different bioprosthesis/valvular tissue interaction and a different physiopathology in this population. Our observation that diabetic patients are significantly younger than their non-diabetic counterparts (81 versus 83 years, P<0.0001) is also consistent with this hypothesis.

Patients Treated Through a Nonfemoral Approach: A Very Specific Group
Another intriguing finding of the present study, not recognized in previous studies, is the very unique behavior of patients treated through a nonfemoral approach. First, patients treated with such an approach have a much lower risk of postprocedural AR than those treated through a femoral approach. This apparent benefit was observed both for patients treated with a BE (relative risk reduction=30%) or a SE (relative risk reduction=55%) device and was confirmed by multivariable analysis. However, when postprocedural AR≥grade 2 occurred in patients treated with such an approach, its impact on outcome was particularly deleterious with a 1-year mortality rate as high as 50%. Interestingly, in patients treated through a nonfemoral approach and no postprocedural AR≥grade 2, mortality at 1 year was ≈10% and close to the mortality observed in patients treated through the femoral approach.

Altogether, this may suggest that a better control of the catheter, as is usually achieved during delivery through a nonfemoral route, is important to improve the precision of delivery and to reduce the rate of AR. In contrast, the very high mortality associated with postprocedural AR in this population likely reflects the poor tolerance of AR in patients with more comorbidities as illustrated by their higher logistic EuroSCORE (23.4±14.1 versus 20.8±13.6, P<0.0001).

Study Limitations
We have to acknowledge that, although a large number of clinical variables were included in the multivariate models, some potentially important Doppler echocardiography (eg, left ventricular dimensions) or computed tomography (eg, aortic valve calcium score) data were not considered for inclusion in the models because these variables were not captured in the registry database.

Diameter as measured by TTE was also the only information available regarding aortic annulus dimension. Measurements derived from transesophageal echocardiography or computed tomography are usually considered more accurate than those derived from TTE, and their availability would have been of interest. However, considering the overall good correlation among the 3 methods to evaluate aortic annulus dimension and the striking difference observed in the present study between SE and BE devices, it is unlikely that the overall interpretation that annulus dimension is much less critical for the SE than the BE device would have been modified.

AR was evaluated at each site without a central reading and this could have induced some heterogeneity in evaluating aortic severity among participating centers. This issue was minimized by specific measures such as AR grading at each site performed by 2 echocardiographers dedicated to the study, and the use of a grading system common to all centers, as well. The benefit of these measures was reflected by the lack of a significant difference in AR severity among centers. This issue was also taken into account in multivariable analyses where an adjustment for participating centers was done.

In addition, although no grading system of post-TAVR ARs has been validated, the one used in the present study is slightly different from those recently proposed, in particular, regarding the separations from grade 2 (moderate) to grade 4 (severe). However, because our analysis is mainly based on the comparison of patients with post-TAVR AR grade 0 (none or trace), grade 1 (mild), and ≥grade 2 (moderate, moderate-to-severe, and severe), and because the criteria used for the distinction of those 3 populations are similar to those recently proposed, the results of our analysis are applicable to current classification systems.

Clinical Implications
The present study provides important information on the clinical significance of postprocedural AR as observed by echocardiography after an otherwise successful TAVR procedure. These results extend previous findings regarding the significance of AR as observed by angiography or by echocardiography with a BE device in the PARTNER trial. They further suggest that postprocedural AR≥grade 2, but not postprocedural AR=grade 1(mild), is a powerful independent
predictor of mortality, whereas the occurrence of such post-procedural AR grade 2 can be specifically deleterious in some populations (renal failure, low transaortic gradient, patients treated through a nonfemoral approach, etc), whereas others have a better tolerance of AR (patients with AR before the procedure).

Our study further demonstrates that the incidence of post-procedural AR grade 2 is higher with SE than with BE devices. This was observed on univariable analysis and confirmed by extensive multivariable analysis, where the use of the SE device was one of the most powerful independent predictors of the occurrence of postprocedural AR grade 2.

The lower rate of postprocedural ARs associated with nonfemoral delivery, in particular, with the SE device, may suggest that improving delivery catheter technology and the precision of delivery during femoral procedures could lead to a significant reduction in the occurrence of such ARs. The difference in the predictors of postprocedural ARs, in particular, the role of aortic annulus and prosthesis diameters, suggests specific pathways of improvement for the BE and SE devices.

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We thank Dr Martin B. Leon for his helpful contribution, in particular, for his constructive comments and review of the manuscript.

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Dr Iung is consultant for Abbott, Bayer, Boehringer Ingelheim, Servier, and Valtech. He received Speaker’s fees from Edwards Lifesciences. Dr Eltchaninoff is proctor and is receiving grants for Edwards-Life Science. Dr Leprince is proctor for Medtronic and received grants from Edwards-Life Science. Dr Leguerrier is a consultant for Saint Jude Medical. Dr Teiger is a proctor and is receiving grants from Medtronic. The other authors report no conflicts.

References


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**CLINICAL PERSPECTIVE**

By demonstrating that postprocedural aortic regurgitation (AR) ≥ grade 2 was observed by echocardiography in 15.8% of successful transcatheter aortic valve replacements and was the strongest independent predictor of 1-year mortality, the present study provides important information on the clinical significance of postprocedural AR after an otherwise successful transcatheter aortic valve replacement procedure. These results extend previous findings regarding the significance of AR as observed by angiography or by echocardiography with a balloon-expandable device in the Placement of Aortic Transcatheter Valve (PARTNER) Trial. They further suggest that postprocedural AR ≥ grade 2, but not postprocedural AR = grade 1 (mild), is a powerful independent predictor of mortality, whereas the occurrence of such postprocedural AR ≥ grade 2 can be specifically deleterious in some populations (renal failure, low transaortic gradient, patients treated through a nonfemoral approach, etc), whereas others have a better tolerance of AR (patients with AR before the procedure). Our study further demonstrates that the incidence of postprocedural AR ≥ grade 2 is higher with self-expandable than balloon-expandable devices (21.5% versus 13.0%, *P* = 0.0001). This was observed on univariable analysis and confirmed by extensive multivariable analysis, where the use of the self-expandable device was one of the most powerful independent predictors of the occurrence of postprocedural AR ≥ grade 2. The lower rate of postprocedural ARs associated with nonfemoral delivery, in particular with a self-expandable device, may suggest that improving delivery catheter technology and the precision of delivery during femoral procedures could lead to a significant reduction in the occurrence of such ARs. The difference in predictors of postprocedural ARs, in particular, the role of aortic annulus and prosthesis diameters, suggests specific pathways of improvement for the balloon-expandable and the self-expandable device.
Postprocedural Aortic Regurgitation in Balloon-Expandable and Self-Expandable Transcatheter Aortic Valve Replacement Procedures: Analysis of Predictors and Impact on Long-Term Mortality: Insights From the FRANCE2 Registry

Eric Van Belle, François Juthier, Sophie Susen, André Vincentelli, Bernard Iung, Jean Dallongeville, Hélène Eltchaninoff, Marc Laskar, Pascal Leprince, Michel Lievre, Carlo Banfi, Jean-Luc Auffray, Cedric Delhaye, Patrick Donzeau-Gouge, Karine Chevreul, Jean Fajadet, Alain Leguerrier, Alain Prat, Martine Gilard and Emmanuel Teiger for the FRANCE 2 Investigators

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SUPPLEMENTAL MATERIAL

for

Post-Procedural Aortic Regurgitation in Balloon-expandable and Self-expandable TAVR Procedures: Analysis of Predictors and Impact on Long-term Mortality - Insights from the FRANCE2 Registry

Eric Van Belle, François Juthier, André Vincentelli, Jean Dallongeville, Bernard Iung, Hélène Eltchaninoff, Marc Laskar, Pascal Leprince, Michel Lievre, Carlo Banfi, Sophie Susen, Jean-Luc Auffray, Patrick Donzeau-Gouge, Karine Chevreul, Jean Fajadet, Alain Leguerrier, Alain Prat, Martine Gilard and Emmanuel Teiger, for the FRANCE 2 Investigators.
SUPPLEMENTAL METHODS

Patient Selection

At the beginning of January 2010, a national TAVR coordination and monitoring program was established in France to analyze patient characteristics and clinical outcomes in 33 medical centers in France and one center in Monaco with the capability of performing TAVR using either a SE or BE device. At each center the multidisciplinary team (MDT) performing the procedure consisted of an interventional cardiologist, cardiothoracic surgeon, cardiologist, echocardiographer, anesthesiologist, imaging specialist, and geriatrician. In all centers, the MDT determined eligibility for TAVR based on systematic clinical, angiographic, multi-slice computed tomographic and echocardiographic assessment.

Transcatheter Aortic Valve Replacement Procedure

There were no prespecified recommendations with respect to the use of femoral or non-femoral (transapical, subclavian or transaortic) approach. All medical criteria for selection of approaches were based on the size and degree of tortuosity, calcification, and atheroma of the aortoiliofemoral arterial tree, as assessed by each MDT. Valve choice was made by individual teams. The optimal size of prosthesis was determined for each patient based on aortic annulus dimension and manufacturer recommendations. BE devices were mainly implanted using the TF, TA, or transaortic routes. SE devices were implanted using the TF, SC, or carotid routes. Transarterial access was obtained percutaneously or by surgical cut-down. Closure was achieved using a suture device (Prostar XL, or Proglide, Abbott, Inc., Chicago, IL, USA) or surgically. The TA approach was facilitated by anterior minithoracotomy. Prostheses were retrogradely or antegradely crossed using super stiff wire and positioned with the aid of aortic root angiography. All subjects received aspirin (≥ 160 mg daily) and clopidogrel (300 mg loading dose, then 75 mg daily) prior to vascular access and aspirin alone for at least one month thereafter.
Trans-thoracic Echocardiography

Complete echocardiographic studies were performed for each patient in a standard fashion. Standard parameters were recorded. Left ventricular (LV) function, left ventricular outflow tract diameter, and aortic annulus diameter were obtained. To assess the severity of AS peak aortic velocity, peak and mean transaortic gradient, and velocity-time integral were measured. Aortic valve area was estimated using the continuity equation method.

Clinical Follow-up

Causes of death were classified as non-cardiovascular: including infection, respiratory failure, renal failure, hepatic failure, multiorgan failure, malignancy, traumatic accident, suicide and other (e.g., gastrointestinal problem, anemia, anorexia, dehydration); or cardiovascular: including myocardial infarction, heart failure, pulmonary embolism, stroke, vascular and rhythmic deaths.

Temporal Analysis

Because the registry took place over a long period temporal analyses of the results, in particular the occurrence of post-procedural AR and the relationship between post-procedural AR and mortality, were performed. For this purpose the consecutive patients are each site were divided into tertiles according to the date of procedure and the first, second and third tertiles of each site were pooled together (all first tertiles together, all second together, all third together). This new variable was named “Experience at each center”, the first tertile was named “Early experience”, the second “Mid experience” and the last “late experience”.

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SUPPLEMENTAL RESULTS

Role of the type of endoprosthesis and delivery approach on post-procedural-AR: Results after exclusion of patients receiving a 29mm-BE device

Because during the time of the registry, the 29-mm device was available for non-femoral delivery but not for femoral delivery. these results of the analysis presented in Figure 2 were repeated after exclusion of all patients treated with a 29-BE device (n=63). These results are presented in Supplemental Figure 1. As can be seen, after exclusion of patients receiving the 29 mm BE, the rate of AR ≥ grade 2 in patients treated through the non-femoral approach increased from 9.6% to 10.3%. Nevertheless, this remained significantly lower compared to patients treated through the femoral approach (14.3%, p=0.01).

Role of the type of endoprosthesis and delivery approach on post-procedural-AR: A temporal analysis

The temporal analysis of the rate of AR post-procedural AR ≥ Grade 2 according to the “Experience at each center” demonstrates that the rate of AR post-procedural AR ≥ Grade 2 did not change significantly overtime (“Early experience”=14.1%, “Mid experience” = 18.0%, “Late experience” =15.3%; p=0.31). Addition of the variable “Experience at each center” in the multivariable analysis of the predictors of post-procedural AR ≥ Grade 2 did not modify the results.

The role of “Experience at each center” on the relation between the rate of post procedure AR post-procedural AR ≥ Grade 2 and the type of device and access route is presented in Supplemental Figure 2. As can be seen, in each tertile the pattern was consistent with the one observed in the whole population: 1) the use of a SE device was associated with more AR post-procedural AR ≥ Grade 2 than the use of a BE device and 2) the use of a femoral approach was associated with more AR post-procedural AR ≥ Grade 2 than the use of non-femoral approach.
**Impact of aortic regurgitation on mortality: a temporal analysis**

An analysis of the impact AR post-procedural AR≥Grade 2 on mortality in each of the 3 tertiles of “Experience at each center” was performed and is presented as Supplementary Figure 3. As can be seen, in each tertile the presence of AR post-procedural AR≥Grade 2 was associated with a more than 2-fold increase in mortality (HR > 2.20).

A trend for a decrease in mortality was observed overtime in our study population. The 1-year actuarial mortality decreased from 14.9% (in the 1st tertile) to 11.6% (in the 3rd tertile, p=0.13). This was concomitant to a significant change in risk profile illustrated by the progressive decrease in Logistic Euroscore overtime: from 22.5% (in the 1st tertile) to 20.1% (in the 3rd tertile, p for trend=0.0005). Because of this association the variable “Experience at each center” was not identified as an independent predictor of mortality and its addition to the multivariable analysis of the predictors of mortality did not modify the results.
SUPPLEMENTAL FIGURE LEGENDS

Supplemental Figure 1: Occurrence of aortic regurgitation ≥ grade 2 according to the type of device (BE vs. SE) and to the type of delivery approach (femoral vs. non-femoral) after exclusion of patients receiving a 29mm BE device.

Supplemental Figure 2: Occurrence of aortic regurgitation ≥ grade 2 according to the type of device (BE vs. SE) and to the type of delivery approach (femoral vs. non-femoral). Results are presented for each tertile of experience: “Early”, “Mid” and “Late”.

Supplemental Figure 3: One-year total mortality rate according to post-procedural aortic regurgitation ≥ grade 2. Results are presented for each tertile of experience: “Early”, “Mid” and “Late”. In each tertile, Hazard Ratio (HR) for mortality associated with the occurrence post-procedural aortic regurgitation ≥ grade 2 is presented.
Supplemental material Figure 1

% of patients with self-expanding femoral and non-femoral stents, and balloon expandable femoral and non-femoral stents, classified by grade:

- Self-expanding femoral: 23.8%, N=731 (81%)
- Self-expanding non-femoral: 10.7%, N=166 (19%)
- Balloon-expandable femoral: 14.3%, N=1354 (72%)
- Balloon-expandable non-femoral: 10.3%, N=518 (28%)

P-values:
- P=0.0001
- P=0.0005
- P=0.01
Supplemental material - Figure 2

- Early experience
  - SE-femoral: 23.5%
  - SE-non-femoral: 7.5%
  - BE-femoral: 11.3%
  - BE-non-femoral: 9.2%
- Mid experience
  - SE-femoral: 25.4%
  - SE-non-femoral: 15.7%
  - BE-femoral: 16.8%
  - BE-non-femoral: 11.9%
- Late experience
  - SE-femoral: 22.5%
  - SE-non-femoral: 8.3%
  - BE-femoral: 14.7%
  - BE-non-femoral: 7.5%

P-values:
- P=0.0001
- P=0.004
- P=0.005
- P=0.01
- P=0.54
- P=0.13
- P=0.14
- P=0.02
- P=0.005
- P=0.004
- P=0.0001
Supplemental material – Figure 3

« Early experience »

HR=2.20 (1.45-3.32)
P=0.0002

« Mid experience »

HR=2.20 (1.45-3.32)
P=0.0002

« Late experience »

HR=2.76 (1.65-4.63)
P<0.0001

Days Post-proc. AR ≥ grade 2

Days Post-proc. AR < grade 2

Mortality, %

Patients at risk:

No -AR
AR
Total

No -AR
AR
Total

No -AR
AR
Total

No -AR
AR
Total