ORIGINAL INVESTIGATIONS

Transcatheter Replacement of Transcatheter Versus Surgically Implanted Aortic Valve Bioprostheses

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ABSTRACT

BACKGROUND Surgical aortic valve replacement and transcatheter aortic valve replacement (TAVR) are now both used to treat aortic stenosis in patients in whom life expectancy may exceed valve durability. The choice of initial bioprosthesis should therefore consider the relative safety and efficacy of potential subsequent interventions.

OBJECTIVES The aim of this study was to compare TAVR in failed transcatheter aortic valves (TAVs) versus surgical aortic valves (SAVs).

METHODS Data were collected on 434 TAV-in-TAV and 624 TAV-in-SAV consecutive procedures performed at centers participating in the Redo-TAVR international registry. Propensity score matching was applied, and 330 matched (165:165) patients were analyzed. Principal endpoints were procedural success, procedural safety, and mortality at 30 days and 1 year.

RESULTS For TAV-in-TAV versus TAV-in-SAV, procedural success was observed in 120 (72.7%) versus 103 (62.4%) patients (p = 0.045), driven by a numerically lower frequency of residual high valve gradient (p = 0.095), ectopic valve deployment (p = 0.081), coronary obstruction (p = 0.091), and conversion to open heart surgery (p = 0.082). Procedural safety was achieved in 116 (70.3%) versus 119 (72.1%) patients (p = 0.715). Mortality at 30 days was 5 (3%) after TAV-in-TAV and 7 (4.4%) after TAV-in-SAV (p = 0.570). At 1 year, mortality was 12 (11.9%) and 10 (10.2%), respectively (p = 0.633). Aortic valve area was larger (1.55 ± 0.5 cm^2 vs. 1.37 ± 0.5 cm^2; p = 0.040), and the mean residual gradient was lower (12.6 ± 5.2 mm Hg vs. 14.9 ± 5.2 mm Hg; p = 0.011) after TAV-in-TAV. The rate of moderate or greater residual aortic regurgitation was similar, but mild aortic regurgitation was more frequent after TAV-in-TAV (p = 0.003).

CONCLUSIONS In propensity score–matched cohorts of TAV-in-TAV versus TAV-in-SAV patients, TAV-in-TAV was associated with higher procedural success and similar procedural safety or mortality. (J Am Coll Cardiol 2021;77:1–14) © 2021 by the American College of Cardiology Foundation.

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**ABBREVIATIONS
AND ACRONYMS**

AR = aortic regurgitation

AS = aortic stenosis

IQR = interquartile range

SAV = surgical aortic valve

TAV = transcatheter aortic valve

TAVR = transcatheter aortic valve replacement

All bioprosthetic aortic valves, whether transcatheter aortic valves (TAVs) or surgical aortic valves (SAVs), can be expected to degenerate over time. Transcatheter aortic valve replacement (TAVR) has become a key treatment for failed SAVs (TAV-in-SAV) and was also shown to be effective and safe for failed TAVs (TAV-in-TAV) (1,2). For native aortic stenosis (AS), TAVR is increasingly being considered as an option in "low surgical risk," otherwise healthy patients (3,4). In patients in whom life expectancy may exceed bioprosthetic valve durability, the choice of initial prosthesis must consider the relative safety and efficacy profiles of potential subsequent interventions. The aim of this study was to compare TAV-in-TAV with TAV-in-SAV in multicenter, propensity-matched cohorts of patients.

METHODS

REGISTRY DESIGN. Redo-TAVR is an investigator-initiated registry commenced in February 2019, designed to collect data on patients who undergo second "redo" TAVR procedures within dysfunctional TAVs, regardless of TAV type (2). A total of 37 centers from Europe, North America, and the Middle East contributed their patient-level data using a dedicated case report form. All consecutive TAV-in-TAV procedures performed at each of the 37 centers were included. For the purpose of this study, data on consecutive patients who underwent TAV-in-SAV during the same period were collected from 13 participating centers. For each valve, implantation date, model, and size were collected. Baseline aortic valve area, mean and maximal gradients, and degree and mechanism of regurgitation were gathered from echocardiographic studies prior to the index procedure and at 30 days and 1 year later. Echocardiographic data from transthoracic echocardiography were site reported according to established guidelines (5). Baseline echocardiographic and multidetector computed tomographic images were transferred and collected into a library of TAV-in-TAV procedures for further core laboratory analysis. The internal diameter of a surgical valve was derived from its label size and manufacturer charts. In cases for which label size was unknown, internal diameter was defined according to available imaging modes, such as computed tomography or echocardiography (6). Inconsistencies were resolved directly by communicating with the local investigators. The inclusion of patients was approved at each center by a local ethics committee.

ENDPOINTS AND DEFINITIONS. Baseline demographics, clinical and echocardiographic features, and procedural and follow-up data were collected by the co-investigators at each institution. Data collection and monitoring regarding the outcomes were assessed according to the Valve Academic Research Consortium-2 definitions (5).

Principal efficacy endpoints were defined as procedural success (a 30-day composite including freedom from mortality, freedom from intervention related to the device or to a major vascular or cardiac structural complication, and technical success with intended

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performance of the valve [mean gradient <20 mm Hg and less than moderate aortic regurgitation (AR)]) and mortality at 30 days and 1 year. The principal safety endpoint was a composite of all-cause mortality, all stroke, major bleeding, major vascular complication, cardiac structural complication (coronary obstruction, annular rupture, and cardiac tamponade), acute kidney injury, moderate or severe AR, new permanent pacemaker, and surgery or intervention related to the device at 30 days. Secondary endpoints included key Valve Academic Research Consortium-2–defined outcomes.

Indications for TAV-in-TAV and TAV-in-SAV were categorized according to the standardized definitions of structural valve degeneration and valve dysfunction mechanism as pure AS, combined AS and AR, or pure AR. Patients with at least a moderate degree of both AS and AR were included in the combined group (7).

A supplementary subgroup analysis categorized patients according to their primary valve label size as small (≤21 mm for surgical valves and ≤23 mm for transcatheter valves), intermediate (>21 and <25 mm for surgical valves and >23 and <29 mm for transcatheter valves), or large (≥25 mm for surgical valves and ≥29 mm for transcatheter valves) to allow 3 tertiles distribution of each cohort (1). A sensitivity analysis was applied using patients who presented to TAV-in-TAV 1 year or later after their first TAVR (2).

STATISTICAL ANALYSIS. Given the possible differences in baseline clinical, echocardiographic, and procedural characteristics between TAV-in-TAV and TAV-in-SAV patients, propensity score matching was applied to identify a cohort of patients with similar characteristics, and thus, clinical outcomes of propensity score-matched cohorts were compared. The propensity score was estimated from a non-parsimonious logistic model to form a sample consisting of pairs of TAV-in-TAV and TAV-in-SAV patients by the nearest neighbor matching algorithm with a caliper of 0.2. All clinical variables (age, sex, body surface area, New York Heart Association functional class, hypertension, diabetes mellitus, estimated glomerular filtration rate, peripheral vascular disease, prior cerebrovascular accident, chronic lung disease, prior percutaneous coronary intervention, prior coronary artery bypass graft, left ventricular ejection fraction, mean aortic valve gradient, and bioprosthesis failure mechanism) as well as procedural data (procedural access and device type [early vs. newer generation, balloon- vs. self-expanding mechanism]) were incorporated in the analysis. For all patients, body surface area was calculated usi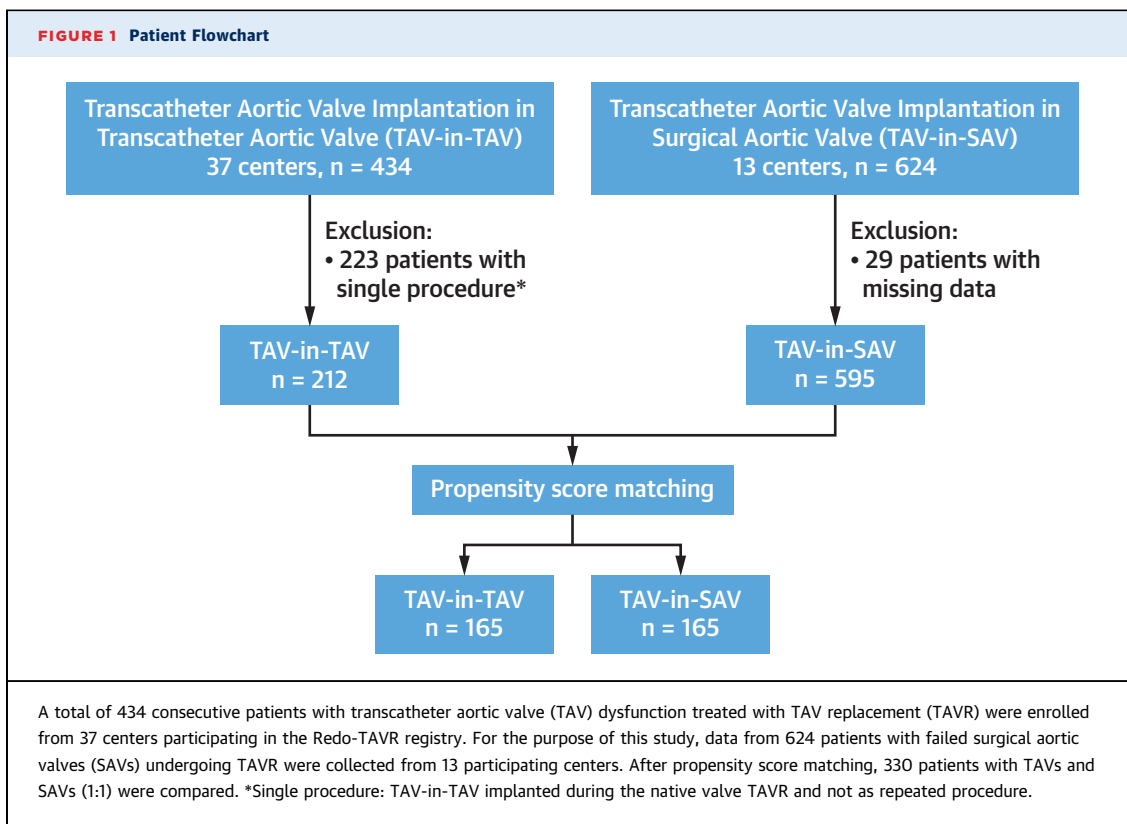ng the Mosteller formula (8). TAVs were classified as early-generation (SAPIEN XT [Edwards Lifesciences, Irvine, California], CoreValve [Medtronic, Minneapolis, Minnesota], and Lotus [Boston Scientific, Natick, Massachusetts]) or newer generation (all other models) devices.

Results are presented as mean ± SD for normally distributed continuous variables, as median (interquartile range [IQR]) for non-normally distributed continuous variables, and as number (percentage) for categorical data. Student's *t*-test was used to compare normally distributed continuous variables, and the Wilcoxon rank sum test was used for variables not normally distributed. The chi-square and Fisher exact tests were used to compare categorical variables. The cumulative incidence of time-to-event outcomes was estimated using the Kaplan-Meier method, and the median duration of follow-up was calculated on the basis of the method of reverse Kaplan-Meier. A 2-sided p value <0.05 was considered to indicate statistical significance. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

BASELINE CHARACTERISTICS. Among 63,876 TAVR patients treated at the 37 participating centers between April 2005 and April 2019, 434 (0.68%) had previously undergone TAVR. Among these consecutive cases, 223 procedures were done as urgent "bailout" procedures at the time of native valve TAVR and another 212 (49%) as redo TAVR 2 days to 11.6 years (median 3 years; IQR: 0 to 5 years) after the native valve TAVR. During the same period, a total of 624 consecutive patients were treated with TAV-in-SAV 9 years (IQR: 6 to 12 years) after the surgery across 13 participating centers. Patients who underwent "bailout" TAV-in-TAV (n = 223) and those with missing 30 day follow-up data (n = 10) were excluded from the analysis. Consequently, 212 TAV-in-TAV and 595 TAV-in-SAV patients were included (**Figure 1**).

Patients' baseline characteristics are presented in **Table 1**. In the unadjusted cohorts, TAV-in-TAV patients presented with lower mean aortic valve gradient (25 mm Hg [IQR: 11 to 44 mm Hg] vs. 35 mm Hg [IQR: 23 to 45 mm Hg]; p < 0.001) and were more likely to have moderate or greater AR (69.6% vs. 58.6%; p = 0.002). Both groups presented at similar age (80 years) and had similar Society of Thoracic Surgeons risk (7.0% among TAV-in-TAV patients and 6.82% among TAV-in-SAV patients; p = 0.613). TAV-in-TAV patients were more likely to be considered frail (41.2% vs. 24.6%; p < 0.001) and to have multiple

FIGURE 1 Patient Flowchart

A total of 434 consecutive patients with transcatheter aortic valve (TAV) dysfunction treated with TAV replacement (TAVR) were enrolled from 37 centers participating in the Redo-TAVR registry. For the purpose of this study, data from 624 patients with failed surgical aortic valves (SAVs) undergoing TAVR were collected from 13 participating centers. After propensity score matching, 330 patients with TAVs and SAVs (1:1) were compared. *Single procedure: TAV-in-TAV implanted during the native valve TAVR and not as repeated procedure.

comorbidities (i.e., diabetes, peripheral arterial disease, and severe pulmonary disease), excluding prior bypass surgery. The TAV-in-TAV and TAV-in-SAV procedures were done via transfemoral access in 88.6% versus 78.7% of patients (p = 0.002), using new-generation TAVs in 70% versus 65% (p = 0.366), and using self-expandable mechanisms in 48.3% versus 67.8% (p < 0.001), respectively. After performing propensity score matching, both groups were well matched, with no significant differences in baseline characteristics, excluding the difference in time between the first (native valve) and second (valve-in-valve) procedures (**Table 1, Figures 2 and 3**). Standardized differences <0.1 for all covariates in propensity score matching indicated balance between treatment and control groups. Detailed model scattering of the first and second valve types in each cohort is available in Supplemental Table 1.

PROCEDURAL AND 30-DAY OUTCOMES. Table 2 summarizes the procedural and 30-day outcomes of the 330 propensity score-matched patients. In TAV-in-TAV versus TAV-in-SAV patients, the rate of procedural success was 120 (72.7%) versus 103 (62.4%) (p = 0.045), respectively. The higher TAV-in-TAV success was driven by a lower frequency of a

residual high (≥20 mm Hg) aortic valve gradient (19 [14.6%] vs. 34 [21.5%]; p = 0.095), ectopic valve deployment (1 [0.6%] vs. 5 [3.3%]; p = 0.081), coronary obstruction (2 [1.2%] vs. 7 [4.2%]; p = 0.091), and conversion to open heart surgery (0 vs. 3 [1.8%]; p = 0.082). At 30 days, aortic valve area was larger (1.55 ± 0.5 cm² vs. 1.37 ± 0.5 cm²; p = 0.040) and the mean residual gradient was lower (12.6 ± 5.2 mm Hg vs. 14.9 ± 5.2 mm Hg; p = 0.011) after TAV-in-TAV. The differences remained significant at 1 year (**Figure 4**).

Early safety was achieved in 116 TAV-in-TAV patients (70.3%) and 119 TAV-in-SAV patients (72.1%) (p = 0.715). Safety concerns that were numerically higher in the TAV-in-TAV cohort included major bleeding (17 [10.3%] vs. 8 [5.2%]; p = 0.061) and acute kidney injury (7 [4.2%] vs. 2 [1.3%]; p = 0.091). The rates of new permanent pacemaker placement and moderate or greater residual AR were 18 (10.9%) versus 12 (7.8%) (p = 0.251) and 10 (8.4%) versus 8 (4.8%) (p = 0.4629) in TAV-in-TAV versus TAV-in-SAV patients, respectively. Notably, the degree of mild AR was higher after TAV-in-TAV (49 [36.1%] vs. 21 [17.2%] [p = 0.003] at 30 days, 49 [36.2%] vs. 14 [12.1%] [p = 0.001] at 1 year). **Figure 5** shows the incidence and grade of residual AR.

TABLE 1 Baseline Characteristics of TAV-in-TAV and TAV-in-SAV Patients

	Before Propensity Score Matching			After Propensity Score Matching		
	TAV-in-TAV (n = 212)	TAV-in-SAV (n = 595)	p Value	TAV-in-TAV (n = 165)	TAV-in-SAV (n = 165)	p Value
Age, yrs	80 (75–84)	80 (75–84)	0.614	80 (75–84)	79.72 (74–84)	0.517
Male	126 (59.7)	307 (54.0)	0.157	99 (60.0)	100 (60.6)	0.910
Body surface area, m^2	1.84 (1.72–1.97)	1.85 (1.71–2.00)	0.631	1.85 (1.74–1.98)	1.86 (1.72–2.02)	0.529
STS risk, %	7.0 (4.8–9.9)	6.82 (4.8–9.79)	0.613	6.83 (4.8–9.5)	6.5 (4.8–9.6)	0.931
Severe pulmonary disease	55 (26.1)	114 (20.1)	0.075	40 (24.2)	39 (23.6)	0.897
Diabetes	63 (29.9)	114 (20.1)	0.004	45 (27.3)	49 (29.7)	0.626
Coronary artery disease	109 (51.7)	290 (51.1)	0.881	85 (51.5)	86 (52.1)	0.912
Bypass surgery	48 (22.7)	172 (30.9)	0.025	43 (26.1)	46 (27.9)	0.710
Peripheral arterial disease	53 (25.1)	102 (18.0)	0.026	40 (24.2)	43 (26.1)	0.704
Atrial fibrillation/flutter	70 (33.2)	167 (29.8)	0.368	47 (28.5)	49 (29.7)	0.809
Estimated GFR, ml/min	49 (37–60)	46 (17–66)	0.028	49 (35–60)	50 (32–67)	0.662
Frailty	87 (41.2)	140 (24.6)	<0.001	61 (37.0)	58 (35.2)	0.731
NYHA functional class I	5 (2.4)	15 (2.6)	0.832	4 (2.4)	6 (3.6)	0.521
NYHA functional class II	38 (18.0)	111 (19.5)	0.629	33 (20.0)	30 (18.2)	0.674
NYHA functional class III	122 (57.8)	367 (64.6)	0.081	102 (61.8)	103 (62.4)	0.910
NYHA functional class IV	47 (22.3)	73 (12.9)	0.001	26 (15.8)	26 (15.8)	1.000
Aortic valve mean gradient	25 (11–44)	35 (23–45)	<0.001	33 (13–47)	30 (18–45)	0.591
Pure aortic stenosis	62 (29.4)	235 (41.4)	0.002	57 (34.5)	59 (35.8)	0.818
Pure aortic regurgitation	94 (44.5)	136 (23.9)	<0.001	58 (35.2)	57 (34.5)	0.908
Mixed stenosis/regurgitation	53 (25.1)	196 (34.5)	0.012	49 (29.7)	48 (29.1)	0.904
LV ejection fraction, %	54 (44–60)	57 (45–60)	0.026	55 (45–60)	55 (45–60)	0.418
Mitral regurgitation moderate or greater	75 (35.5)	178 (31.3)	0.265	58 (35.2)	50 (30.3)	0.348
Second valve: self-expandable	102 (48.3)	385 (67.8)	<0.001	95 (57.6)	100 (60.6)	0.576
Second valve: old generation	63 (30.0)	206 (35.0)	0.366	55 (33.0)	46 (28.0)	0.407
Access: transfemoral	187 (88.6)	447 (78.7)	0.002	142 (86.1)	145 (87.9)	0.624

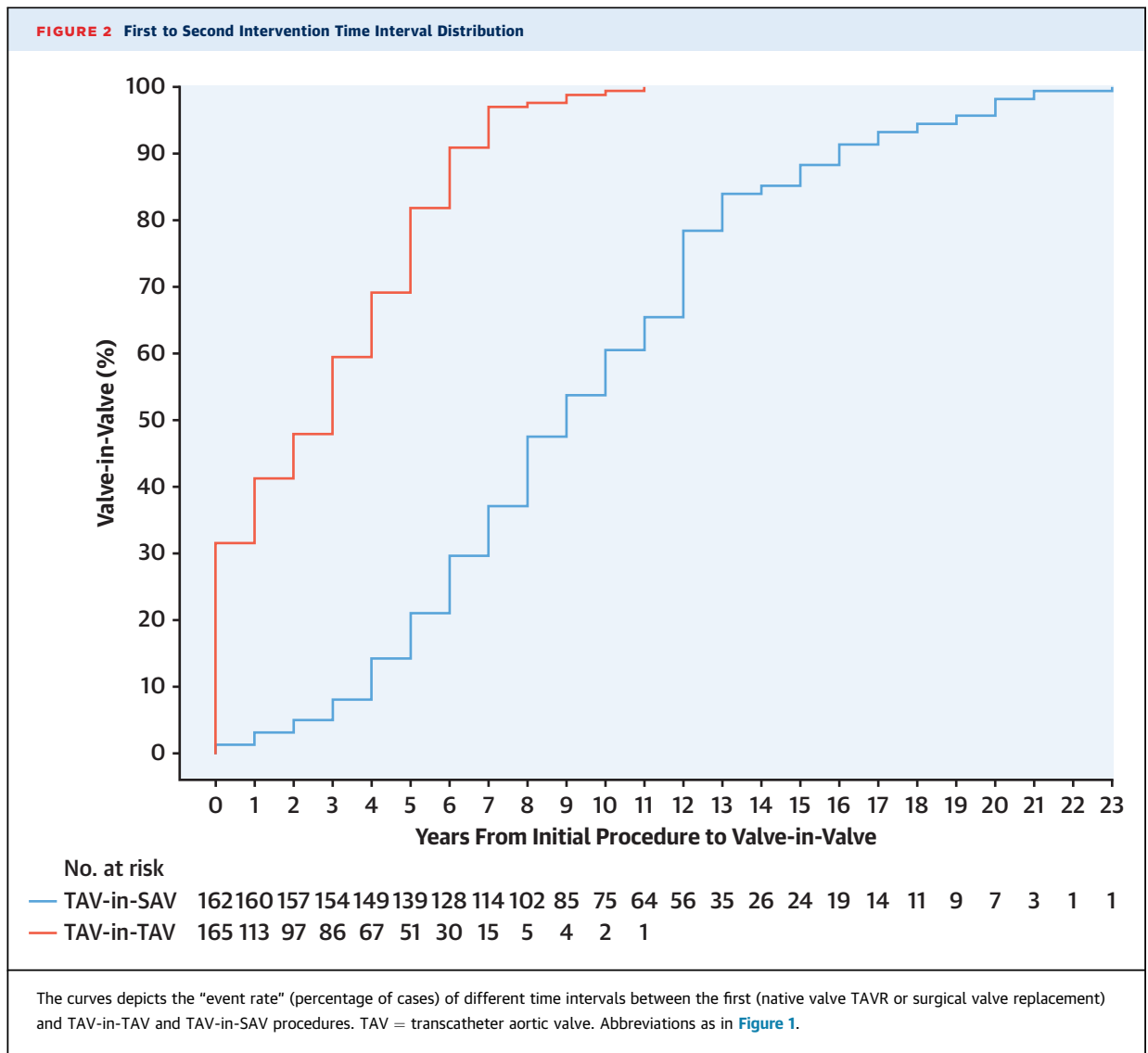Values are median (interquartile range) or n (%).

GFR = glomerular filtration rate; LV = left ventricular; NYHA = New York Heart Association; SAV = surgical aortic valve; STS = Society of Thoracic Surgery; TAV = transcatheter aortic valve.

SYMPTOMATIC BENEFIT AND MORTALITY. Median follow-up time was 425 days (IQR: 76 to 1,073 days), and no patient was lost to follow-up. Both TAV-in-TAV and TAV-in-SAV were associated with symptomatic alleviation at 30 days (p < 0.001). This benefit was persistent at 1 year and similar between the 2 cohorts (Supplemental Figure 1). Mortality rates at 30 days were 5 (3%) in TAV-in-TAV patients and 7 (4.4%) in TAV-in-SAV patients (p = 0.570). At 1 year, mortality rates was 12 (11.9%) and 10 (10.2%), respectively (p = 0.633). Time-to-event curves are depicted in Figure 6.

OUTCOMES AMONG THE UNADJUSTED COHORTS. A comparison of outcomes between the 2 groups prior to matching (212 TAV-in-TAV vs. 595 TAV-in-SAV) showed consistent findings: similar procedural safety and mortality and higher procedural success after TAV-in-TAV. Secondary measures also remained unchanged, granting that the higher rate of patients with high residual gradient after TAV-in-SAV became statistically significant. These data are available in Supplemental Table 2 and Supplemental Figures 2 to 4.

SUBGROUP ANALYSIS. In subgroup analysis, 41 of 165 TAV-in-SAV patients (25%) and 45 of 164 TAV-in-TAV patients (27%) were categorized as having small primary valves, which were associated with worse hemodynamic outcomes in both groups (Figure 7). TAV-in-SAV success rate was lower in patients with small versus intermediate or large SAVs (19 [46.3%] vs. 84 [67.7%]; p = 0.014), with a higher frequency of a residual high gradient (15 [39.5%] vs. 16 [15.1%]; p = 0.002). The rate of TAV-in-TAV success was comparable in patients with small versus intermediate or large primary TAVs (31 [68.9%] vs. 90 [75%]; p = 0.429). There was no association between the size of the primary bioprosthesis and procedural safety or mortality in either group (Supplemental Table 3).

Applying the same propensity analysis using only patients who presented 1 year or later after their first TAVR (n = 138) resulted in 123 TAV-in-TAV and 123 TAV-in-SAV patients with similar characteristics. After TAV-in-TAV and TAV-in-SAV, the rates of procedural success were 88 (71.5%) and 79 (64.2%) (p = 0.219), of procedural safety were 85 (69.1%) and
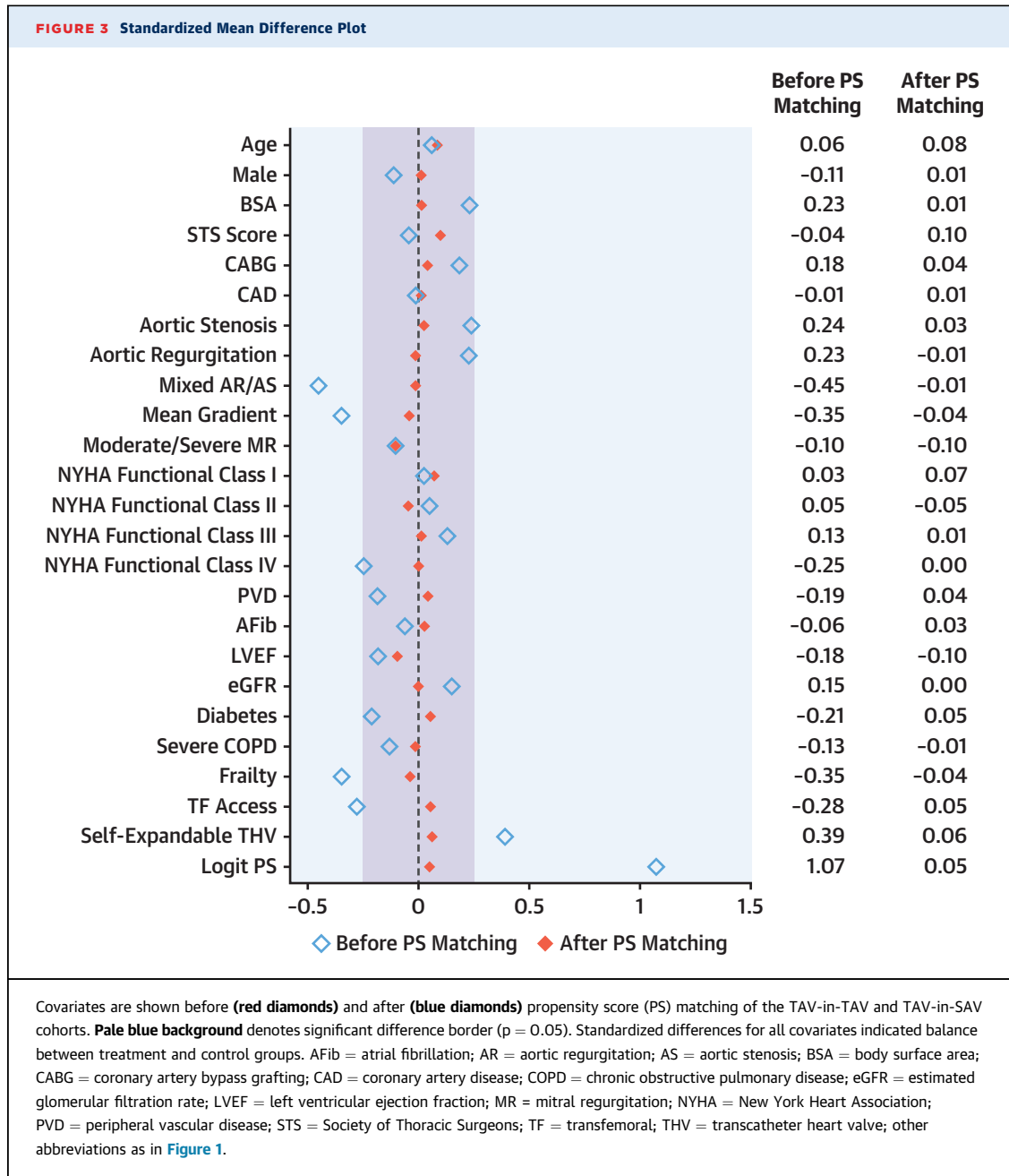
FIGURE 2   First to Second Intervention Time Interval Distribution

No. at risk																							
TAV-in-SAV	162	160	157	154	149	139	128	114	102	85	75	64	56	35	26	24	19	14	11	9	7	3	1	1
TAV-in-TAV	165	113	97	86	67	51	30	15	5	4	2	1												

The curves depicts the "event rate" (percentage of cases) of different time intervals between the first (native valve TAVR or surgical valve replacement) and TAV-in-TAV and TAV-in-SAV procedures. TAV = transcatheter aortic valve. Abbreviations as in **Figure 1**.

94 (76.4%) (p = 0.197), and of mortality at 1 year were 12 (12.1%) and 15 (14.9%) (p = 0.522), respectively (Supplemental Tables 4 and 5, Supplemental Figures 5 and 6).

DISCUSSION

In surgery, the use of bioprosthetic, as opposed to mechanical, valves has considerably increased in younger patients who may well outlive their valves (9). Similarly, current TAVs are exclusively bioprosthetic and are increasingly used in patients with longer life expectancy (3,4). Long-term assessment of TAV durability has been possible only in recent years, with few reports directly comparing TAV and SAV durability (10–14). Even though SAV follow-up exceeds that of TAVs, many studies assessed only rates of explantation, and recent studies using formal evaluation of hemodynamic parameters have documented relatively comparable rates of SAV and TAV degeneration (14). In any scenario, a considerable proportion of patients with native AS currently treated with either TAVR or surgery will develop valve failure that may require reintervention. Understanding better the expected outcomes of each type of reintervention may assist in upstream clinical decisions. The present study is the first to compare the performance of TAVR in failed transcatheter versus surgical bioprostheses (Central Illustration). The major findings are as follows: 1) in propensity score-matched cohorts, TAV-in-TAV was associated with more frequent procedural success compared with TAV-in-SAV, driven largely by lower residual aortic valve gradient; 2) there was no

FIGURE 3 Standardized Mean Difference Plot

	Before PS Matching	After PS Matching
Age	0.06	0.08
Male	−0.11	0.01
BSA	0.23	0.01
STS Score	−0.04	0.10
CABG	0.18	0.04
CAD	−0.01	0.01
Aortic Stenosis	0.24	0.03
Aortic Regurgitation	0.23	−0.01
Mixed AR/AS	−0.45	−0.01
Mean Gradient	−0.35	−0.04
Moderate/Severe MR	−0.10	−0.10
NYHA Functional Class I	0.03	0.07
NYHA Functional Class II	0.05	−0.05
NYHA Functional Class III	0.13	0.01
NYHA Functional Class IV	−0.25	0.00
PVD	−0.19	0.04
AFib	−0.06	0.03
LVEF	−0.18	−0.10
eGFR	0.15	0.00
Diabetes	−0.21	0.05
Severe COPD	−0.13	−0.01
Frailty	−0.35	−0.04
TF Access	−0.28	0.05
Self-Expandable THV	0.39	0.06
Logit PS	1.07	0.05

◇ Before PS Matching   ◆ After PS Matching

Covariates are shown before **(red diamonds)** and after **(blue diamonds)** propensity score (PS) matching of the TAV-in-TAV and TAV-in-SAV cohorts. **Pale blue background** denotes significant difference border (p = 0.05). Standardized differences for all covariates indicated balance between treatment and control groups. AFib = atrial fibrillation; AR = aortic regurgitation; AS = aortic stenosis; BSA = body surface area; CABG = coronary artery bypass grafting; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NYHA = New York Heart Association; PVD = peripheral vascular disease; STS = Society of Thoracic Surgeons; TF = transfemoral; THV = transcatheter heart valve; other abbreviations as in **Figure 1.**

difference in early safety or in mortality up to 1 year after TAV-in-TAV versus TAV-in SAV; and 3) the residual aortic valve gradient was lower, while the frequency and grade of AR were higher, after TAV-in-TAV compared with TAV-in-SAV.

The first report from the Redo-TAVR registry recently demonstrated acceptable outcomes up to 1 year after TAV-in-TAV (2). Although that study indicated that TAV-in-TAV can be performed safely for selected patients with valve dysfunction after TAVR,

residual AR appeared somewhat more common, while residual valve gradient seemed more favorable than observed after TAVR in surgical valves (1,15,16). Yet heterogeneity among studies, patients, and definitions required further investigation to enable better comparison. For this reason, we collected data on TAV-in-SAV patients from centers participating in the Redo-TAVR registry and performed propensity score matching to identify a cohort of patients with similar baseline variables. Attention was given to

TABLE 2 30-Day Outcomes for the Matched Cohort			
	TAV-in-TAV (n = 165)	TAV-in-SAV (n = 165)	p Value
Procedural success*	120 (72.7)	103 (62.4)	0.045
Procedural safety†	116 (70.3)	119 (72.1)	0.715
Mortality	5 (3.0)	7 (4.4)	0.556
Stroke	1 (0.6)	1 (0.6)	1.000
Myocardial infarction	1 (0.6)	4 (2.4)	0.176
Valve malposition			
Valve embolization/migration	1 (0.6)	1 (0.6)	1.000
Ectopic valve deployment	1 (0.6)	5 (3.3)	0.081
Coronary obstruction	2 (1.2)	7 (4.2)	0.091
Conversion to open heart surgery	0 (0.0)	3 (1.8)	0.082
Major vascular complication	13 (7.9)	11 (6.7)	0.672
Major bleeding	17 (10.3)	8 (5.2)	0.061
Acute kidney injury	7 (4.2)	2 (1.3)	0.091
New permanent pacemaker	18 (10.9)	12 (7.8)	0.251
High residual gradient (mean ≥20 mm Hg)	19 (14.6)	34 (21.5)	0.095
Moderate or severe aortic regurgitation	10 (8.4)	8 (4.8)	0.239
Days in hospital	6 (4–9)	6 (4–8)	0.992

Values are n (%) or median (interquartile range). *Composite of freedom from all-cause mortality, freedom from intervention related to the device or to a major vascular or cardiac structural complication (coronary obstruction, annular rapture, or cardiac tamponade), and technical success with intended performance of the valve (mean gradient <20 mm Hg and less than moderate aortic regurgitation) at 30 days. †Composite of freedom from all-cause mortality, all stroke, major bleeding, major vascular complication or cardiac structural complication, acute kidney injury, moderate or severe aortic regurgitation, new permanent pacemaker, and surgery or intervention related to the device at 30 days.

Abbreviations as in Table 1.

the fact that the 2 cohorts had similar body surface areas, valve failure mechanisms, and procedural techniques (i.e., access, valve generation, and opening mechanism). Likely because of the relative novelty of TAVR and higher competing risk for mortality in patients previously undergoing TAVR, the time between the first and second procedures was significantly shorter after TAVR (relative to surgery) and thus could not be included in the propensity analysis without excluding many patients from the analysis. Instead, a sensitivity analysis was applied and demonstrated consistent outcomes after excluding patients who presented relatively shortly after their native valve TAVR. It is therefore imperative to emphasize that more study of TAV durability is obligatory before TAVR can be offered up front to younger patients.

We used composite endpoint definitions to capture the complexity of the procedures. Both procedural success and safety encompass short-term procedure- or valve-related concerns that take place after achieving technical success and additionally include the early performance of the valve. We expected any potential discrepancy between TAV-in-TAV and TAV-in-SAV outcomes to be derived from the valve-in-valve interface variances.

Residual aortic valve gradients, often referred to as the Achilles' heel of valve-in-valve procedures, were more favorable after TAV-in-TAV (p = 0.011). The incidence of high residual gradients was 14.6% after TAV-in-TAV and 21.5% after TAV-in-SAV (p = 0.095). The rate of high residual gradients in the largest TAV-in-SAV series was 28% (17). The larger internal diameter and lack of a sewing ring with greater expandability of TAVs (vs. SAVs) can explain these more favorable outcomes. Notably, bioprosthetic valve fracture can improve this caveat if done for TAV-in-SAV patients, and overexpansion of TAV may reduce the residual gradient after TAVR (18). Unfortunately, data on valve fracture were not available. In subgroup analysis, small primary SAVs had a detrimental effect on procedural success, while small primary TAVs did not. Although bioprosthesis valve fracture and high implantation of valves with supra-annular leaflets are used to mitigate these liabilities in TAV-in-SAV, their need and implication in TAV-in-TAV remains to be studied.

At 30 days and 1 year after TAV-in-TAV, 91% of patients had mild or greater AR. However, mild AR was more common after TAV-in-TAV (p = 0.003). Two speculative mechanisms may explain this. First, as data on leak location are lacking, this may reflect the presence and persistence of paravalvular regurgitation associated with the initial TAV implant. Therefore, collecting imaging data for further core laboratory analysis looking at TAV failure mechanism with regard to leak location is required. Second, as was recently learned from in vitro testing, a relatively low implantation of a short-frame TAV into a tall-frame TAV with supra-annular leaflets may result in "leaflet overhang" of the outer valve and high regurgitant fraction (Video 1). Accordingly, when we examined the rate of residual mild or greater AR in the subgroup of patients with balloon-expandable TAVs in self-expandable TAVs, it was higher than in other TAV-in-TAV combinations: 66% (n = 27 of 42) versus 54% (self-expandable-in-self-expandable; n = 46 of 70), 35% (balloon-expandable-in-balloon-expandable; n = 11 of 32), and 29% (self-expandable-in-balloon-expandable; n = 6 of 21) (p = 0.038) at 30 days. Optimal TAV-in-TAV positioning needs further investigation looking at particular combinations of TAV designs and leaflets heights.
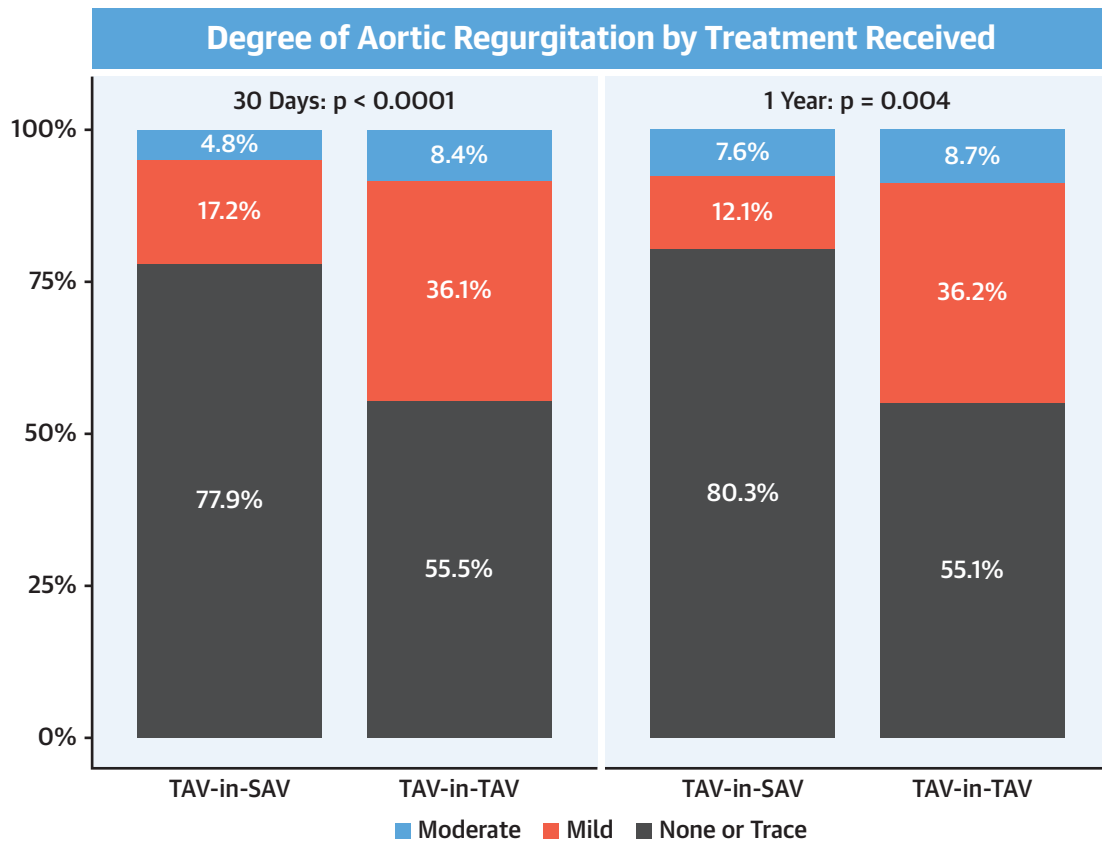
The rate of ectopic valve deployment was 1 (0.6%) in TAV-in-TAV and 5 (3.3%) in TAV-in-SAV (p = 0.081). Notably, 4 of the latter episodes happened in patients with radiolucent or semi-radiolucent SAVs (2 Freedom Solo [Sorin, Saluggia, Italy], 2 Toronto SPV, and 1 Trifecta [St. Jude Medical, St. Paul, Minnesota]). The fact that all TAVs are radio-

FIGURE 4 AV Areas and Mean Gradients at Baseline, 30 Days, and 1 Year
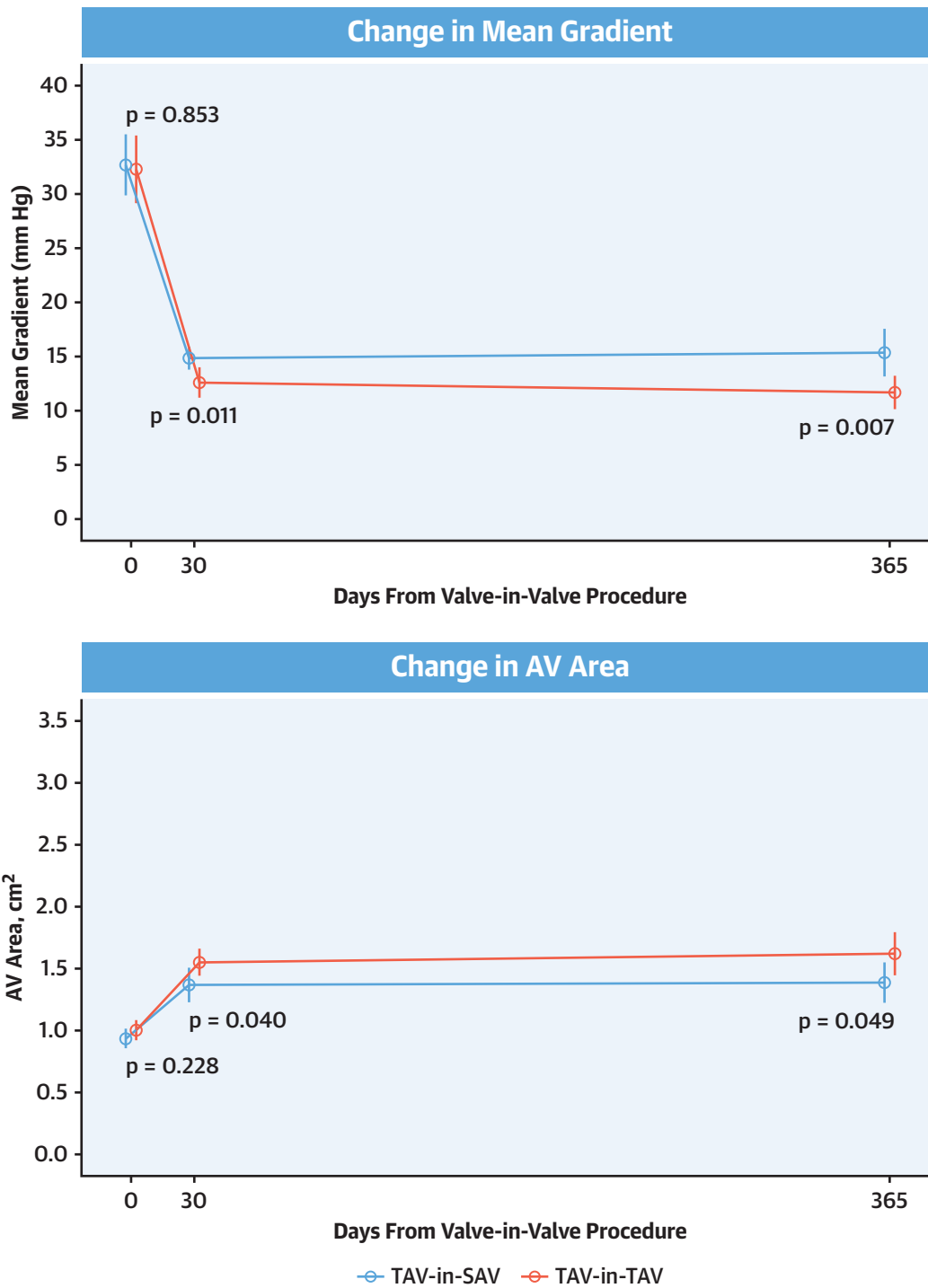
In propensity score–matched cohorts of TAV-in-TAV and TAV-in-SAV patients, baseline measurements were similar, while outcome measurements showed larger valve area and lower residual gradient after TAV-in-TAV. Assessed by echocardiography. AV = aortic valve; other abbreviations as in **Figure 1**.

FIGURE 5 Aortic Regurgitation at 30 Days and 1 Year

Degree of Aortic Regurgitation by Treatment Received

30 Days: p < 0.0001

	TAV-in-SAV	TAV-in-TAV
Moderate	4.8%	8.4%
Mild	17.2%	36.1%
None or Trace	77.9%	55.5%

1 Year: p = 0.004

	TAV-in-SAV	TAV-in-TAV
Moderate	7.6%	8.7%
Mild	12.1%	36.2%
None or Trace	80.3%	55.1%

■ Moderate ■ Mild ■ None or Trace

This **bar graph** presents the degree of aortic regurgitation as assessed by echocardiography. The p values refer to the differences between TAV-in-TAV and TAV-in-SAV in general. The rate of mild regurgitation is about 3 times higher after TAV-in-TAV (p = 0.003). The rate of moderate regurgitation is numerically higher after TAV-in-TAV, but this was not statistically significant. Abbreviations as in **Figure 1**.

opaque may be advantageous in this regard, as well as better familiarity of TAVR operators with TAV (vs. SAV) design.

Although an anticipated high risk for coronary obstruction may have excluded patients from either procedure, coronary obstruction was infrequent after TAV-in-TAV, which is reassuring considering the poor outcomes associated with this complication. The rate of coronary obstruction after TAV-in-SAV was higher than expected (4.2%) but based on a small number of events and not significantly different from the TAV-in-TAV cohort. Certain anatomic and procedural characteristics predict higher risk for coronary obstruction after TAV-in-SAV, but these may differ after TAV-in-TAV ([19](#)). Higher TAV (vs. SAV) leaflet commissures and stent frames, neoskirt formation, and nonalignment may all hypothetically predispose to higher risk for coronary obstruction and access

difficulties after TAV-in-TAV and are essential for further research ([20](#)).

STUDY LIMITATIONS. This was an observational study without independent adjudication of events or an independent core laboratory imaging analysis. Although propensity score matching is a well-accepted approach in observational research to address differences in baseline characteristics, it cannot account for unmeasured bias. Although this is the largest reported TAV-in-TAV cohort, the absolute number of cases remains relatively small, and the duration of follow-up is limited.

CONCLUSIONS

In propensity score-matched cohorts of TAV-in-TAV versus TAV-in-SAV patients, TAV-in-TAV was associated with a higher rate of procedural success, while

FIGURE 6 Kaplan-Meier Survival Curves After Valve-in-Valve for Each Group
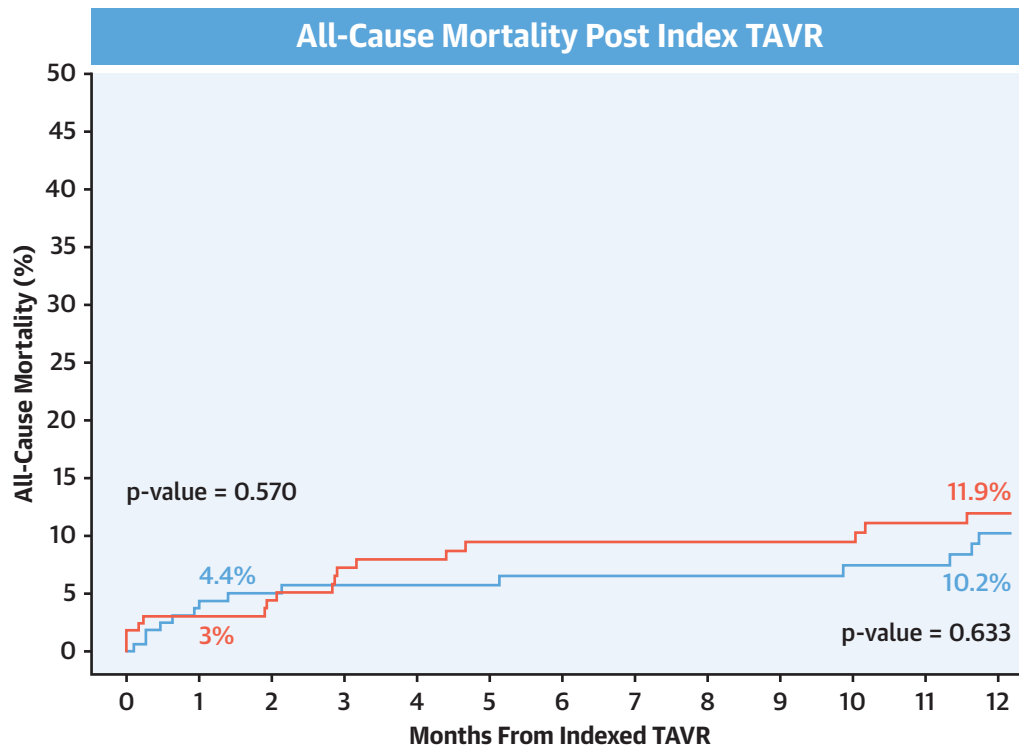
In propensity score-matched cohorts of TAV-in-TAV and TAV-in-SAV patients, 30-day and 1-year mortality (all-cause) rates were similar. Abbreviations as in **Figure 1**.

there was no difference in procedural safety or mortality up to 1 year. More study is needed to improve TAV-in-TAV outcomes as well as the upstream management of patients with AS with long life expectancy.

AUTHOR DISCLOSURES

FIGURE 7   Aortic Valve Mean Gradients According to Primary Valve Label Size
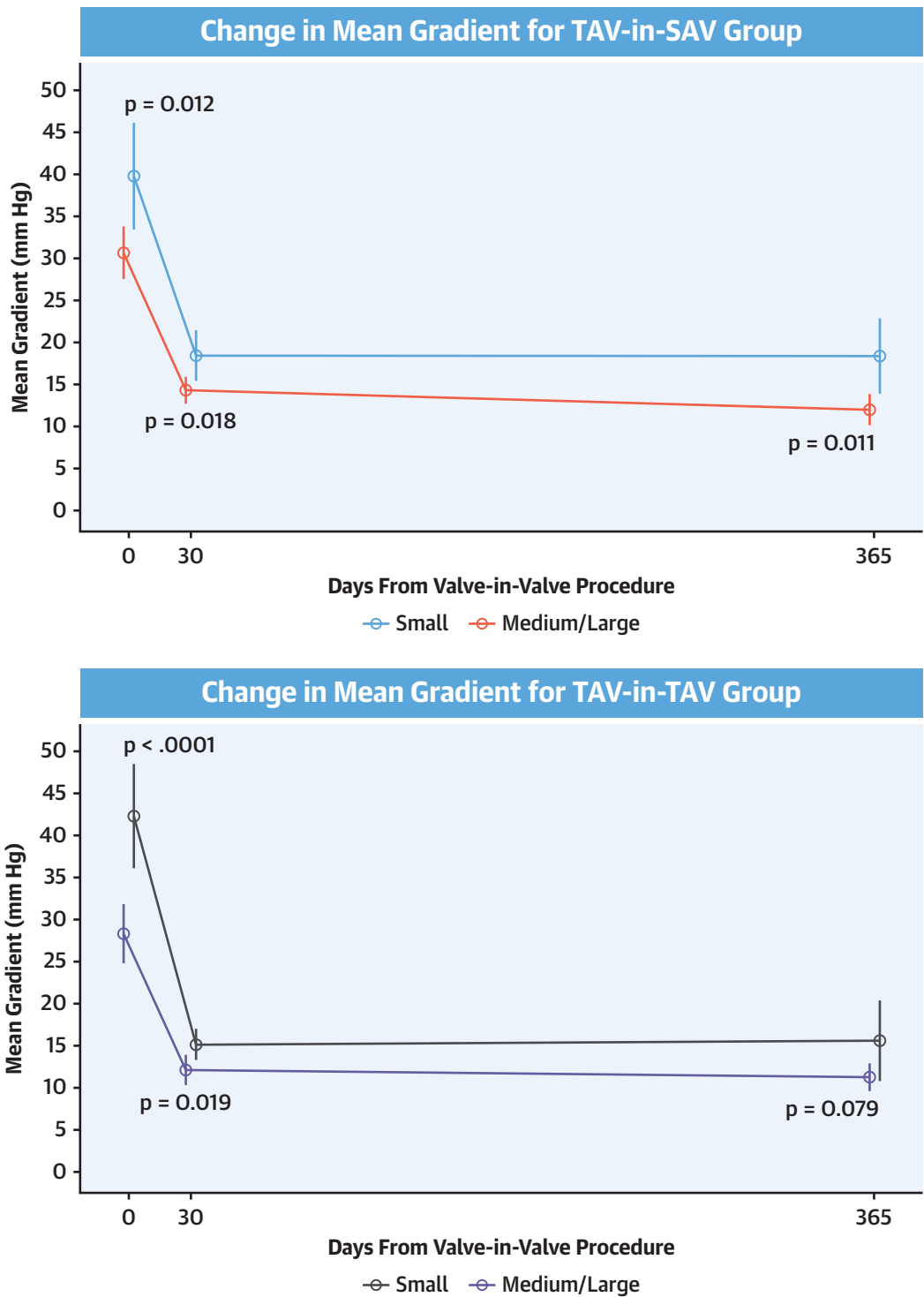
In both groups, about one-quarter of patients were categorized as having small primary valves, and this was associated with worse hemodynamic outcomes. Small (≤21 mm for surgical valves and ≤23 mm for transcatheter valves), intermediate (>21 and <25 mm for surgical valves and >23 and <29 mm for transcatheter valves), and large (≥25 mm for surgical valves and ≥29 mm for transcatheter valves). Abbreviations as in **Figure 1**.

CENTRAL ILLUSTRATION Transcatheter Aortic Valve-in-Transcatheter Aortic Valve Versus Transcatheter Aortic Valve-in-Surgical Aortic Valve
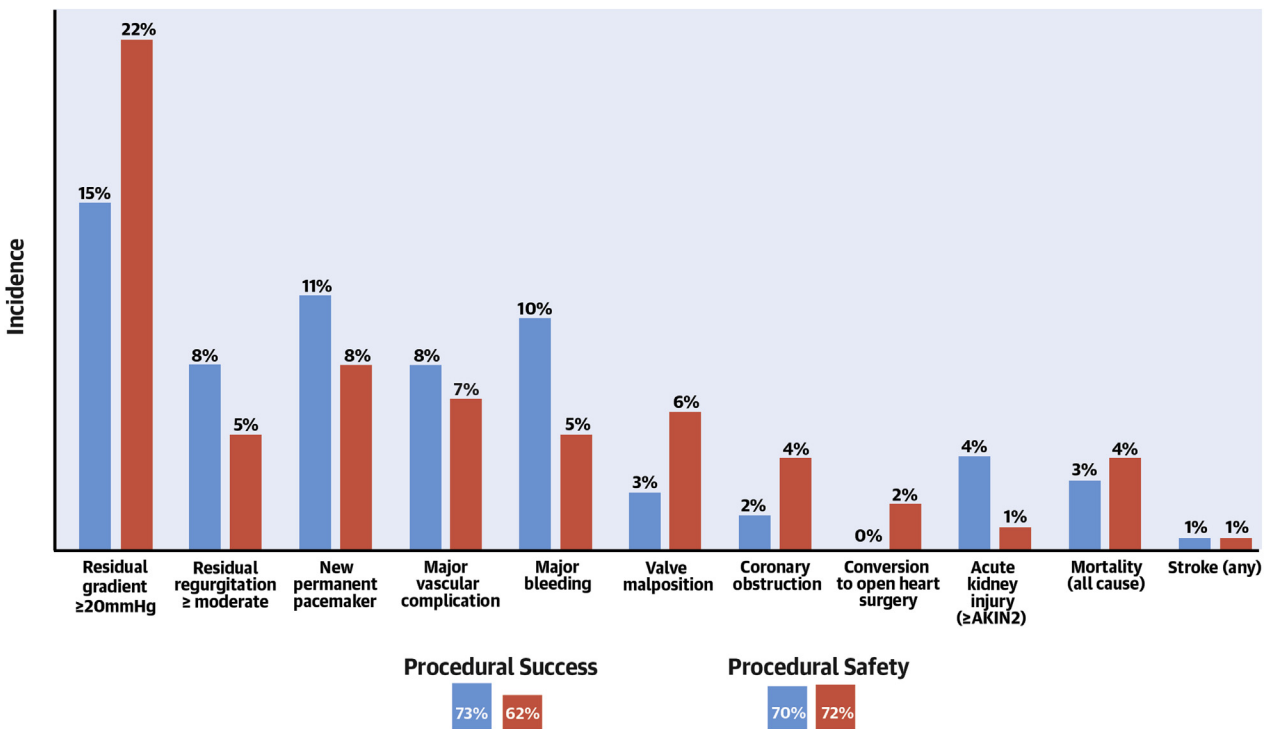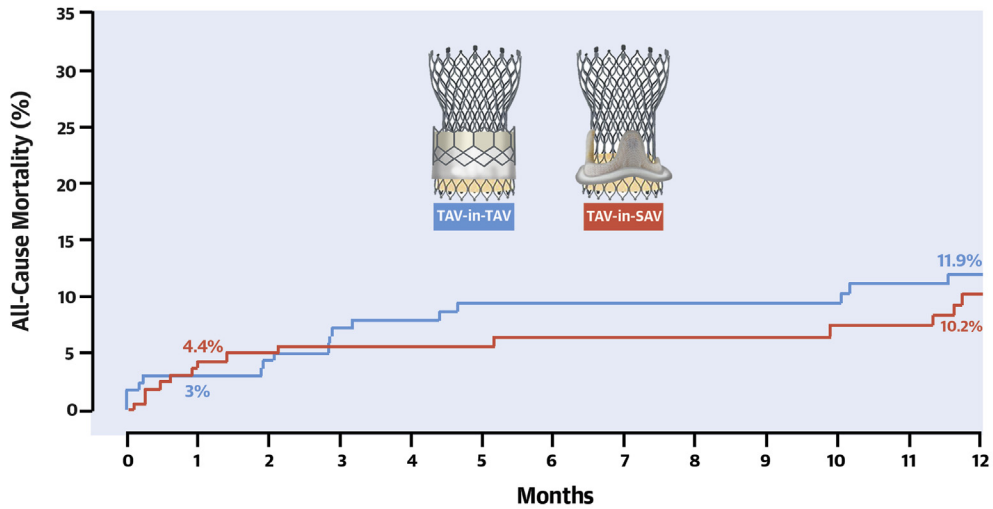
Landes, U. et al. J Am Coll Cardiol. 2021;77(1):1-14.

This illustration summarizes the outcomes in propensity score–matched cohorts of both procedures. All outcomes were measured at 30 days except the Kaplan-Meier mortality curve, which is up to 1 year. AKIN = Acute Kidney Injury Network; SAV = surgical aortic valve; TAV = tricuspid aortic valve.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: TAVR-in-SAVR is associated with procedural safety, initial success, and 1-year mortality similar to that of TAVR-in-TAVR.

TRANSLATIONAL OUTLOOK: Further studies should seek to establish the generalizability of outcome comparisons with these procedures for secondary intervention in various subgroups of patients with degenerated aortic valve bioprostheses.

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KEY WORDS Redo-TAVR, surgical aortic valve, TAVR, transcatheter aortic valve, valve-in-valve

APPENDIX For supplemental tables, figures, and a video, please see the online version of this paper.