Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Transcatheter Aortic Valve Replacement for Degenerated Transcatheter Aortic Valves

The TRANSIT International Project

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BACKGROUND: Transcatheter aortic valve replacement (TAVR) has determined a paradigm shift in the treatment of patients with severe aortic stenosis. However, the durability of bioprostheses is still a matter of concern, and little is known about the management of degenerated TAV. We sought to evaluate the outcomes of patients with a degenerated TAV treated by means of a second TAVR.

METHODS: The TRANSIT is an international registry that included cases of degenerated TAVR from 28 centers. Among around 40 000 patients treated with TAVR in the participating centers, 172 underwent a second TAVR: 57 (33%) for a mainly stenotic degenerated TAV, 97 (56%) for a mainly regurgitant TAV, and 18 (11%) for a combined degeneration. Overall, the rate of New York Heart Association class III/IV at presentation was 73.5%.

RESULTS: Valve Academic Research Consortium 2 device success rate was 79%, as a consequence of residual gradient (14%) or regurgitation (7%). At 1 month, the overall mortality rate was 2.9%, while rates of new hospitalization and New York Heart Association class III/IV were 3.6% and 7%, respectively, without significant difference across the groups. At 1 year, the overall mortality rate was 10%, while rates of new hospitalization and New York Heart Association class III/IV were 7.6% and 5.8%, respectively, without significant difference across the groups. No cases of valve thrombosis were recorded.

CONCLUSIONS: Selected patients with a degenerated TAV may be safely and successfully treated by means of a second TAVR. This finding is of crucial importance for the adoption of the TAVR technology in a lower risk and younger population.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT04500964.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: bioprosthesis ■ heart failure ■ transcatheter aortic valve replacement

See Editorial by Barbanti and Costa

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The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCINTERVENTIONS.120.010440.

For Sources of Funding and Disclosures, see page 638.

Circulation: Cardiovascular Interventions is available at www.ahajournals.org/journal/circinterventions

WHAT IS KNOWN

- Structural valve deterioration rarely occurs after transcatheter aortic valve replacement (TAVR).
- Considering the growing number of patients treated by means of TAVR, structural valve deterioration will become more frequent.
- The treatment of a degenerated TAV is still poorly investigated.

WHAT THE STUDY ADDS

- A second TAVR can be safely and successfully performed.
- The type of degenerated TAVR and the anatomy of the aortic root pose patient-specific issues (ie, coronary obstruction/sinus sequestration/difficult coronary access and patient-prosthesis mismatch).

Nonstandard Abbreviations and Acronyms

AR	aortic regurgitation
AS	aortic stenosis
CO	coronary obstruction
HR	hazard ratio
NYHA	New York Heart Association
PPM	patient-prosthesis mismatch
SVD	structural valve deterioration
TAV	transcatheter aortic valve
TAVR	transcatheter aortic valve replacement
VARC-2	Valve Academic Research Consortium 2
VIF	variance inflation factor

Transcatheter aortic valve replacement (TAVR) has determined a paradigm shift in the treatment of patients with severe aortic stenosis, at any level of surgical risk.[1–6] However, the durability of TAVR bioprostheses is still a matter of concern, although recent data show encouraging results at long-term follow-up.[7]

Although the rate of structural valve deterioration (SVD) and of bioprosthetic valve failure is very low,[7] it is likely that the expanding adoption of TAVR, in particular to patients with longer life expectancy, will result in an increasing number of degenerated TAV.[8]

In this scenario, a second TAVR is an obvious and intriguing option, however, its outcome is not yet fully elucidated.[9]

We thus sought to evaluate in a multicenter, international registry, the mode of failure of the index TAVR, the prosthesis selection criteria for the second TAVR, and its procedural and clinical outcomes.

METHODS

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

The TRANSIT project (Transcatheter aortic valve replacement for degenerated transcatheter aortic valves) is an investigator-initiated registry that started collecting data in January 2020. More than 60 centers worldwide have been initially contacted, however, 32 could not participate due to the lack of suitable cases despite a large volume of TAVR. As such, a final group of 28 centers took part to the project: 22 in Europe, 4 in North America, 1 in South America, and 1 in the Middle East. Among a total number of about 40 000 procedure performed since 2008, 172 cases of consecutive TAVR for a degenerated transcatheter aortic valve (TAV) have been collected.

Data concerning the first TAVR have been collected with a specific focus on the procedural results, echocardiographic parameters after the first TAVR, and mode of failure at last available follow-up before the second TAVR, as well as on the possible presence of patient-prosthesis mismatch (PPM). For the latter, we focused on the selection criteria of the specific type of transcatheter bioprosthesis as well as on the procedural results. Data concerning the last available follow-up thereafter were also collected. The study was approved by an institutional review committee and the subjects gave informed consent.

Definitions

The principal investigator at each center took responsibility of the data collection regarding the baseline demographics, clinical, and echocardiographic features, as well as of procedural and follow-up data. Importantly, cases of TAVR in TAVR due to a suboptimal implantation and result of the index TAVR (eg, implantation too deep or too high, insufficient expansion and so on) were not considered, as such, this registry exclusively collected cases of degenerated TAV which have been evaluated according to mode of failure (mainly stenotic, mainly regurgitant, and mixed cause when the 2 conditions were both at least moderate).

The Valve Academic Research Consortium 2 (VARC-2) definitions were adopted for procedural and clinical end points,[8] along with a modified classification of the European Society of Cardiology–European Association of Cardio-Thoracic Surgery consensus document described by Testa et al[7] for the definitions of SVD and bioprosthetic valve failure.

PPM after the first TAVR was classified on the basis of the discharge echocardiographic Effective Orifice Area (calculated with the continuity equation) Indexed to body surface area as severe (<0.65 cm^2/m^2), moderate (0.65–0.85 cm^2/m^2), or none (>0.85 cm^2/m^2).[8]

Statistical Analysis

Descriptive statistics are reported as mean and SD for normally distributed continuous variables, as median and 25th to 75th percentile otherwise. Absolute and relative frequencies are reported for categorical variables. For continuous variables, the comparisons were done either with ANOVA or with a nonparametric test (Kruskal-Wallis). For categorical variables, comparisons among groups were done with χ^2 tests or Fisher exact tests. All cause and CV death were reported using Kaplan–Meier estimates together with their 95% CI. Echocardiographic data have been reported throughout the

overall follow-up by means of the most appropriate graphical representation. In addition, mean gradients and aortic regurgitation (AR) were presented in paired analysis for all time points after procedure and at postprocedure and longest follow-up. Wilcoxon signed rank-sum test was used for comparison of echo parameters in paired analyses. The cumulative incidences of clinical events at follow-up were assessed with the Kaplan-Meier method and log-rank test.

Parameters with a *P* value of <0.1 in the univariable analysis were included in the multivariable model with a forward likelihood ratio method. The variables tested at univariable analysis were age >75, male gender, end stage renal disease, chronic obstructive pulmonary disease, nontransfemoral access, age (per 10-year increase), reduced left ventricle ejection fraction (per 10% decrease), postprocedural mean gradient ≥20 mm Hg, residual AR ≥moderate, stenotic degenerated TAV, regurgitant degenerated TAV, mixed cause degenerated TAVR, degenerated TAV size <23.

Collinearity was evaluated with VIF (variance inflation factors), and parameters with a VIF of >5 were not included in the multivariable analyses. Proportional-hazards assumption was confirmed through testing based on Schoenfeld residuals. Multivariable correlates are presented as hazard ratios (HRs) and 95% CIs. A 2-sided *P* value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 23 (IBM Corporation, Armonk, New York, NY)

RESULTS

Among around 40 000 patients treated in the participating centers since the beginning of the TAVR program, 172 were treated for a degenerated TAVR. All patients had device success at the first TAVR implantation according to VARC-2 definitions, that is, no cases of high (>20 mm Hg) mean residual gradient nor of AR >1 were included.[8] Patients were grouped and analyzed according to the type of degeneration, as such, 57 (33%) had a mainly stenotic degenerated TAV, 97 (56%) a mainly regurgitant TAV, 18 (11%) a combined degeneration (Table 1). Six patients have been treated within a year since the first TAVR.

Overall, mean age was 79.9±7.9 and the male gender was slightly more frequent (57.6%) while the rate of New York Heart Association (NYHA) class III/IV was 73.5% with a consistent distribution across the groups. Euroscore I was 19.9±15.0, Euroscore II 8.8±3.4, and STS score 6.1±5.7 without statistically significant difference across the groups.

A moderate or severe PPM after the first TAVR was significantly less frequent in the group with a severely regurgitant TAV (Table 1). There was no difference in the time between the first and the second TAVR in patients with moderate PPM (597.5±132.2 days) or severe PPM (702±946.1) versus those without (980.6±906.7 days, *P*=0.4 and *P*=0.2, respectively).

Seven cases of valve thrombosis leading to a severe dysfunction of the first TAVR were recorded: 5 among patients presenting with a severely stenotic degenerated TAVR, 1 in the group of regurgitant TAVR, and 1 in the group with mixed cause. These patients were treated while on anticoagulation. The most frequent degenerated TAVR model was CoreValve (Medtronic, Minneapolis, MN; 84 [48%]) followed by Sapien XT (Edwards Lifesciences, Irvine, CA; 60 [35%]). Details concerning the valve size of the first and second TAVR are reported in Tables in the Data Supplement.

See Figure 1 for the mean and median time from implant to degeneration according to the valve type.

Procedural Results

For the second TAVR, the operators opted for a self-expanding valve in 104 cases (61%), the majority of them were Corevalve/Evolut (87, 83%). Of note, 53 (63%) cases of degenerated Corevalve were treated with an Evolut, 25 cases (29%) with an Edwards, while 33 cases (55%) of degenerated Edwards were treated with another Edwards, and 21 (35%) with an Evolut (See Tables in the Data Supplement). The choice of the second TAVR appears to be related to a case-by-case evaluation based on local experience and availability of the TAVR platforms. We could not find specific or generalizable criteria.

VARC-2 device success rate was 79%, as a consequence of residual gradient >20 mm Hg (24 patients, 14%) or AR >1+ (11 patients, 7%). No cases of valve malpositioning occurred. The group of patients with stenotic first TAV had a significantly higher residual mean gradient, while the group of regurgitant TAV had a significantly higher rate of AR >2 (Table 2).

Clinical Outcomes

In Hospital Events

The mortality rate was 4.1%, and all cases were due to cardiovascular causes without differences across the groups (Table 3). Overall, major vascular complications occurred in 2.3% of the cases, while the need for a permanent PM was 4.1%. The overall rate of cerebrovascular events was 3.5%, with a significant higher rate in the group with mixed degeneration, that is, 16.7%. An acute kidney injury occurred in 7% of the cases. No cases of valve thrombosis nor coronary obstruction (CO) were observed.

Thirty-Day Follow-Up

Cumulative overall mortality rate was 7%, no further cases of cardiovascular death were recorded (Table 4). Rates of NYHA class III/IV and hospitalization for HF were 7.0% and 3.6%, respectively, without differences across groups. No events of MI, stroke/TIA, CO were recorded after hospitalization (see Table 3), while 3 cases of valve thrombosis occurred (1.4%).

Table 1. Baseline Characteristics of the Study Population

Variables	Overall (N=172)	Stenosis (N=57)	Regurgitation (N=97)	Mixed (N=18)	*P* value
Age	79.9±7.9	77.5±8.8	77.9±7.2	79.4±8.8	0.669
Male	99 (57.6%)	28 (49.1%)	63 (64.9%)	8 (44.4%)	0.078
Hypertension	147 (85.5%)	50 (87.7%)	81 (83.5%)	16 (88.9%)	0.704
Dyslipidemia	114 (67.1%)	42 (73.7%)	59 (62.1%)	13 (72.2%)	0.300
Diabetes	48 (27.9%)	20 (35.1%)	23 (23.7%)	5 (27.8%)	0.357
Smoker	51 (29.7%)	17 (29.6%)	29 (30.1%)	5 (27.8%)	0.981
COPD	39 (22.7%)	18 (31.6%)	17 (17.5%)	4 (22.2%)	0.163
PM	54 (31.3%)	13 (22.8%)	35 (36.1%)	6 (33.3%)	0.185
Atrial fibrillation	63 (36.8%)	14 (24.6%)	42 (43.3%)	7 (38.9%)	0.076
Previous cardiac surgery	33 (19.4%)	10 (17.5%)	18 (18.6%)	5 (27.8%)	0.636
MI	43 (25.0%)	13 (22.8%)	25 (25.8%)	5 (27.8%)	0.882
Previous PCI	71 (41.3%)	27 (47.4%)	39 (40.2%)	5 (27.8%)	0.330
Severe renal failure	33 (19.2%)	10 (17.5%)	17 (17.5%)	6 (33.3%)	0.286
Creatinine	1.5±1.1	1.5±1.4	1.4±0.7	1.9±1.3	0.250
Dialysis	8 (4.7%)	3 (5.3%)	2 (2.1%)	3 (16.7%)	0.264
PAD	32 (18.6%)	10 (17.5%)	21 (21.6%)	1 (5.6%)	0.264
Stroke	9 (5.2%)	2 (3.5%)	6 (6.2%)	1 (5.6%)	0.770
NYHA III/IV	125 (73.5%)	39 (70.9%)	73 (75.3%)	13 (72.2%)	0.836
RBBB	8 (4.7%)	2 (3.5%)	6 (6.2%)	0 (0.0%)	0.510
LBBB	49 (28.5%)	17 (19.2%)	32 (33.0%)	6 (33.3%)	0.164
Euroscore I	19.9±15.0	21.0±17.0	18.1±13.1	24.7±17.0	0.266
Euroscore II	8.8 ±3.4	7.8±3.3	8.9±3.5	11.3±0.6	0.262
STS Score	6.1±5.7	6.0±4.1	5.8±5.4	8.3±9.8	0.307
SAPT	69 (40.1%)	26 (45.6%)	35 (36.1%)	8 (44.4%)	0.469
DAPT	47 (27.3%)	17 (29.8%)	27 (27.8%)	3 (16.7%)	0.543
NAO/Vka	56 (32.6%)	22 (21.1%)	26 (16.5%)	8 (33.3%)	0.243
Self-expanding TAVR	112 (65.1%)	30 (52.6%)	70 (72.2%)	12 (66.7%)	0.058
Balloon expanding TAVR	60 (34.9%)	27 (47.4%)	27 (27.8%)	6 (33.3%)	0.056
Moderate PPM	10 (5.8%)	6 (10.5%)	2 (2%)	2 (11.1%)	0.014
Severe PPM	5 (2.9%)	4 (7%)	0	1 (5.5%)	0.012

COPD indicates chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; LBBB, left bundle branch block; MI, myocardial infarction; NAO, novel oral anticoagulant; NYHA, New York Heart Association; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PM, pace maker; PPM, patient prosthesis mismatch; RBBB, right bundle branch block; SAPT, single antiplatelet therapy; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; and vKa, vitamin K antagonist.

One-Year Follow-Up

The cumulative overall mortality rate was 10%, with a cardiovascular mortality rate of 5.8% (Table 5 and Figure 2). The rate of NYHA class III/IV was 12.8% (Figure 3) while that of new hospitalization for HF was 11%.

No differences across the groups were detected. Of note, no further cases of valve thrombosis, MI, stroke, or valve dysfunction requiring new intervention were recorded.

In the multivariable analysis, nontransfemoral access (HR, 1.53 [95% CI, 1.18–1.89]), age (per 10-year increase HR, 1.21 [95% CI, 1.03–1.48]), reduced left ventricle ejection fraction (per 10% decrease, HR, 1.45 [95% CI, 1.16–1.58]), severe renal failure (HR, 1.40 [95% CI, 1.16–1.94]) were independently associated with decreased patient survival. Postprocedural mean gradient ≥20 mm Hg or residual AR ≥moderate were not independent predictors of mortality from discharge to 1 year.

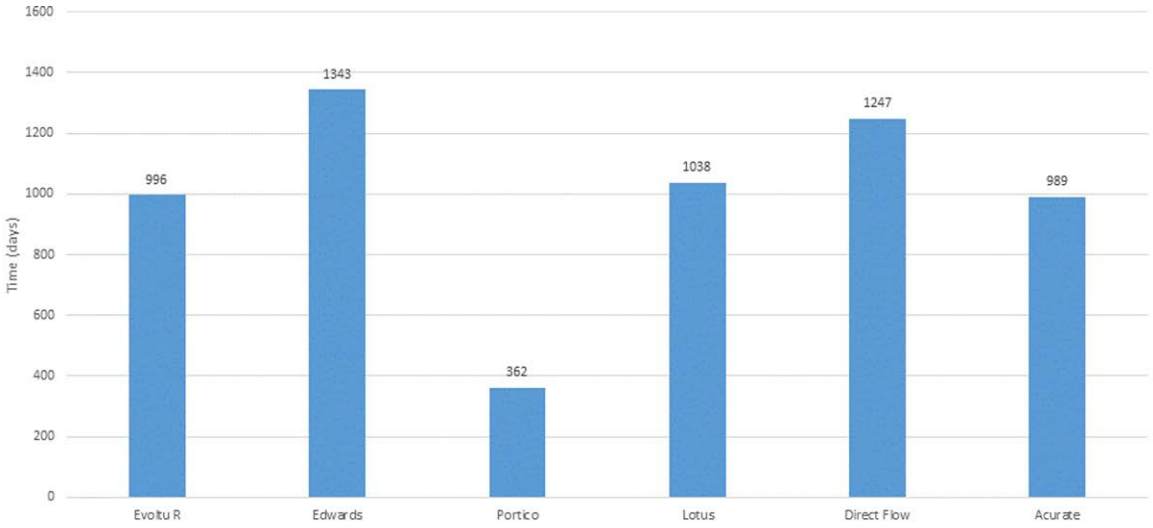
Clinical Events After 1 Year

The clinical events have been reported up to 6-year follow-up, although concerning a limited number of patients (see Table VII in the Data Supplement).

Echocardiographic Findings

Echocardiographic data were available for 90% of the patients at 1 year.

Figure 4 shows the comparison between baseline (before the second TAVR), discharge and last available echocardiographic follow-up with respect to the rate of AR. After the second TAVR, the rate of AR 2 to 3 was



	Evolut R	Edwards	Portico	Lotus	Direct flow	Acurate Neo
Mean time	996 ± 879.4	1343± 1056.1	362 ± 337.8	1038 ± 759.9	1247 ± 411.9	989 ± 1157
Median time	624 [257:1460]	1176 [385:2349]	268 [118:373]	712 [712:1826]	1323 [916:1553]	617 [64:1434]

Figure 1. Time from first to second transcatheter aortic valve replacement.
Corevalve Platform: 84 patients, Edwards-Sapien, Sapien S3, Sapien XT: 60 patients; Portico: 5 patients, Lotus: 5 patients, DirectFlow: 10 pts, Acurate: 8 patients.

12.7%, while, at 1 month and 1 year it was 7% and 8.1%, respectively.

In paired analysis, the mean transprosthetic aortic gradient decreased significantly from baseline, that is, before the second TAVR (25±19 mm Hg) to discharge (11±5 mm Hg, $P<0.001$) but did not significantly change from discharge throughout follow-up (Figure 5).

DISCUSSION

Moderate or severe SVD rarely occurs after TAVR,[7] but its management is scarcely studied. A second TAVR appears to be a reasonable approach although the evidence is still very limited.

The international TRANSIT project collected the largest available registry exclusively concerning degenerated TAVR.[9–12] No cases of unsuccessful (according to VARC-2 definition) first TAVR implantation were included.[9] The results can be summarized as follows:

1. A second TAVR procedure was associated with a 79% rate of device success according to VARC-2 criteria.
2. Cases of unsuccessful second TAVR were mostly related to a residual significant gradient in patients with a severely stenotic degenerated TAV.
3. Severe and moderate PPM were significantly more frequent in patients with a stenotic degenerated TAV.
4. Rates of all cause as well as cardiac mortality were low within 1-year follow-up (10% and 5.8%, respectively).
5. The clinical benefit of a second TAVR, in terms of NYHA class, is significant regardless the mechanism of failure of the first TAVR, and sustained at 1 year.
6. No cases of CO were observed.

The indication to TAVR will conceivably expand to younger and lower risk patients, following recent encouraging results.[5,6] As such, a population with longer life expectancy will presumably experience a higher rate of moderate or severe SVD than that available from the literature,[7] considering that data on SVD mostly relate to a traditional elderly TAVR population, at high or prohibitive surgical risk. Indeed, a clearer understanding of how to manage cases of degenerated TAV is needed.[9–12]

Clinical Presentation

Degenerated TAV almost invariably presented with signs and symptoms of heart failure as documented by the high rate of NYHA class III/IV, and the prevalent mode of failure was regurgitation (56%), differently from what Landes et al[9] reported. In their overall cohort, the modes of failure were almost equally divided in the 3 groups; on the contrary, they actually found in patients treated within 1 year from the first TAVR a very high rate of severe

Table 2. Procedural Data

Variables	Overall (N=172)	Stenosis (N=57)	Regurgitation (N=97)	Mixed (N=18)	*P* value
Transfemoral approach	158 (91.9%)	53 (93.0%)	88 (90.7%)	17 (94.4%)	0.809
Predilatation	36 (20.9%)	11 (19.3%)	20 (20.6%)	5 (27.8%)	0.738
Postdilatation	71 (41.3%)	24 (42.1%)	36 (37.1%)	11 (61.1%)	0.163
Contrast	95.3±57.1	98.4±68.9	95.4±53.6	83.4±25.4	0.708
Aortic dissection	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Annulus rupture	1 (0.6%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0.678
Valve embolization	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Myocardial infarction	1 (0.6%)	0 (0.0%)	0 (0.0%)	1 (5.6%)	0.014
Emergency surgery	1 (0.6%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0.678
Coronary obstruction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Stroke/TIA	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Cardiac tamponade	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Major vascular complication	3 (1.7%)	2 (3.5%)	1 (1.0%)	0 (0.0%)	0.440
Ventricular arrhythmias	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Self-expanding TAVR	104 (61)	38 (67%)	53 (55%)	13 (72%)	0.09
Balloon expanding	68 (39)	19 (33%)	44 (45%)	5 (18%)	0.05
Device success	137 (79.7%)	45 (78.9%)	76 (78.4%)	16 (88.9%)	0.587
Mean gradient, mm Hg	10.9±5.3	12.5±6.0	10.1±2.8	10.2±3.0	0.029
AR 0–1	150 (87.2%)	54 (94.7%)	79 (81.4%)	17 (94.4%)	0.001
AR 2	19 (11.0%)	2 (3.5%)	16 (16.5%)	1 (5.6%)	0.008
AR 3	3 (1.7%)	1 (1.8%)	2 (2.1%)	0 (0.0%)	0.303

In the stenosis group, all patients without a device success had a residual mean gradient >20 mm Hg; in the regurgitation group, all 5 patients had a residual mean gradient >20 mm Hg, the remaining 18 had a residual AR >2; in the mixed group, 1 patient had a residual AR >2, 4 had a residual mean gradient >20 mm Hg. AR indicates aortic regurgitation; TAVR, transcatheter aortic valve replacement; and TIA, transient ischemic attack.

regurgitation (73%). Of note, as explained by the authors, these cases were classified as possible first TAVR procedural failure, instead of a true degeneration. This may explain the difference between the 2 cohorts.

We observed a rate of baseline bioprosthetic valve thrombosis of 4%; however, a robust rate of clinical/subclinical leaflet thrombosis was not measurable as the computed tomography scan was not available in all cases.

In terms of transcatheter valve platform, a self-expanding valve, in particular, the first generation of the CoreValve is the most represented in this cohort and its most

Table 3. In-Hospital Events

Variables	Overall (N=172)	Stenosis (N=57)	Regurgitation (N=97)	Mixed (N=18)	*P* value
All cause mortality	7 (4.1%)	1 (1.8%)	5 (5.2%)	1 (5.6%)	0.55
Cardiovascular mortality	7 (4.1%)	1 (1.8%)	5 (5.2%)	1 (5.6%)	0.55
New onset LBBB	2 (1.2%)	0 (0.0%)	1 (1.0%)	1(5.6%)	0.157
Postprocedural LBBB	1 (0.6%)	0 (0.0%)	1 (1.0%)	0 (0.0%)	0.678
New onset AF	6 (3.5%)	4 (7.0%)	2 (2.1%)	0 (0.0%)	0.188
New PM	7 (4.1%)	5 (8.8%)	2 (2.1%)	0 (0.0%)	0.082
Stroke/TIA	6 (3.5%)	1 (1.8%)	2 (2.1%)	3 (16.7%)	0.006
Major vascular complications	4 (2.3%)	1 (1.8%)	3 (3.1%)	0 (0.0%)	0.683
Major bleeding (≥BARC-3a)	9 (5.2%)	5 (2.9%)	4 (2.3%)	0 (0.0%)	0.263
Life-threatening bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
MI	2 (1.2%)	0 (0.0%)	1 (1.0%)	1 (5.6%)	0.157
Valve thrombosis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
AKI (≥AKIN-2)	12 (7.0%)	2 (3.5%)	9 (9.3%)	1 (5.6%)	0.386
Sepsis	8 (4.7%)	2 (3.5%)	5 (5.2%)	1 (5.6%)	0.880

AF indicates atrial fibrillation; AKI, acute kidney injury; BARC, Bleeding Academic Research Consortium; LBBB, left bundle branch block; MI, myocardial infarction; PM, pace maker; and TIA, transient ischemic attack.

Table 4. Cumulative Rates of Clinical Events at 30-Day Follow-Up

Variables	Overall (N=172)	Stenosis (N=57)	Regurgitation (N=97)	Mixed (N=18)	*P* value
All cause death	12 (7.0%)	5 (8.8%)	6 (6.1%)	1 (5.6%)	0.179
Cardiovascular death	7 (4.1%)	1 (1.8%)	5 (5.2%)	1 (5.6%)	0.55
NYHA III/IV	12 (7.0%)	5 (8.8%)	7 (7.2%)	0 (0.0%)	0.457
Hospitalization for HF	6 (3.6%)	1 (2.0%)	4 (3.9%)	1 (7.1%)	0.646
MI	2 (1.2%)	0 (0.0%)	1 (1.0%)	1 (5.6%)	0.157
Stroke/TIA	6 (3.5%)	1 (1.8%)	2 (2.1%)	3 (16.7%)	0.006
Valve endocarditis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Valve thrombosis	3 (1.4%)	3 (4.3%)	0 (0.0%)	0 (0.0%)	0.140
Valve dysfunction requiring reintervention	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…

HF indicates heart failure; MI, myocardial infarction; NYHA, New York Heart Association; and TIA, transient ischemic attack.

frequent mode of failure seemed to be regurgitation. On the contrary, the degeneration of Edwards/Sapien valves tended to be equally distributed in stenosis or regurgitation. These data, however, do not infer on specific TAV platforms durability as this kind of analysis can only be done in a context of competing risk analysis.[7]

Patient Prosthesis Mismatch

A moderate or severe PPM after the first TAVR was more frequently associated with a stenotic degenerated TAV, while it was rarely observed in patients with a regurgitant first TAV: this finding was not previously reported in the literature,[9–12] and it is consistent with the physiopathology of the PPM as suggested since its first description by Rahimtoola.[14] Indeed, the mismatch between the hemodynamic performance of the prosthesis and the cardiac output requirements of the patient is largely related to the body size, and almost invariably leads to a stenotic prosthesis.

Key Procedural Observations

The second TAVR procedure was actually very safe considering the low rate of complications we observed, and the hemodynamic results were encouraging. The majority of the cases were treated with the same transcatheter valve platform (see Figure 6 for examples of same-platform second TAVR, and different–platform second TAVR). The rate of device success (79%) according to VARC-2 definition was lower than that of a traditional TAVR population,[1,2] mainly because of significant residual gradient: in some circumstances, a balloon aortic valvuloplasty alone to treat stenotic degenerated TAV might be considered; on the contrary, a surgical option to treat a degenerated TAV must obviously be weighted with its inherent risk of comorbidity and mortality.

Cerebral embolic protection devices may capture debris in the majority of patients undergoing TAVR.[13] We did not evaluate the use of cerebral embolic protection in this registry. Whether systematic use of cerebral embolic protection devices in the context of a failing transcatheter heart valve could reduce neurological event rate is intriguing and requires further study.

Clinical Benefit

Survival rate was very encouraging considering the clinical features of the population enrolled, reaching 10% at 1 year thus being quite consistent with the 11.7% of the late redo TAVR of the cohort of Landes et al[9] (Figure 2). The clinical benefit was also confirmed by the significantly improved NYHA classes distribution before and after the second TAVR (Figure 3). The neurological

Table 5. Clinical Events at 1-Year Follow-Up

Variables	Overall (N=172)	Stenosis (N=57)	Regurgitation (N=97)	Mixed (N=18)	*P* value
All cause death	17 (10.0%)	5 (8.6%)	10 (10.6%)	2 (11.1%)	0.942
Cardiovascular mortality	10 (5.8%)	1(1.8%)	8 (8.2%)	1 (5.6%)	0.535
NYHA III/IV	22 (12.8%)	6 (10.5%)	14 (14.4%)	2 (11.1%)	0.229
Hospitalization for HF	19 (11%)	8 (14%)	8 (8.2%)	3 (16.6%)	0.367
MI	2 (1.2%)	0 (0.0%)	1 (1.0%)	1 (5.6%)	0.157
Stroke	6 (3.5%)	1 (1.8%)	2 (2.1%)	3 (16.7%)	0.006
Valve endocarditis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…
Valve thrombosis	3 (1.4%)	3 (4.3%)	0 (0.0%)	0 (0.0%)	0.140
Valve dysfunction requiring reintervention	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	…

HF indicates heart failure; MI, myocardial infarction; and NYHA, New York Heart Association.

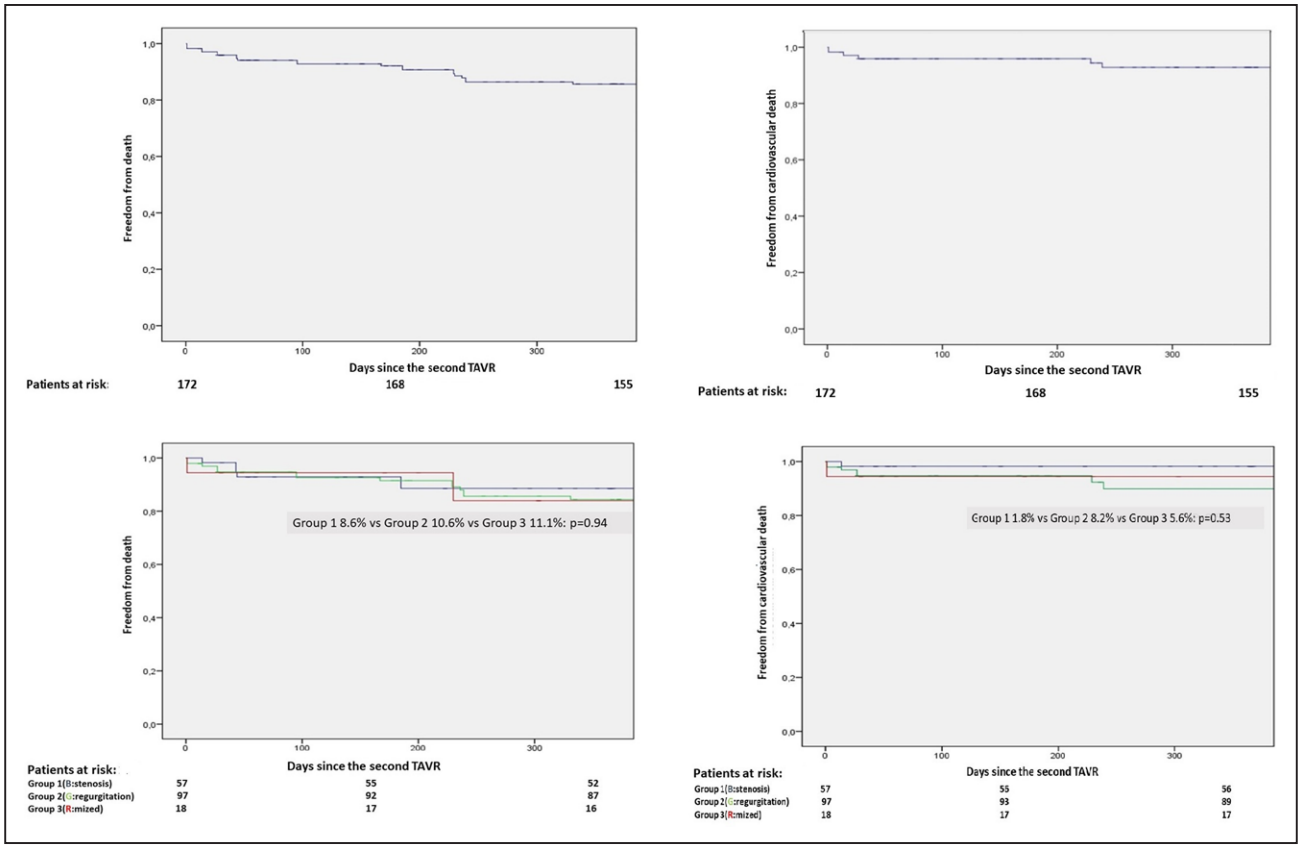


Figure 2. Survival analysis.
Top left: All cause mortality (overall). **Top right**: Cardiovascular mortality (overall). **Bottom left**: Overall mortality (subgroups). **Bottom right**: Cardiovascular mortality (subgroups). TAVR indicates transcatheter aortic valve replacement.

event rate was high in patients with a mixed mechanism of degeneration (Table 3): this signal should be evaluated in larger populations before deriving any conclusion.

Echocardiographic Findings

Echocardiographic parameters showed the expected reduction of moderate or severe AR after the second TAVR (Figure 4), as well as of the mean aortic gradient, and these results persisted at 1 year (Figure 5).

Unanswered Questions and Avenues for Future Research

It is conceivable that a percentage of patients with a degenerated TAV might be unsuitable for a second TAVR, in particular, for technical/anatomic reasons: we did not observe any case of CO, however, it cannot be excluded that this is a consequence of a selection bias, that is, patients with a prohibitive risk of CO might have been rejected for a second TAVR. A recent study from Ochiai et al[15] tried to evaluate the risk of CO due to sinus sequestration in redo TAVR using post-TAVR computed tomography. Redo TAVR was considered at risk of CO due to sinus sequestration if (1) the prior TAV commissure level was above the sinotubular junction and (2) the distance between TAV and sinotubular junction was <2.0 mm in each coronary sinus. The combination of a low sinotubular junction and high TAV commissures was found to increase the risk of CO. This conclusion, however, must be contextualized as it is based on a computed tomography scan derived model, not on clinical data. Moreover, in the setting of a degenerated TAVR, the risk of CO, a potentially lethal complication, should be evaluated along with the risk of coronary flow impairment and difficult/impossible coronary access[16]: it seems logic that small anatomies and self-expanding with high leaflet commissures TAV platforms might be the worst combination, however, self-expanding transcatheter aortic bioprostheses, with larger effective orifice areas, might potentially be associated with better durability.[17]

The PPM after a second TAVR should also be further investigated, as it will conceivably be even more relevant than after the first TAVR: theoretically, the balloon expandable platforms to treat a degenerated balloon expandable platform in a small anatomy seem to be the worst combination, however, as mentioned above, the issue of CO cannot be neglected, especially when evaluating a self-expanding platform to treat a degenerated TAV.

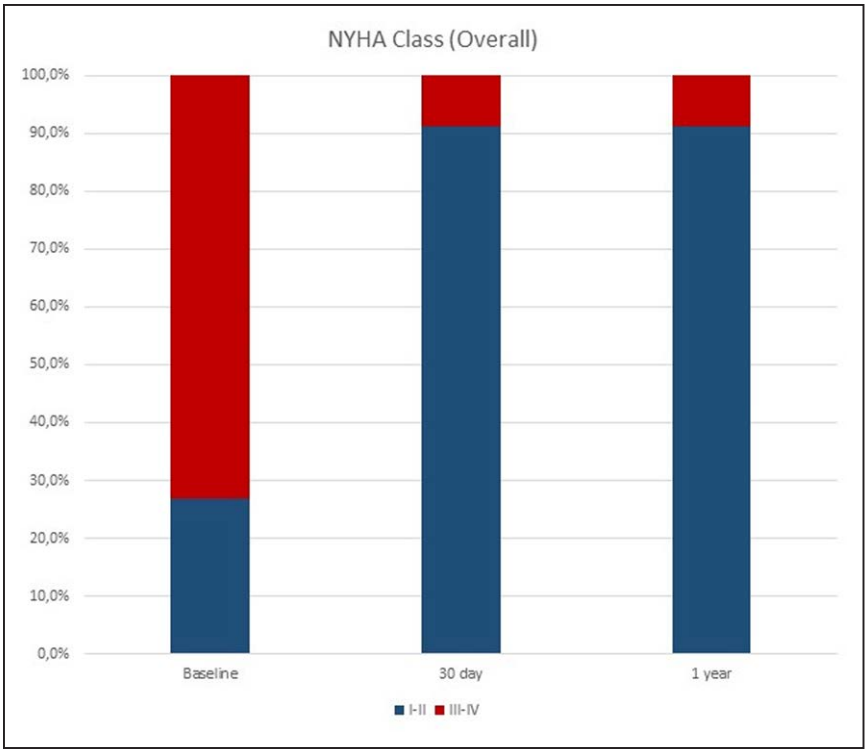


Figure 3. New York Heart Association (NYHA) class distribution before the second transcatheter aortic valve replacement, after and at follow-up.

Overall, a tailored approach at the time of the first TAVR, that is, when the aortic valve journey begins, is becoming critically important and the development of implantation techniques aiming at the commissure-to-commissure alignment should be pursued to minimize the subsequent risk of CO, coronary flow impairment and difficult coronary re-access.

This should also be kept into account in future TAV platforms iterations.

Finally, further research is needed to better depict the distinctive role of a second TAVR, the surgical approach despite its high mortality,[18] the balloon aortic valvuloplasty, and the optimized medical therapy.

Limitations

This is an investigator-initiated registry that involved high-volume centers in 3 continents, however, no central

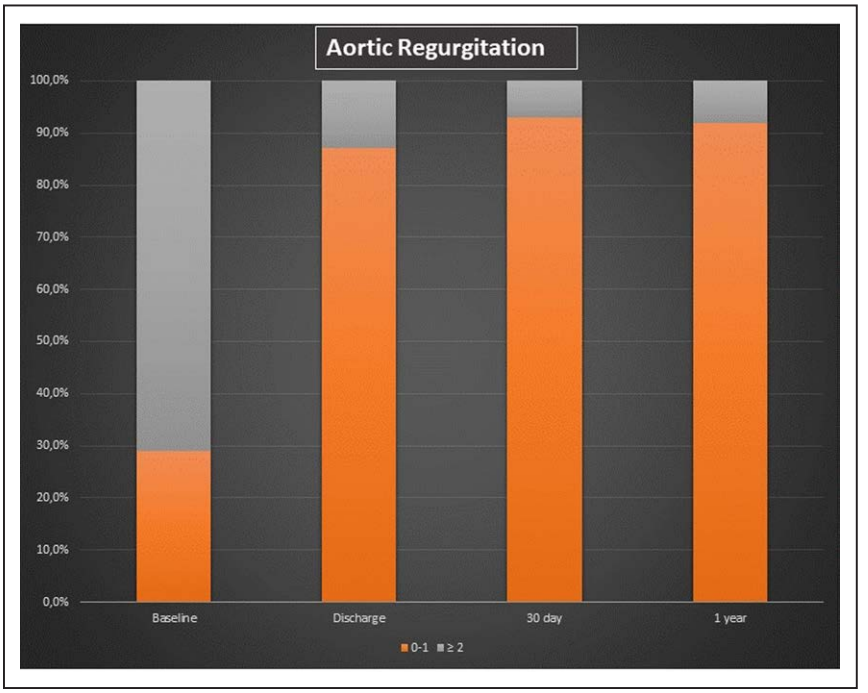


Figure 4. Temporal change of aortic regurgitation before the second transcatheter aortic valve replacement (TAVR), after the second TAVR, and at follow-up.

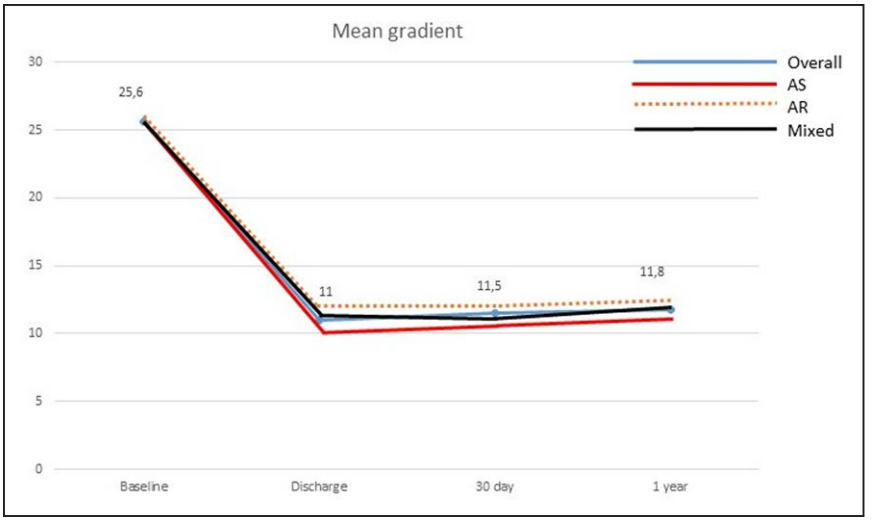


Figure 5. Temporal change of mean transaortic gradient before the second transcatheter aortic valve replacement (TAVR), after the second TAVR, and at follow-up.
Numbers are reported for the overall population (baseline: 25.6±12 mm Hg; discharge: 11±4 mm Hg; 30-day FU: 11.5±5 mm Hg; 1-year FU: 11.8±5 mm Hg). AR indicates aortic regurgitation; and AS, aortic stenosis.

adjudication of events has been performed, and we cannot rule out that results might be different in less experienced centers.

An Echo Core Lab is also lacking and the echo data have been collected by the participating centers: as such a reliable distinction between central AR and PVL was not possible. Likewise, a detailed analysis of PPM after the second TAVR was also unfeasible. A computed tomography scan analysis was not available in the majority of the cases, thus making the complete assessment of leaflet thrombosis actually impossible. As clearly stated, patients come from different countries and were treated with different devices thus mirroring the current real-world practice, however, differently from previous reports, they were all treated because of a degenerated TAV, that is, this is a relatively homogeneous population.

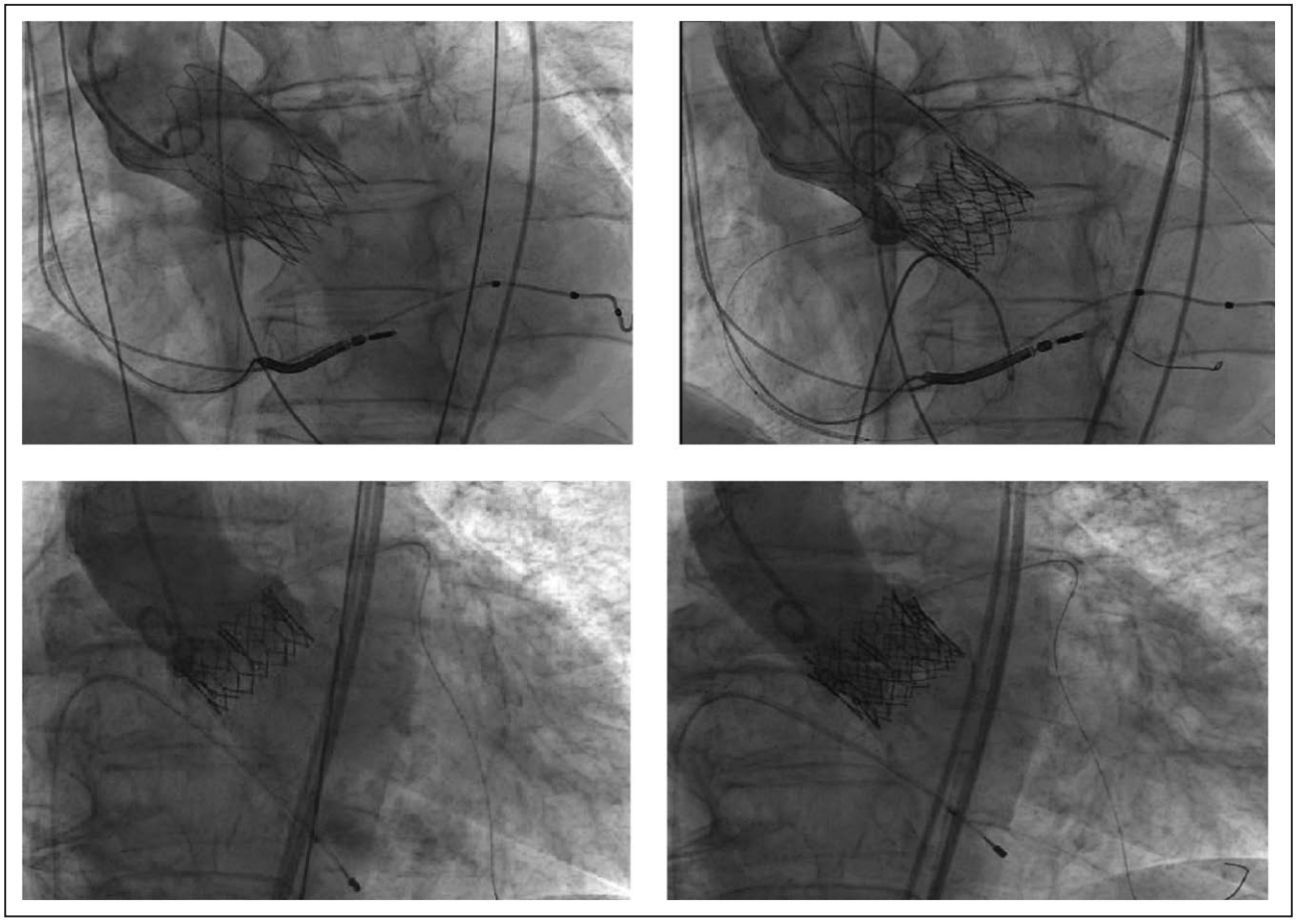


Figure 6. Examples of transcatheter aortic valve replacement (TAVR) in TAVR with same platform vs different platform.
Top left: Aortogram showing a severely regurgitant Acurate Neo valve, treated by means of MyVal (**top right**). **Bottom right**: Case of severely regurgitant Edwards Sapien XT, treated by means of an Edwards Sapien XT (**bottom right**).

This registry did not consider those patients who were rejected for a second TAVR because of prohibitive risk of CO and treated surgically.

Conclusions

Selected patients with a degenerated TAV may be safely and successfully treated by means of a second TAVR. Notwithstanding some unanswered questions needing further investigations, these findings are of crucial importance for the adoption of the TAVR technology in a lower surgical risk and younger population.

ARTICLE INFORMATION

Received October 2, 2020; accepted February 25, 2021.

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Acknowledgments

We would like to thank all the colleagues who participated in the data collection.

Sources of Funding

None.

Disclosures

None.

Supplemental Materials

Online Tables I–IV

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