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ORIGINAL RESEARCH

Comparison of Early Surgical or Transcatheter Aortic Valve Replacement Versus Conservative Management in Low-Flow, Low-Gradient Aortic Stenosis Using Inverse Probability of Treatment Weighting: Results From the TOPAS Prospective Observational Cohort Study

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BACKGROUND: No randomized comparison of early (ie, ≤3 months) aortic valve replacement (AVR) versus conservative management or of transcatheter AVR (TAVR) versus surgical AVR has been conducted in patients with low-flow, low-gradient (LFLG) aortic stenosis (AS).

METHODS AND RESULTS: A total of 481 consecutive patients (75±10 years; 71% men) with LFLG AS (aortic valve area ≤0.6 cm^2/m^2 and mean gradient <40 mm Hg), 72% with classic LFLG and 28% with paradoxical LFLG, were prospectively recruited in the multicenter TOPAS (True or Pseudo Severe Aortic Stenosis) study. True-severe AS or pseudo-severe AS was adjudicated by flow-independent criteria. During follow-up (median [IQR] 36 [11–60] months), 220 patients died. Using inverse probability of treatment weighting to address the bias of nonrandom treatment assignment, early AVR (n=272) was associated with a major overall survival benefit (hazard ratio [HR], 0.34 [95% CI, 0.24–0.50]; *P*<0.001). This benefit was observed in patients with true-severe AS but also with pseudo-severe AS (HR, 0.38 [95% CI, 0.18–0.81]; *P*=0.01), and in classic (HR, 0.33 [95% CI, 0.22–0.49]; *P*<0.001) and paradoxical LFLG AS (HR, 0.42 [95% CI, 0.20–0.92]; *P*=0.03). Compared with conservative management in the conventional multivariate model, trans femoral TAVR was associated with the best survival (HR, 0.23 [95% CI, 0.12–0.43]; *P*<0.001), followed by surgical AVR (HR, 0.36 [95% CI, 0.23–0.56]; *P*<0.001) and alternative-access TAVR (HR, 0.51 [95% CI, 0.31–0.82]; *P*=0.007). In the inverse probability of treatment weighting model, trans femoral TAVR appeared to be superior to surgical AVR (HR [95% CI] 0.28 [0.11–0.72]; *P*=0.008) with regard to survival.

CONCLUSIONS: In this large prospective observational study of LFLG AS, early AVR appeared to confer a major survival benefit in both classic and paradoxical LFLG AS. This benefit seems to extend to the subgroup with pseudo-severe AS. Our findings suggest that TAVR using femoral access might be the best strategy in these patients.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT01835028.

Key Words: aortic stenosis ■ low flow ■ low gradient ■ surgical aortic valve replacement ■ survival ■ transcatheter aortic valve replacement

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CLINICAL PERSPECTIVE

What Is New?

- According to this large prospective observational cohort study, early aortic valve replacement is superior to clinical surveillance in both classic and paradoxical low-flow, low-gradient aortic stenosis, whether with true-severe or pseudo-severe (ie, moderate) aortic stenosis. Transcatheter aortic valve replacement appears to be the best therapeutic option, especially using femoral access.

What Are the Clinical Implications?

- Early aortic valve replacement, especially with transcatheter transfemoral approach should be considered in symptomatic patients with low-flow, low-gradient AS.

Nonstandard Abbreviations and Acronyms

AS	aortic stenosis
AVA	aortic valve area
AVA_{Proj}	projected aortic valve area at normal flow rate
AVR	aortic valve replacement
ConsRx	conservative management
IPTW	inverse probability of treatment weighting
LFLG	low flow, low gradient
PSAS	pseudo-severe aortic stenosis
SAVR	surgical aortic valve replacement
SMD	standardized mean difference
TAVR	transcatheter aortic valve replacement
TOPAS	True or Pseudo Severe Aortic Stenosis
TSAS	true-severe aortic stenosis
wHR	weighted hazard ratio

Close to 40% of patients with aortic stenosis (AS) with aortic valve area (AVA) ≤1.0 cm^2 have a low mean gradient (<40 mm Hg), thereby raising uncertainty as to the actual severity of the disease and whether aortic valve replacement (AVR) is warranted.[1,2] In a large proportion of these patients, the small AVA–low-gradient pattern is related to a low-flow state, which is defined as a stroke volume index ≤35 mL/m^2. This low-flow, low-gradient (LFLG) AS entity may occur with either a depressed left ventricular ejection fraction (LVEF; <50%) (ie, classic LFLG AS) or with a preserved LVEF (ie, paradoxical LFLG AS), a phenotype close to heart failure with preserved LVEF.[3] According to guidelines, AVR is recommended (class I or IIa) in patients with LFLG AS if the presence of true-severe AS (TSAS) is confirmed using dobutamine stress echocardiography or aortic valve calcium scoring by computed tomography.[4–6] However, because of low sensitivity (35%), only a minority of patients with classic LFLG AS would qualify for AVR according to dobutamine stress criteria for TSAS proposed in the guidelines.[7] Moreover, studies reported that 50% to 78% of patients with LFLG AS have TSAS based on aortic valve calcification scoring.[8,9] On the other hand, patients with pseudo-severe AS (PSAS) (ie, moderate AS and left ventricular systolic heart failure) have a poor outcome under conservative management (ConsRx), and data suggest they may benefit from surgical AVR (SAVR).[10,11] Thus, most patients with LFLG AS might benefit from AVR. There is no randomized trial comparing the different treatment strategies in patients with LFLG AS. In this report, inverse probability of treatment weighting (IPTW) was used to compare AVR versus ConsRx and SAVR versus transcatheter AVR (TAVR) in a large prospective observational study of patients with LFLG AS.

METHODS

Population

The data that support the findings of this study are available from the corresponding author on reasonable request. A total of 481 patients were prospectively recruited in the TOPAS (True or Pseudo Severe Aortic Stenosis) study from 5 centers. The design and methods of this prospective multicenter observational study have been previously described (https://clinicaltrials.gov; NCT 01835028).[12–14] Briefly, patients were included in the TOPAS study if they had a mean gradient <40 mm Hg and an indexed AVA ≤0.6 cm^2/m^2 and were classified as classic LFLG AS if LVEF was <50% and paradoxical LFLG AS if it was ≥50%. Patients with preserved LVEF and a stroke volume index >35 mL/m^2 were excluded, whereas those with depressed LVEF were recruited regardless of stroke volume. Patients were also excluded if they had more than mild aortic regurgitation, more than moderate mitral regurgitation, or more than mild mitral stenosis (following multiparameter integrative approach, as recommended).[15–17] Other exclusion criteria were end-stage chronic kidney disease, severe cognitive impairment (also excluded for inability to sign informed consent), acute coronary syndrome or acutely decompensated heart failure within 3 months before inclusion, and any severe illness with an expected survival of <1 year. The institutional review board committee of the participating

centers approved the study. All the subjects provided written informed consent. Study enrollment started in 2002, and the last patient was recruited in 2016. Collected baseline clinical data were age, sex, body surface area, Duke activity status index, hypertension, hyperlipidemia, diabetes mellitus, chronic kidney disease (as defined by an estimated glomerular filtration rate <60 mL/s following Cockroft and Gault method), atrial fibrillation/flutter, history of myocardial infarction, history of coronary artery bypass grafting, coronary artery disease (ie, ≥50% coronary artery stenosis on coronary angiography), history of stroke or transient ischemic attack, peripheral artery disease, the European System for Cardiac Operative Risk Evaluation II score, congestive heart failure, New York Heart Association functional class, acute pulmonary edema, and chronic obstructive pulmonary disease. Resting and peak dobutamine stress AVA, mean gradient, and LVEF values were collected. NT-proBNP (N-terminal pro-B-type natriuretic peptide) was measured at baseline (Roche Diagnostics). Starting from 2012, an amendment was performed to add aortic valve calcification scoring using multidetector computed tomography in the study protocol. Echocardiographic and tomographic analyses were performed in a CoreLab at the Institut Universitaire de Cardiologie et de Pneumologie de Québec, Québec, QC, Canada. After SAVR, the explanted valves were collected. The treatment strategy (ie, early AVR [SAVR or TAVR] or ConsRx) was left to the discretion of the treating physician and heart team. If AVR was performed within 3 months following the inclusion date, the strategy was considered as early AVR, whereas if AVR was not performed during follow-up or was performed >3 months following inclusion, the strategy was considered as ConsRx. We recorded any combined revascularization (combined coronary artery bypass grafting or percutaneous revascularization within 30 days of the TAVR procedure) or other heart valve intervention. Patients were prospectively followed up with yearly scheduled visits or by telephone until study completion (ie, at 5 years of follow-up).

Adjudication of AS Severity

The determination of true AS severity was based on at least one of the following flow-independent parameters:

1. Aortic valve calcification ratio (n=154). This ratio is calculated by dividing the aortic valve calcium score (using the Agatston method) by the currently recommended sex-specific cut points for TSAS (ie, 1200 and 2000 arbitrary units in women and men, respectively).[8,18] A value of aortic valve calcification ratio ≥1.0 defined TSAS.
2. Projected AVA at normal flow rate (AVA_{Proj}; n=206) with a value ≤1.0 cm^2 to define TSAS (see Data S1 for detailed AVA_{Proj} method).[7,19]
3. Aortic valve weight ratio (n=106) calculated by dividing the actual valve weight by the previously reported sex-specific cut points for TSAS (ie, 1.2 g for women and 2.0 g for men).[20] A value of aortic valve weight ratio ≥1.0 defined TSAS.
4. Confirmation of stenosis severity by a macroscopic evaluation of the valve performed by the surgeon at the time of SAVR (n=131), following a standardized and previously validated method.[12,13]

Patients were categorized as having TSAS if at least one of the criteria was fulfilled, regardless to the results of the others. Patients with no available flow-independent parameters of AS severity were considered as having indeterminate AS severity.

Statistical Analysis

Continuous variables are expressed as mean±SD or median (25th–75th percentile) for normally and not normally distributed variables, respectively (as tested by Shapiro-Wilk test) and were compared using Student *t* test (or *U* test of Wilcoxon-Mann-Whitney, as appropriate) and ANOVA (followed by Tukey post hoc test or Kruskall-Wallis followed by Dunn test) for multiple comparison. Proportions are expressed as percentages and compared using χ^2 test or Fisher exact test, as appropriate. IPTW was used to address the bias related to nonrandom assignment of treatment.[21] This method allows increasing the weight of underrepresented observations to reduce the imbalances related to treatment allocation, thereby simulating the effect of randomization on baseline characteristics. Details on IPTW method are provided in Data S1. Briefly, a propensity score was built using multiple logistic regression (Table S1), taking early AVR versus ConsRx as a binary end point. To compare the different types of AVR, the propensity score using the same regression model was recalculated for TAVR versus ConsRx, SAVR versus ConsRx, and TAVR versus SAVR. Second, each patient was weighted by the inverse probability of treatment (eg, 1/propensity score for patients undergoing AVR and 1/[1−propensity score] for patients receiving ConsRx; see weight distribution in Figure S1). The balance between the treatment groups was assessed using weighted standardized mean difference (SMD; ie, percentage of the pooled SD). An SMD value ≤20% was considered acceptable. The association of treatment with 3-year all-cause death was analyzed using weighted Kaplan-Meier curves and Cox proportional hazards regression with a robust variance estimator to calculate weighted hazard ratios (wHRs) (95% CIs).

Table 1. Baseline Characteristics of the Overall TOPAS Cohort and Comparison According to Type of Treatment

Characteristic	Overall TOPAS Cohort (n=481)	ConsRx (n=207; 43%)	SAVR (n=176; 37%)	TAVR (n=98; 20%)	*P* Value
Year of inclusion	2009 (2006–2013)	2008 (2005–2012)	2009 (2005–2010)	2013 (2010–2014)	<0.001
Clinical data					
Age, y	75±10	75±10*, †	71±10†, ‡	80±7*, ‡	<0.001
Male sex, n (%)	341 (71)	158 (73)	127 (72)	64 (66)	0.48
Body mass index, kg/m^2	27.6±5.6	27.5±5.7	28.3±5.8†	26.5±4.7*	0.03
Diabetes mellitus, n (%)	165 (34)	71 (33)	61 (35)	36 (37)	0.73
Hypertension, n (%)	355 (74)	150 (73)	118 (67)	87 (90)	<0.001
Hyperlipidemia, n (%)	331 (69)	134 (65)	125 (71)	72 (74)	0.38
Chronic kidney disease (ie, eGFR ≤60 mL/min), n (%)	136 (28)	51 (23)	39 (22)	47 (49)	<0.001
Chronic obstructive pulmonary disease, n (%)	120 (25)	43 (21)	46 (27)	35 (38)	0.009
Previous CABG, n (%)	124 (26)	52 (25)	27 (15)	45 (46)	<0.001
Previous myocardial infarction, n (%)	176 (37)	100 (46)	47 (27)	37 (38)	<0.001
Coronary artery disease, n (%)	295 (61)	110 (53)	63 (112)	73 (75)	<0.001
Previous stroke or transient ischemic attack, n (%)	69 (14)	30 (15)	22 (12)	17 (18)	0.51
History of peripheral artery disease, n (%)	40 (8)	18 (9)	4 (2)	18 (19)	<0.001
Atrial fibrillation/flutter, n (%)	78 (16)	27 (13)	27 (15)	25 (27)	0.011
Heart rate, bpm	71±13	71±14	72±14	70±12	0.39
Systolic/diastolic blood pressure, mm Hg	123±20/71±12	124±20/71±11†	122±20/73±12†	122±21/68±13*, ‡	0.56/0.004
Symptoms and functional status					
History of CHF, n (%)	250 (52)	115 (57)	83 (48)	56 (62)	0.07
Previous acute pulmonary edema, n (%)	84 (18)	30 (15)	34 (19)	20 (21)	0.32
Functional class, n (%)					<0.001
I	43 (9)	34 (17)	9 (5)	0 (0)	
II	173 (36)	84 (41)	61 (35)	28 (29)	
III	216 (45)	71 (35)	88 (51)	57 (59)	
IV	44 (9)	16 (8)	16 (9)	12 (12)	
Duke activity status index	19 (10–31)	24 (13–38)*, †	19 (13–29)†, ‡	10 (7–16)*, ‡	<0.001
Aortic valve hemodynamics					
Aortic valve area, cm^2	0.81±0.22	0.88±0.24*, †	0.76±0.17‡	0.76±0.22‡	<0.001
Indexed aortic valve area, cm^2/m^2	0.43±0.12	0.47±0.13*, †	0.40±0.09‡	0.42±0.11‡	<0.001
Mean gradient, mm Hg	26±9	23±9*, †	28±8‡	27±8‡	<0.001
Peak aortic jet velocity, m/s	3.3 (2.9–3.7)	3.1±1.9*, †	3.5±1.8‡	3.4±1.8‡	<0.001
True AS severity					
Adjudicated true severe AS, n/n$_{available}$ (%)	293/425 (69)	86/172 (50)	145/169 (86)	62/84 (74)	<0.001
AVA$_{Proj}$, cm^2	0.99±0.21	1.05±0.2*, †	0.92±0.19‡	0.89±0.16‡	<0.001
AVA$_{Proj}$ ≤1.0 cm^2, n/n$_{available}$ (%)	121/206 (59)	53/118 (45)	48/64 (75)	20/24 (83)	<0.001
Aortic valve calcification ratio§	1.20±0.68	1.04±0.66	1.26±0.62	1.38±0.69‡	0.01
Aortic valve calcification ratio ≥1.0, n/n$_{available}$ (%)	88/154 (57)	29/65 (45)	20/27 (74)	39/62 (63)	0.02
Aortic valve weight ratio§	1.25±0.45	NA	1.25±0.45	NA	
Aortic valve weight ratio ≥1.0, n/n$_{available}$ (%)	72/106 (68)	NA	72/106 (68)	NA	
Macroscopic assessment of surgically explanted valve, n/n$_{available}$ (%)	91/131 (70)	NA	91/131 (70)	NA	
Indeterminate AS severity, n (%)	56 (12)	35 (17)	8 (5)	13 (13)	
Left ventricular function					
Stroke volume index, mL/m^2	31 (26–34)	32 (26–37)*	30 (27–33)‡	30 (24–33)‡	0.04
LVEF, %	38±17	32 (25–43)*	35 (25–60)†, ‡	30 (25–40)*	0.06

(*Continued*)

Table 1. Continued

Characteristic	Overall TOPAS Cohort (n=481)	ConsRx (n=207; 43%)	SAVR (n=176; 37%)	TAVR (n=98; 20%)	*P* Value
Indexed LVEDD, mm/m^2	29 (25–32)	30 (26–35)*	28 (24–31)‡	29 (26–32)	<0.001
Classic/paradoxical LFLG, n (%)	344 (72)/137 (28)	155 (75)/52 (25)	115 (65)/61 (35)	74 (76)/24 (24)	0.07
Mitral regurgitation, n (%)					0.56
None	61 (34)	79 (38)	49 (28)	33 (34)	
Mild	269 (56)	108 (62)	112 (63)	49 (50)	
Moderate	48 (10)	20 (12)	16 (9)	12 (16)	
Severe	0 (0)	0 (0)	0 (0)	0 (0)	
Systolic pulmonary artery pressure, mm Hg	43±13	43±13	42±13	43±14	0.95
NT-proBNP, pg/mL	2304 (827–4771)	1526 (541–4269)†	2455 (829–4888)	2616 (1396–5182)‡	0.02
Operative risk					
EuroSCORE II, %	5.1 (2.3–8.7)	4.9 (2.4–8.0)*, †	3.1 (1.7–6.1)†, ‡	9.6 (7.0–15.2)*, ‡	<0.001

Values are mean±SD, median (interquartile range), and number (percentage). *P* value is for the ANOVA between treatment groups. AS indicates aortic stenosis; AVA_{Proj}, projected aortic valve area at normal flow (ie, mean systolic flow rate 250 mL/s); bpm, beats per minute; CABG, coronary artery bypass grafting; CHF, congestive heart failure; ConsRx, conservative management; eGFR, estimated glomerular filtration rate; LVEDD, left ventricular end diastolic diameter; LFLG, low flow, low gradient; LVEF, left ventricular ejection fraction; NA: not applicable; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; and TOPAS, True or Pseudo Severe Aortic Stenosis.

*Post hoc $P<0.05$ vs SAVR.

†Post hoc $P<0.05$ vs TAVR.

‡Post hoc $P<0.05$ vs ConsRx.

§Aortic valve calcification ratio was calculated by dividing the actual aortic valve calcium score by the sex-specific threshold that defines severe AS (ie, 1200 and 2000 arbitrary units for women and men, respectively). Similarly, aortic valve weight ratio is the actual valve weight divided by the sex-specific valve weight that defines true severe AS (ie, 1.2 and 2.0 g for women and men, respectively).[20]

Proportional hazard's assumption was verified using Schoenfield residuals. Residual differences between treatment groups after IPTW were adjusted for by forcing the insufficiently balanced variables into the weighted model (providing adjusted wHR). To mimic the intention-to-treat analysis of a randomized trial, patients receiving ConsRx who "crossed over" to AVR were analyzed in the ConsRx group. We also analyzed delayed AVR as a time-dependent variable. To study the benefit of AVR according to true AS severity and according to the type of LFLG AS (classic and paradoxical), we performed interaction-term and subgroup analyses. Standard (ie, with no weighting) Kaplan-Meier curves and univariable and multivariable Cox proportional hazards regression were used to analyze both SAVR and TAVR (femoral and alternative access) versus ConsRx (referent) and to verify the consistency with IPTW analyses. A 2-sided $P<0.05$ was considered for statistical significance. Statistical analyses were performed with SPSS version 25 (SPSS, Inc, Chicago, IL) and STATA version 15.1 (StataCorp 2017, College Station, TX).

RESULTS

Baseline characteristics of the population are summarized in the Table. The mean age was 75±10 years, and 71% of the study population were men. The average indexed AVA and mean gradient values were 0.43±0.12 cm^2/m^2 and 26±9 mm Hg, respectively. The average LVEF was 38±17%, and 72% (n=344) had classic LFLG (LVEF <50%) and 28% (n=137) had paradoxical LFLG AS (LVEF ≥50%). There was a high prevalence of comorbidities in these patients (Table). The prevalence of stage III to IV New York Heart Association functional class (55%; n=259) and the low Duke activity status index (median, 19 [25th–75th percentile, 10–31]) reflected poor functional status. Among patients who underwent a flow-independent assessment of AS severity (n=425), 69% (n=293) were confirmed with TSAS: 68% in the classic LFLG group and 72% in the paradoxical LFLG group ($P=0.33$). Among the 80 patients with both a priori (either AVA_{Proj} or aortic valve calcification score) and a posteriori (either aortic valve weight or macroscopic assessment at the time of SAVR), 13 (16%) had PSAS with both evaluations. The results of each grading scheme are reported in the Table. A total of 411 patients (97%) had at least one quantitative grading scheme (aortic valve calcification or weight ratios and AVA_{Proj}). A comparison between patients with PSAS and TSAS is provided in Table S2 and described in Data S1. The adjudication of AS severity revealed that the vast majority of patients with confirmed PSAS had a moderate stenosis, which was close to the severe AS cut points, therefore suggesting that AS severity was moderate or moderate to severe in this group with unlikely occurrence of mild AS. Finally, 274 patients (57%) underwent early AVR (ie, with a median delay from inclusion of 0 [25th–75th percentile, 0–1] months). Of these patients, 189 had

classic LFLG and 85 had paradoxical LFLG AS (55% and 62%, respectively; *P*=0.16).

Survival Benefit Associated With Early AVR

A comparison of baseline characteristics between early AVR and ConsRx groups is described in Data S1 and summarized in Table S3. All of the baseline differences were balanced after IPTW except residual borderline differences in LVEF (SMD=24%) and peripheral artery disease (SMD=25%). Of note, although 42% of ConsRx group versus 76% in the AVR group had a confirmed TSAS before IPTW, this variable was evenly distributed between treatment groups (60% versus 66%, respectively; SMD=12%) after IPTW.

During a median follow-up of 36 months (25th–75th percentile, 11–60 months), 220 patients died and 4 (<1%) were lost to follow-up (2 patients from the ConsRx group and 2 from the AVR group [1 from SAVR and 1 from TAVR subgroups]). Early AVR was associated with major survival benefit (wHR, 0.33 [95% CI, 0.23–0.48]; adjusted wHR, 0.34 [95% CI, 0.24–0.50]; both *P*<0.0001; Figure 1A) compared with ConsRx. This result was consistent in the nonweighted population and was not altered by clustering effect of the participating centers (Figure S2; adjusted hazard ratio [HR], 0.42 [95% CI, 0.28–0.61]; *P*<0.001 using mixed effect survival model). More important, 38 patients from the ConsRx group eventually crossed over to AVR after a median time of 12 (25th–75th percentile, 8–24) months from inclusion. When entering delayed (ie, performed >3 months after inclusion) AVR as a time-dependent covariate, there was a trend toward improved outcome (adjusted HR, 0.39 [95% CI, 0.14–1.08]; *P*=0.07), whereas early AVR remained strongly and independently associated with lower mortality (adjusted HR, 0.41 [95% CI, 0.30–0.56]; *P*<0.001). Analyzing both overall AVR (early and delayed) as a time-dependent covariate provided similar results (adjusted HR, 0.46 [95% CI, 0.34–0.63]; *P*<0.001).

The forest plot in Figure 1B shows the association of early AVR with mortality across the study subgroups. Interestingly, the survival benefit associated with AVR was observed not only in the subgroup with TSAS (wHR, 0.30 [95% CI, 0.19–0.48]) but also in the patients with PSAS (wHR, 0.38 [95% CI, 0.18–0.81], *P*=0.01; adjusted wHR, 0.36 [95% CI, 0.17–0.78], *P*=0.009). Moreover, no significant interaction was found between TSAS/PSAS status and early AVR with respect to mortality (*P*=0.54). As shown in Figure 1C, the worst 3-year survival rate was observed in the patients with TSAS with initial ConsRx (wHR, 1.54 [95% CI, 0.96–2.48]; *P*=0.07) compared with conservatively managed patients with PSAS, whereas patients with TSAS or PSAS undergoing early AVR had the best survival despite higher 30-day mortality (4.9% and 8.0% for TSAS and PSAS, respectively, after AVR versus 6.7% and 0.8%, respectively, with ConsRx; *P*=0.05). These results were consistent in the nonweighted population (Figure S3). We also found no interaction between classic/paradoxical LFLG and AVR with mortality (*P*=0.50 for interaction) and, as shown in Figure 1B and Figure S4, the better survival associated with early AVR was consistent in classic (wHR, 0.33 [95% CI, 0.22–0.49]; *P*<0.001) and paradoxical LFLG AS (wHR, 0.42 [95% CI, 0.20–0.92]; *P*=0.03).

Survival Benefit Associated With Early TAVR Versus SAVR

Baseline characteristics according to the treatment type (ie, SAVR [n=175], TAVR [n=97], and ConsRx [n=205]) are summarized in the Table. Briefly, patients undergoing TAVR had the highest baseline risk profile: they were the oldest (80±7 versus 71±10 and 75±10 years old in the SAVR and ConsRx groups, respectively; *P*<0.001 and all post hoc *P*<0.05), with the worst functional status, as measured by the New York Heart Association class (71% New York Heart Association class III–IV versus 61% and 43% in SAVR and ConsRx groups, respectively; *P*<0.001) or the Duke activity status index (median, 10 [25th–75th percentile, 7–16] versus 19 [25th–75th percentile, 13–29] and 24 [25th–75th percentile, 13–38] in SAVR and ConsRx groups, respectively; *P*<0.001 and all post hoc *P*<0.05), and the highest prevalence of cardiac and noncardiac comorbidities, resulting in the highest EuroSCORE II (9.6% [25th–75th percentile, 7.0%–15.2%] versus 3.1% [25th–75th percentile, 1.7%–6.1%] and 4.9% [25th–75th percentile, 2.4%–8.0%] in SAVR and ConsRx groups, respectively; *P*<0.001 and all post hoc *P*<0.05). TSAS was present in 50% of ConsRx group versus 86% and 74% of the SAVR and TAVR groups, respectively (*P*<0.001).

During follow-up, patients with ConsRx had the worst survival (Figure 2A). TAVR (HR, 0.67 [95% CI, 0.46–0.98]; *P*=0.04) and SAVR (HR, 0.32 [95% CI, 0.22–0.48]; *P*<0.001) were associated with a significantly better survival compared with ConsRx. In multivariable analysis performed in the nonweighted population and taking ConsRx as the referent group, both SAVR (adjusted HR, 0.36 [95% CI, 0.23–0.56]; *P*<0.001) and TAVR (HR, 0.36 [95% CI, 0.23–0.55]; *P*<0.001) were independently associated with a better survival. When subdividing the TAVR group into transfemoral TAVR and alternative-access TAVR, patients who underwent transfemoral TAVR (n=49) had a similar good outcome as the patients who underwent SAVR (Figure 2B; crude HR, 0.43 [95% CI, 0.23–0.77], *P*=0.005; and crude HR, 0.32 [95% CI, 0.22–0.48],

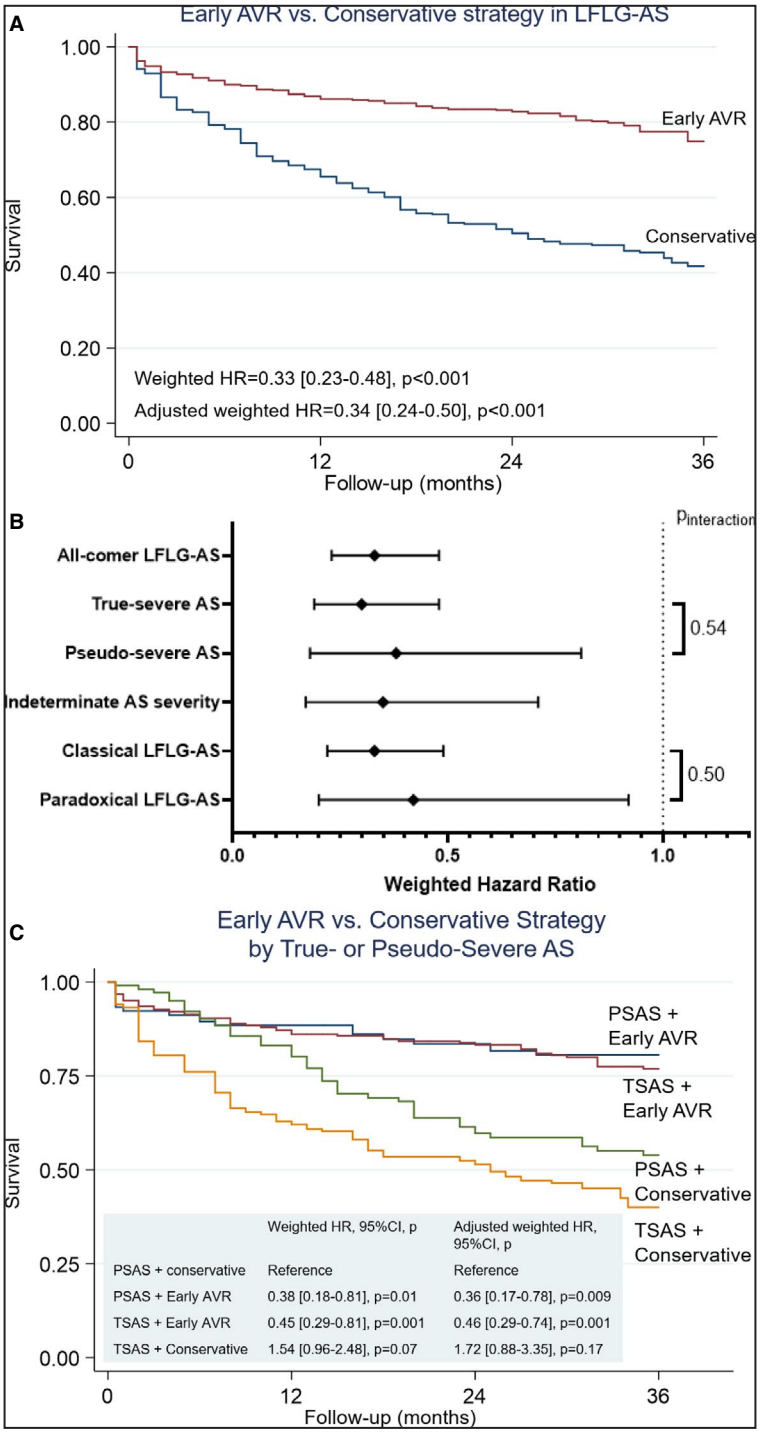

Figure 1. Survival benefit associated with aortic valve replacement (AVR) in low-flow, low-gradient aortic stenosis (LFLG AS) using inverse probability of treatment weighting (IPTW).
In **A**, early (ie, ≤3 months) AVR (red line) is compared with conservative management or clinical surveillance and delayed AVR (blue line). The forest plot in (**B**) shows the weighted hazard ratio (HR) associated with AVR in the different study subgroups. In (**C**), the survival curves are stratified according to the initial management strategy and the severity of AS, excluding patients with indeterminate AS severity. The survival curves are adjusted using IPTW. The weighted numbers at risk are simulated and thus not shown (see Figure S1 for the weights' distributions). The adjusted weighted HRs are adjusted for residual differences after IPTW (Table S3). PSAS indicates pseudo-severe AS; and TSAS, true-severe AS.

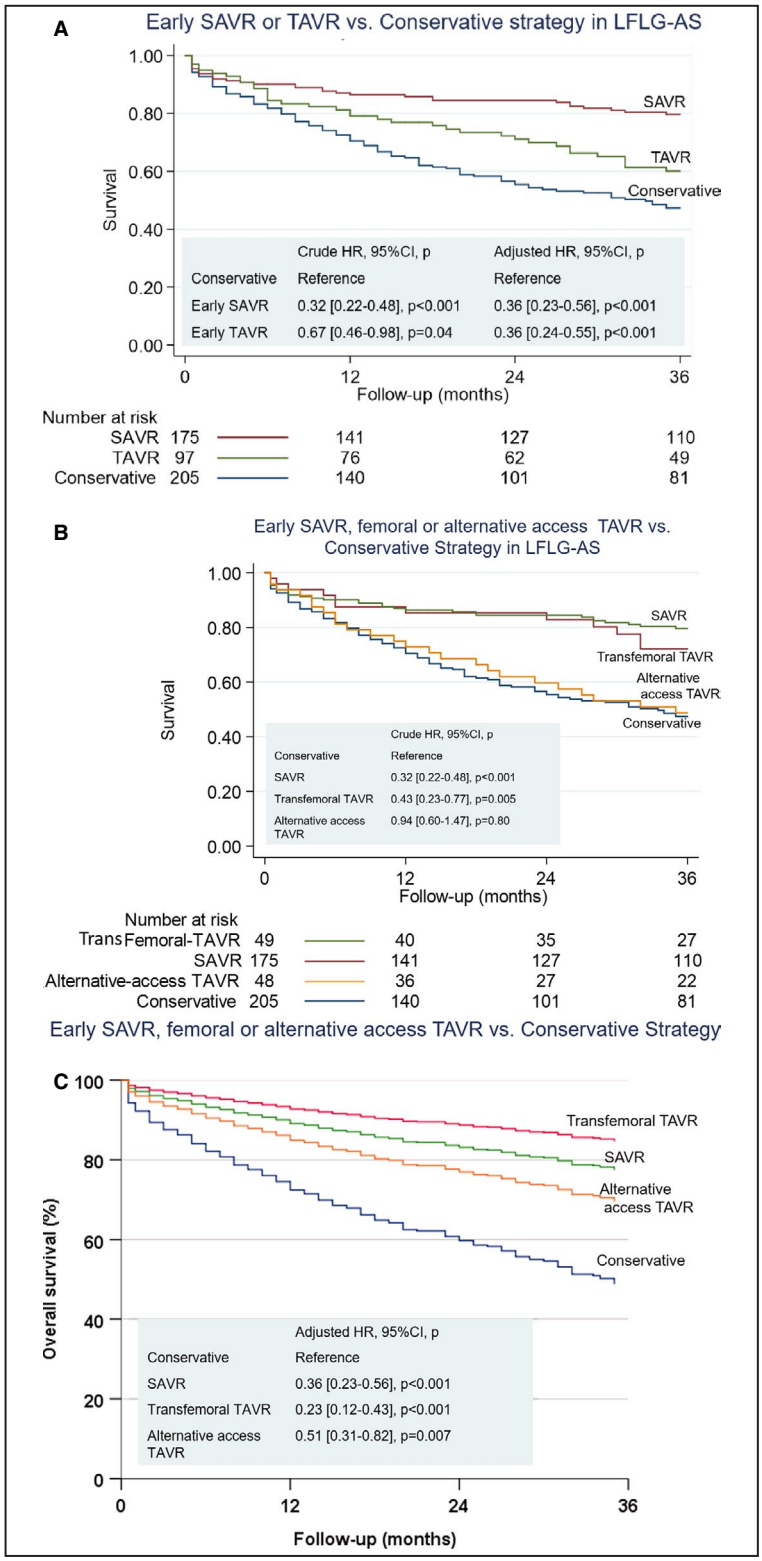

Figure 2. Survival benefit of surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) in low-flow, low-gradient aortic stenosis (LFLG AS) and pooled analysis of the different treatment modalities.

Standard Kaplan-Meier survival curves for the 3 treatment modalities (**A**) and after splitting the TAVR group into trans femoral and alternative access subgroups (**B**). **C**, Adjusted Survival Curves for the Cox proportional hazards model. See Data S1 for details about multivariate analysis. HR indicates hazard ratio.

P<0.001, respectively, versus ConsRx), whereas patients who underwent alternative access TAVR (n=48) had a worse survival, similar to the patients with ConsRx (HR, 0.94 [95% CI, 0.60–1.47]; *P*=0.80). After multivariate adjustment in the nonweighted population, transfemoral TAVR appeared to be the best therapeutic option (Figure 2C), with an adjusted HR of 0.23 (95% CI, 0.12–0.43; *P*<0.001), followed by SAVR (adjusted HR, 0.36 [95% CI, 0.23–0.56]; *P*<0.001) and alternative access TAVR (adjusted HR, 0.51 [95% CI, 0.31–0.82]; *P*=0.007).

After IPTW, although most of the characteristics were balanced for each pair of treatment, there were residual differences (Table S4 for SAVR versus ConsRx, Table S5 for TAVR versus ConsRx, and Table S6 for TAVR versus SAVR). SAVR (wHR, 0.36 [95% CI, 0.21–0.62]; *P*<0.001; Figure 3A) and TAVR (wHR, 0.38 [95% CI, 0.22–0.64]; *P*<0.001; Figure 3B) were confirmed as being associated with a better survival compared with ConsRx. Further adjustment for the residual differences (after IPWT) did not alter the results (adjusted wHR, 0.38 [95% CI, 0.22–0.65], *P*<0.001 for SAVR versus ConsRx and adjusted wHR, 0.40 [95% CI, 0.18–0.88], *P*=0.02 for TAVR versus ConsRx). Outcome after TAVR was comparable to SAVR (wHR, 1.27 [95% CI, 0.64–2.55]; *P*=0.49; Figure 3C). However, after IPTW, the TAVR weighted group remained significantly older (SMD=36%), had a higher prevalence of peripheral artery disease (SMD=29%), had a much lower Duke activity status index (SMD=90%), and had a higher EuroSCORE II (SMD=50%). After adjusting for these residual differences, there was a trend toward superiority of TAVR (adjusted wHR, 0.56 [95% CI, 0.26–1.24]; *P*=0.16). When dichotomizing TAVR according to access route, transfemoral TAVR was associated with improved survival versus SAVR (Figure 3D; adjusted wHR, 0.28 [95% CI, 0.11–0.72]; *P*=0.008).

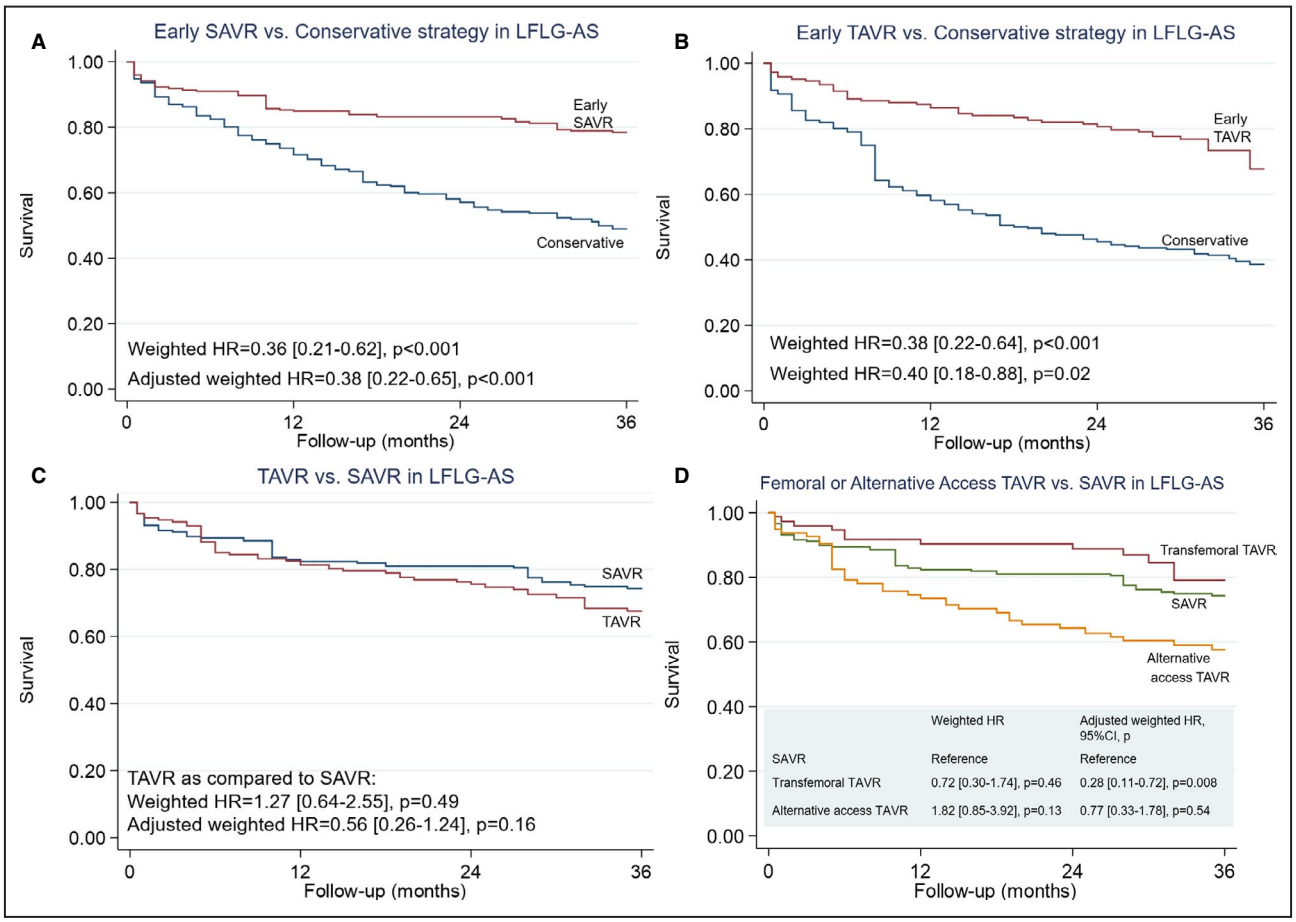

Figure 3. Survival benefit of surgical aortic valve replacement (SAVR) and transcatheter aortic valve replacement (TAVR) in low-flow, low-gradient aortic stenosis (LFLG AS) using inverse probability of treatment weighting (IPTW).
Pairwise treatment comparison using inverse probability weighting. **A**, SAVR vs conservative management (ConsRx). **B**, TAVR vs ConsRx. **C**, SAVR vs TAVR. **D**, SAVR vs TAVR, subdivided into trans femoral and alternative access groups. The survival curves are adjusted using IPTW. The weighted numbers at risk are simulated and are, thus, not shown (see Figure S1 for the weights). Adjusted weighted hazard ratio (HR): adjusted for baseline differences that remained significant despite IPTW (Tables S4, S5 and S6).

DISCUSSION

This study, which includes the largest prospective cohort of patients with LFLG AS with the longest follow-up, is the first to compare the association between the different therapeutic strategies (ie, SAVR, TAVR, and ConsRx) in the different types of LFLG AS (ie, classic or paradoxical LFLG). The main findings of this study are that early (<3 months) AVR, compared with a strategy combining ConsRx or delayed AVR, is associated with an important survival benefit in both the classic and paradoxical subsets of LFLG AS and in both true-severe and pseudo-severe AS. The other important finding is that TAVR appears to provide the best therapeutic option in this high-risk population with AS.

Benefit of AVR in LFLG AS

One of the important findings of this study is that both patients with TSAS and those with PSAS had poor outcome with ConsRx, but derived an important survival benefit with AVR. These findings are consistent with the concept that PSAS, which generally corresponds to moderate or moderate-to-severe AS, may be well tolerated by patients with normal left ventricular function and no heart failure but poorly tolerated by patients with heart failure and a low-flow state.[22]

Classic LFLG AS is the heart failure with reduced LVEF form of AS, whereas paradoxical LFLG AS is the heart failure with preserved LVEF form of AS. These patients with heart failure may not tolerate the left ventricular pressure overload associated with AS, even if it is only moderate. van Gils et al reported that moderate AS is associated with poor outcomes in patients with reduced LVEF.[10] Mohty et al reported that prosthesis-patient mismatch, which is equivalent to moderate residual AS, is associated with reduced survival following SAVR. We previously demonstrated the cutoff value of AVA_{Proj} below which mortality is increased in patients with LFLG AS under ConsRx is 1.2 cm^2, which is larger than the cutoff value for severe AS in the guidelines (<1.0 cm^2) and further suggests that moderate AS may be detrimental in these patients.[7,13,23] In the present study, the vast majority (87%) of patients who underwent dobutamine stress echocardiography had an AVA_{Proj} <1.2 cm^2. The results of this study provide support for considering AVR at milder degree of AS severity in symptomatic patients with LFLG AS. For AVA_{Proj}, the threshold appears to be close to 1.2 cm^2, which corresponds to the upper range of moderate AS. However, Sato et al demonstrated that PSAS, as defined by AVA_{Proj} >1.0, predicted no survival benefit from AVR.[24] Further studies are needed to determine whether we should use lower cutoff values of aortic valve calcification score (than those recommended in the guidelines: 2000 arbitrary units in men and 1200 arbitrary units in women) to consider AVR in patients with LFLG AS. The benefit and safety of early TAVR in patients with moderate AS and systolic heart failure are currently being assessed in the TAVR UNLOAD (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Patients With Advanced Heart Failure) trial.[25]

SAVR Versus TAVR for LFLG AS

Patients with LFLG AS, and especially those with classic LFLG and no contractile or flow reserve on dobutamine stress echocardiography, are at increased risk of 30-day mortality following SAVR.[26–29] Despite the relatively high mortality, several studies and meta-analysis have shown that patients with classic or paradoxical LFLG severe AS derive a major survival benefit with AVR versus ConsRx.[30] In the present study, trans femoral TAVR appeared to confer similar survival as SAVR in univariate analysis (Figure 2B). However, given that baseline risk profile was generally worse in the TAVR versus SAVR group, the adjusted curves (Figure 2C) and the fully adjusted IPTW model suggested a possible superiority of TAVR (adjusted wHR, 0.56 [95% CI, 0.26–1.24]; *P*=0.16), especially with trans femoral access (adjusted wHR, 0.28 [95% CI, 0.11–0.72]; *P*=0.008) over SAVR. The less invasive nature of TAVR, and especially trans femoral TAVR, offers the opportunity to improve outcomes in patients with LFLG AS who are generally at high surgical risk. A post hoc analysis of the Placement of Aortic Transcatheter Valves (PARTNER) trial revealed that TAVR was associated with a major survival benefit versus ConsRx in LFLG patients with prohibitive surgical risk (cohort B) and had similar survival compared with SAVR in LFLG patients with high surgical risk.[31] In the TOPAS TAVI (Transcatheter Aortic Valve Implantation) registry, patients with classic LFLG AS had low 30-day mortality and excellent 1-year outcomes following TAVR, regardless of the presence or absence of flow reserve on dobutamine stress echocardiography.[32] The present study suggests that TAVR, and particularly transfemoral TAVR, might be superior to SAVR for the therapeutic management of both classic and paradoxical LFLG AS. Patients with LFLG have more extensive cardiac damage and more vulnerable left ventricular function and may thus benefit more from a less invasive procedure, such as transfemoral TAVR.

Limitations and Strengths

First, this nonrandomized study is subject to treatment allocation bias. To overcome this limitation and allow

robust comparison of the different treatment strategies, we used an IPTW analysis.[33,34] We elected to use IPTW over propensity score matching because the latter method would have required the exclusion of a large number of unmatched patients. We also used Cox proportional regression adjustment as a secondary method, and both methods provided consistent results. However, the ability of IPTW to balance between TAVR and SAVR groups was limited given the small overlap between these 2 treatment groups. Unmeasured confounding factors may also have introduced an additional source of bias by influencing therapeutic decision making and outcome. One of such factors could be the newly developed frailty indexes, which have been reported to influence therapeutic decision making and patient outcome.[35] We tried to limit this source of bias by excluding patients with severe cardiac and noncardiac comorbidities who are usually considered unsuitable candidates for AVR. Second, the observed results in the PSAS or paradoxical LFLG subcohorts are subject to bias related to subgroup analysis because the IPTW model allowed for an adjustment for the initial management decision (AVR versus ConsRx), but not for the actual severity of AS nor for the type of LFLG AS. Hence, the observed benefit in the PSAS and paradoxical LFLG subgroups remains hypothesis generating. Third, we pooled classic and paradoxical LFLG AS. However, patients with classic LFLG are at increased surgical risk, whereas patients with paradoxical LFLG generally have an intermediate-risk profile. Although we found no interaction between type (classic or paradoxical) of LFLG AS and AVR with mortality, further studies are needed to address the benefit of AVR separately in each subset.

CONCLUSIONS

In this large prospective series of LFLG AS, early AVR was associated with a major survival benefit compared with ConsRx in both classic and paradoxical LFLG AS and in both TSAS and PSAS. Our results also suggest that transfemoral TAVR might be the best approach in patients with LFLG AS. The potential benefit of AVR in the subset of patients with PSAS and the superiority of transfemoral TAVR in patients with LFLG AS need to be confirmed in future randomized trials.

ARTICLE INFORMATION

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Supplementary Material

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SUPPLEMENTAL MATERIAL

Data S1.

SUPPLEMENTAL METHODS

Baseline Doppler echocardiography at rest and under dobutamine stress

Resting Doppler echocardiograms and under dobutamine stress were performed using commercially available ultrasound systems. Echo analyses were performed in the Echo CoreLab of Quebec Heart and Lung Institute using the Tomtec Arena software (Tomtec Corporation USA, Chicago, IL, USA). LV dimensions were measured at rest according to American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations[14,35] . AVA was calculated by the continuity equation; MG was obtained by the Bernoulli formula; LVEF was measured using the biplane Simpson method[36] . Projected aortic valve area (AVA_{Proj}) at a normal transvalvular flow rate (250ml/min) was calculated using the formula[18,11] :

$$AVA_{Proj} = AVA_{Rest} + \frac{AVA_{Peak} - AVA_{Rest}}{Q_{Peak} - Q_{Rest}} \times (250 - Q_{Rest})$$

Where AVA_{Rest} and AVA_{Peak} are the AVA at rest and at peak stress, and Q_{Rest} and Q_{Peak} were mean transvalvular flows at rest and at peak stress. This method reduces the flow dependence of AVA under dobutamine stress by standardizing AVA to a fixed normal flow rate of 250 ml/s. AVA_{Proj} was previously demonstrated to be superior to AVA_{Peak} and MG at peak stress to distinguish true from pseudo-severe AS and to predict death under conservative management[6] .

Statistical analysis

- *Inverse probability-of-treatment-weighting to limit confusion*

Inverse probability-of-treatment-weighting allows improving baseline imbalances between treatment groups by giving a higher or lower weight to underrepresented and overrepresented

observations, respectively. A propensity score was built using multiple logistic regression taking early AVR vs. ConsRx as a binary endpoint (Table S1). We chose the variables with significantly different distributions between treatment arms in addition to those associated with all-cause mortality in multivariate analysis (see below). The C-index of the propensity score to predict early AVR vs. conservative management was 0.85 ([0.82-0.88], p<0.001). To compare the different types of AVR, the propensity score using the same regression model was recalculated for each of the following pairs of treatments: TAVR vs ConsRx (C-index=0.92 [0.89-0.95], p<0.001), SAVR vs ConsRx (C-index=0.88 [0.85-0.92], p<0.001), TAVR vs SAVR (C-index=0.96 [0.94-0.98], p<0.001). Each patient was weighted by the inverse probability of treatment (e.g. 1/propensity score for AVR patients and 1/(1-propensity score) for ConsRx patients). Trimming of the 99th percentile outliers of the resulting weights (25.1 [n=4], 18.1 [n=2], 19.0 [n=2] and 16.8 [n=6] respectively in the AVR vs. ConsRx, SAVR vs. ConsRx, TAVR vs. ConsRx, and TAVR vs. SAVR pars of treatment) allowed preventing excessive weighting. The resulting weights' distributions stratified by the treatment arm are illustrated in Figure S1. Then, baseline characteristics were compared between treatment groups in the resulting pseudo-population using weighted standardized mean difference (SMD i.e. percentage of the pooled standard deviation). SMD values were considered acceptable when ≤20%. In case of significant residual differences (SMD>20%), Cox multivariate regression adjustment was done by forcing the variables that remained unbalanced in the unadjusted IPTW model.

- Outcome analyses in the non-weighted population

A Cox proportional hazards regression model was built to predict all-cause mortality comprising clinically relevant variables in addition to variables with a p value <0.1 in univariate analysis. The resulting model comprised age, sex, true severe AS, previous coronary artery bypass grafting, chronic obstructive pulmonary disease, diabetes, chronic kidney disease

(eGFR<60 ml/min/1.73m²), New York Heart Association functional class III-IV, classical/paradoxical low-flow, beta-blockers, and the need for diuretics. The different treatment types were forced into this model to calculate adjusted hazard ratios of all cause mortality. In all multivariate analyses, the number of events per independent variable was maintained ≥10.[37] To assess clustering effect, we used multilevel mixed effect survival models. In this method, the conventional univariable and multivariable models were enhanced by a random effect term i.e. representing the participating centers. We used the *mestreg* command of Stata software. When the enhancement was significant (likelihood ratio test p<0.05) the results of the mixed effect survival model was reported. Otherwise, we reported the results of the conventional analysis.

SUPPLEMENTAL RESULTS

Comparison of baseline characteristics between TSAS and PSAS patients:

Baseline characteristics according to the actual AS severity (i.e TSAS or PSAS) are summarized in Table S2. PSAS patients had a higher prevalence of chronic kidney disease (35% vs 24%, p=0.02) and previous myocardial infarction (49% vs 33%, p=0.002), but less atrial fibrillation (9% vs 21%, p=0.004). The mean age and the median EuroSCORE were similar between treatment groups (p>0.05). Symptoms were more severe in the TSAS group as reflected by a higher prevalence of NYHA functional class III-IV (47% versus 58%, p=0.02), although the median Duke activity status index was comparable between groups. The indexed LV diastolic diameter was 1 mm/m² larger in the PSAS group, while median NT-proBNP was comparable. Baseline AVA was smaller and MG and peak jet velocity were higher in the TSAS group (Table S2). The results of the different flow-independent AS grading schemes (also detailed in Table S2) are illustrated in Figure S3.

Baseline characteristic before and after inverse-probability-of-treatment weighting:

Fifty seven percent of the patients had early AVR (n=274) and 43% had ConsRx (n=207). Baseline characteristics before and after IPTW are summarized in Table S3. The most important differences between Early AVR and ConsRx group were in the year of inclusion SMD=32%), previous myocardial infarction (SMD=29%), chronic obstructive pulmonary disease (SMD=25%), coronary artery disease (SMD=30%), NYHA functional class III-IV (SMD=41%), Duke Activity Status Index (SMD=64%), AVA (SMD=30%), MG (SMD=35%), and TSAS (SMD=74%). After IPTW, all differences were well balanced (SMD≤20%). However slight differences emerged in LVEF (SMD=24%) and peripheral artery disease (SMD=25%).

Baseline characteristics according to the type of AVR i.e. SAVR (n=176) and TAVR (n=96) are reported and briefly described in the main manuscript. Pairwise comparisons of baseline characteristics before and after IPTW are reported in tables S4, S5 and S6. Briefly:

- Between ConsRx vs. SAVR: before weighting, there were important differences regarding age (SMD=40%), chronic obstructive pulmonary disease (SMD=25%), previous coronary artery bypass grafting (SMD=25%), myocardial infarction (SMD=38%), peripheral artery disease (SMD=28%), New York Heart Association functional class (SMD=34%), Duke Activity Status Index (SMD=28%), AVA (SMD=41%), MG (SMD=69%), TSAS (SMD=91%), LVEF (SMD=29%), and the EuroSCORE II (SMD=29%). After IPTW, all these imbalances were corrected except peripheral artery disease (weighted SMD=26%) and a slight difference in sex category emerged (weighted SMD=21).
- Between TAVR and ConsRx groups there were differences in age (SMD=59%), hypertension (SMD=45%), chronic kidney disease (SMD=51%), chronic obstructive pulmonary disease (SMD=39%), coronary artery disease (SMD=48%), peripheral

atery disease (SMD=29%), atrial fibrillation/flutter ((SMD=33%), diastolic blood pressure (SMD=26%), New York Heart Association functional class III-IV (SMD=56%), Duke Activity Status Index (SMD=117%), mean gradient (SMD=47%), TSAS (SMD=47%), NT-proBNP (SMD=40%), and the EuroSCORE II (SMD=90%). These major differences were partially balanced after IPTW. DASI was refractory to IPTW (weighted SMD=121%), while the differences in age (weighted SMD=33%), hypertension (weighted SMD=25%), chronic kidney disease (weighted SMD=23%), mean gradient (weighted SMD=27%), and the euroSCORE II (weighted SMD=33%) were attenuated but not balanced. These differences were only equilibrated with unacceptably high weights. A difference in pulmonary hypertension not present before emerged after IPTW (weighted SMD=23%). Of note, except for pulmonary hypertension, all the residual balances favored a healthier conservative treatment group.

- Between TAVR vs. SAVR, there were also major baseline differences in age (SMD=104%), body mass index (SMD=34%), hypertension (SMD=59%), chronic kidney disease (SMD=56%), chronic obstructive pulmonary disease (SMD=22%), previous coronary artery bypass grafting (SMD=70%), previous myocardial infarction (SMD=25%), coronary artery disease (SMD=28%), peripheral artery disease (SMD=58%), atrial fibrillation/flutter (SMD=25%), diastolic blood pressure (SMD=39%), congestive heart failure (SMD=21%), New York Heart Association function class II-IV (SMD=22%), Duke activity status index (SMD=90%), mean gradient (SMD=21%), TSAS (SMD=40%), LVEF (SMD=40%), NTproBNP (SMD=31%) and the euroSCORE II (SMD=116%). Duke activity status index was refractory to IPTW (weighted SMD=90%). The remaining differences were corrected (weighted SMD≤20%), except for age (weighted SMD=36%), peripheral artery

disease (weighted SMD=29%), TSAS (weighted SMD=21%) and the euroSCORE II (weighted SMD=50%) which were only attenuated. Again, these differences would have required unacceptably high weights to be addressed.

Table S1. Multiple Logistic Regression to Predict Aortic Valve Replacement. This Model Allowed Generating the Propensity Score Used For Inverse Probability-Of-Treatment Weighting.

	β coefficient ±	Wald	p value
Year of inclusion	0.16±0.04	17.694	<0.001
Age	-0.03±0.01	5.332	0.021
Female	-0.1±0.28	0.138	0.710
True severe AS	1.54±0.28	29.732	0.000
Previous coronary artery bypass grafting	0.36±0.33	1.190	0.275
Peripheral artery disease	-1.08±0.46	5.532	0.019
Diabetes	0.08±0.26	0.106	0.745
Chronic kidney disease	-0.53±0.3	3.192	0.074
Hypertension	0.04±0.3	0.016	0.900
Previous stroke	0.18±0.34	0.268	0.605
Hyperlipidemia	-0.32±0.28	1.308	0.253
Chronic obcructive pulmonary disease	-0.82±0.28	8.365	0.004
Previous myocardial infarcyun	0.93±0.28	10.786	0.001
Any coronary artery disease	-1.01±0.48	4.494	0.034
Multivessel coronary artery disease	0.08±0.19	0.197	0.657
Congestive heart failure	0.23±0.29	0.607	0.436
History of pulmonary oedema	-1.1±0.38	8.513	0.004
Body mass index	0±0.02	0.005	0.945
Systolic blood pressure	-0.01±0.01	1.668	0.197
Diastolic blood pressure	0.01±0.01	0.755	0.385
Heart rate	-0.01±0.01	0.906	0.341
Paced rhythm	-0.21±0.26	0.606	0.436
Atrial fibrillation	0.3±0.33	0.816	0.366
EuroSCORE II	0.03±0.03	1.524	0.217
Betablockers	0.16±0.25	0.437	0.509
Diuretics	0.31±0.27	1.281	0.258
New York Heart Association functional class III-IV	0.83±0.25	10.914	0.001
Mean gradient	0.01±0.04	0.149	0.700
Aortic valve area	-0.43±0.63	0.464	0.496
Left ventricular ejection fraction	0.02±0.02	1.906	0.167
Paradoxical vs. Classical LFLG-AS	-0.39±0.51	0.586	0.444
Duke Activity Status Index	-0.03±0.01	3.090	0.079
Intercept	-315.35±75.11	17.628	0.001

Results are β coefficients ± standard errors

Table S2. Baseline Characteristics in Patients with True Severe Aortic Stenosis (TSAS) Compared to Patients with Pseudo-Severe Aortic Stenosis (PSAS).

	True-severe AS (n=293)	Pseudo-severe AS (n=133)	P value
Clinical data			
Age, y	74±11	74±9	0.61
Male sex, n(%)	203(69)	102(77)	0.09
Diabetes, n(%)	101(35)	44(33)	0.82
Chronic kidney disease i.e. eGFR≤60ml/min, n(%)	71(24)	46(35)	0.02
Chronic obstructive pulmonary disease, n(%)	69(24)	40(30)	0.14
Previous CABG	76(26)	38(29)	0.54
Previous myocardial infarction, n(%)	97(33)	64(49)	0.002
Coronary artery disease	184(63)	84(64)	0.87
Peripheral artery disease, n(%)	26(9)	7(5)	0.20
Previous stroke/transient ischemic attack	40(14)	21(16)	0.56
Atrial fibrillation/flutter, n(%)	60(21)	12(9)	0.004
Heart rate, bpm	72±14	69±13	0.06
Systolic/diastolic blood pressure, mmHg	121±20/71±11	126±16/72±11	0.03/0.57
Symptoms and functional status			
History of CHF, n(%)	147(50)	77(58)	0.12
NYHA Functional class, n(%)			0.03
I-II	123(42)	70(53)	
III-IV	170(58)	61(47)	
Duke activity status index	19[18-31]	19[12-36]	0.24
The Aortic valve hemodynamics			
Aortic valve area, cm^2	0.76±0.18	0.92±0.25	<0.001
Mean gradient, mmHg	29±8	20±7	<0.001
Peak aortic jet velocity, m/s	3.5±1.8	3.0±1.8	<0.001
True AS severity			
Confirmed true severe AS, n(%)	281(100)	0(0)	<0.001
AVA_{Proj}, cm^2	0.89±0.16	1.19±0.13	
AVA_{Proj} ≤1.0 cm^2, $n/n_{available}$ (%)	121/140(86)	0/66(0)	
Aortic valve calcification ratio*	1.51±0.62	0.59±0.25	
Aortic valve calcification ratio ≥1.0, $n/n_{available}$ (%)	88/100(88)	0/54(0)	
Aortic valve weight ratio*	1.34±0.42	0.81±0.11	
Aortic valve weight ratio ≥1.0, $n/n_{available}$ (%)	72/93(77)	0/13(0)	
Macroscopic assessment of surgically explanted valve, $n/n_{available}$ (%)	91/117(78)	0/14(0)	
Left ventricular function			
Stroke volume index, ml/beat/m^2	31[25-36]	32[26-36]	0.80
LVEF, %	32[25-49]	33[25-50]	0.99
Indexed LVEDD, mm/m^2	29±5	30±6	0.02
Classical/Paradoxical LFLG n(%)	204(70)	98(74)	0.33
NT-proBNP, pg/ml	2216 [918-4329]	1478 [560-4096]	0.13
Systolic pulmonary artery pressure	44±13	40±13	0.02
Operative risk			
EuroSCORE, %	6.6±5.7	6.8±6.0	0.77

Values are mean ±SD, median [IQR], and n (%)

*Aortic valve calcification ratio was calculated by dividing the actual aortic valve calcium score by the sex-specific threshold that defines severe AS i.e. 1200 and 2000 arbitrary units respectively for women and men. Similarly, aortic valve weight ratio is the actual valve weight divided by the sex-specific valve weight that defines true severe AS i.e. 1.2 g and 2.0 g respectively for women and men (13)

eGFR: estimated filtration rate; COPD: chronic obstructive pulmonary disease; NYHA: New York Heart Association; DASI: Duke activity status index; AVA: aortic valve area; AVAProj projected AVA at normal flow i.e. mean systolic flow 250 ml/s; AS: aortic stenosis ; LVEF: left ventricular ejection fraction ; LVEDD: left ventricular end diastolic volume ; NT-proBNP: aminoterminal proB-type natriuretic peptide.

Table S3. Baseline Characteristics in Patients Undergoing Early Aortic Valve Replacement (AVR) Compared to Patients Conservatively Managed (ConsRx) Before and After Inverse Probability-of-Treatment Weighting.

	Before IPTW			After IPTW		
	Early AVR (n=274)	Conservative (n=207)	SMD (%)	Early AVR (n=476)	Conservative (n=446)	SMD (%)
Year of surgery	2009.6±3.4	2008.4±4.1	32	2009.0±3.7	2009.3±4.1	08
Age, y	74.0±10.0	75.0±10.0	10	73.8±10.4	75.7±9.8	19
Male sex, %	70.1	72.5	5	66.2	73.1	15
Body mass index, kg/m²	27.7±5.5	27.5±5.7	4	27.3±5.3	27.2±5.3	2
Diabetes, %	35.4	32.9	5	32.4	36.8	9
Hypertension, %	25.2	27.5	5	70.3	70.0	1
Hyperlipidemia, %	71.9	64.7	16	66.9	72.2	12
Chronic kidney disease i.e. eGFR≤60ml/min, %	31.4	24.2	16	25.5	29.8	10
Chronic obstructive pulmonary disease, %	29.6	18.8	25	22.9	23.3	1
Previous CABG, %	26.3	25.1	3	23.4	29.1	13
Previous myocardial infarction, %	30.7	44.4	29	32.0	39.0	15
Coronary artery disease, %	67.5	53.1	30	57.8	64.6	14
Previous stroke or transient ischemic attack, %	14.2	14.5	1	14.1	13.5	2
History of peripheral artery disease, %	8.0	8.7	3	5.7	12.8	**25**
Atrial fibrillation/flutter, %	19.0	13.0	16	15.3	19.3	11
Heart rate, bpm	71±12	71±13	0	71±12	72±14	8
Systolic blood pressure, mmHg	122±20	124±19	10	123±18	121±19	11
Diastolic blood pressure, mmHg	71±11	71±10	0	72±12	71±11	9

History of CHF, %	51	54	6	51	59	18
Previous acute pulmonary oedema, %	19.7	14.5	14	17.5	11.9	16
NYHA III-IV, %	64	44	41	57.6	56.7	02
Duke activity status index	18±13	27±15	64	23.4±16.6	23.4±15.6	0
Aortic valve area, cm^2	0.78±0.19	0.85±0.21	35	0.80±0.19	0.82±0.2	10
Mean gradient, mmHg	27±8	22±8	63	25.5±7.8	24.6±8.2	11
Confirmed true severe AS, %	75.5	41.5	74	65.9	60.1	12
LVEF, %	39±17	36±15	19	38±18	34±14	**24**
Classical LFLG, %	75	69	13	69.7	81.8	**29**
Moderate mitrale regurgitation, %	12	12	0	10.7	12.2	05
SPAP >35 mmHg, %	50	45	10	45.1	50.1	10
Ln NT-proBNP	7.8±1.4	7.1±6.3	15	7.7±1.3	7.9±1.7	13
EuroSCORE II, %	7.1±6.3	6±4.9	19	6.4±6.1	6.6±4.9	04

Values are mean ±SD and %

In bold: variables with SMD >20 i.e. insufficiently balanced

eGFR: estimated filtration rate; IPTW: inverse probability-of-treatment weighting; LFLG: low-flow, low-gradient; LVEF: left ventricular ejection fraction ; NYHA: New York Heart Association; SMD: standardized mean difference; SPAP: systolic pulmonary artery pressure

Table S4. Baseline Characteristics in Patients Undergoing Early Surgical Aortic Valve Replacement (SAVR) Compared to Patients Conservatively Managed (ConsRx) Before and After Inverse Probability-of-Treatment Weighting.

	Before IPTW			After IPTW		
	SAVR (n=177)	Conservative (n=207)	SMD (%)	SAVR (n=397)	Conservative (n=316)	SMD (%)
year of inclusion	2008.0±3.3	2008.0±4.1	2	2008.0±3.4	2008.0±4	3
Age, y	70.8±10.3	75.0±10.0	41	72.5±10.1	74.1±10.3	-15
Male sex, %	72.2	72.5	1	67.0	76.0	**21**
Body mass index, kg/m²	28.3±5.7	27.5±5.7	14	27±5.5	27.5±5.4	8
Diabetes, %	34.1	32.9	3	28.0	33.2	11
Hypertension, %	50.6	44.9	11	43.5	46	6
Hyperlipidemia, %	70.5	64.7	12	67.2	68.6	2
Chronic kidney disease i.e. eGFR≤60ml/min, %	22.2	24.2	5	21.3	22.3	3
Chronic obstructive pulmonary disease, %	15.3	25.1	25	23.2	23.9	0
Previous CABG, %	15.3	25.1	25	23.0	23.6	0
Previous myocardial infarction, %	26.7	44.4	38	32.1	39.1	15
Coronary artery disease, %	63.1	53.1	20	54.0	57.0	5
Previous stroke or transient ischemic attack, %	11.9	14.5	8	12.4	13.4	4
History of peripheral artery disease, %	2.3	8.7	28	2.2	7.1	**26**
Atrial fibrillation/flutter, %	15.3	12.6	8	11.1	15.2	13
Heart rate, bpm	72.0±13.2	71.0±13.3	7	71.7±12.2	71.4±13	2
Systolic blood pressure, mmHg	121.6±19.1	123.8±19.4	12	123.4±18.2	123.1±18.9	2
Diastolic blood pressure, mmHg	72.7±11.2	71.1±10.3	15	73.1±11.2	72.2±10.8	8
History of CHF, %	47.2	53.6	13	53.4	55.0	5
Previous acute pulmonary oedema, %	18.8	14.5	12	17.1	14.2	8

NYHA III-IV, %	60.2	43.5	34	58	49	18
Duke activity status index	22.7±14.1	26.7±15.3	28	26±15.5	26.5±15.7	3
Aortic valve area, cm^2	0.7±0.1	0.8±0.2	41	0.8±0.1	0.8±0.2	17
Mean gradient, mmHg	27.7±7.5	22.2±8.2	69	25.2±7.2	23.7±8.3	19
Confirmed True Severe AS, %	81.8	41.5	91	58	54	9
LVEF, %	41.4±18.7	36.3±16	29	37.9±18.4	34.9±15.4	18
Classical LFLG, %	65.3	74.9	21	72	77	10
Moderate mitrale regurgitation. %	10.0	12.0	6	9	9	0
SPAP >35 mmHg, %	50.6	44.9	11	43	46	6
Ln NT-proBNP	7.5±1.5	7.4±1.5	9	7.6±1.4	7.4±1.5	11
EuroSCORE II, %	4.6±4.4	6±4.8	29	5.3±4.4	5.9±4.6	15

Values are mean ±SD and %

In bold: variables with SMD >20 i.e. insufficiently balanced

eGFR: estimated filtration rate; IPTW: inverse probability-of-treatment weighting; LFLG: low-flow, low-gradient; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; SMD: standardized mean difference; SPAP: systolic pulmonary artery pressure

Table S5. Baseline Characteristics in Patients Undergoing Early Transcatheter Aortic Valve Replacement (TAVR) Compared to Patients Conservatively Managed (ConsRx) Before and After Inverse Probability-of-Treatment Weighting.

	Before weighting			After weighting		
	TAVR (n=98)	Conservative (n=207)	SMD (%)	TAVR (n=202)	Conservative (n=320)	SMD (%)
year of inclusion	2011.7±2.3	2008.4±4.1	97	2011.2±2.5	2009.7±4.1	**45**
Age, y	80.2±7.4	75.0±10.0	59	79.8±8.1	76.9±9.2	**33**
Male sex, %	66.3	72.5	13	70.9	75.9	11
Body mass index, kg/m²	26.5±4.6	27.5±5.7	19	27±4.8	27.7±5.3	14
Diabetes, %	37.8	32.9	10	34.2	35.3	2
Hypertension, %	89.8	72.8	45	89.2	80.3	25
Hyperlipidemia, %	74.5	64.7	21	73.9	71.8	5
Chronic kidney disease i.e. eGFR≤60ml/min, %	48.0	24.2	51	38.6	27.9	23
Chronic obstructive pulmonary disease, %	35.7	18.8	39	29.2	31.9	6
Previous CABG, %	45.9	25.1	45	38.6	38.2	1
Previous myocardial infarction, %	37.8	44.4	13	44.3	38.9	11
Coronary artery disease, %	75.5	53.1	48	73.9	64.7	20
Previous stroke or transient ischemic attack, %	18.4	14.5	11	19.2	19.4	1
History of peripheral artery disease, %	18.4	8.7	29	13.9	11.9	6
Atrial fibrillation/flutter, %	25.5	12.6	33	22.2	15.9	16
Heart rate, bpm	69.6±10.7	71±13.3	12	69.8±10.5	68.9±14.3	7
Systolic blood pressure, mmHg	122.2±18.7	123.8±19.4	9	126.3±18.6	126.0±19.0	2

Diastolic blood pressure, mmHg	68.3±11.4	71.1±10.3	26	69.5±10.6	70.0±10.5	5
History of CHF, %	57.1	53.6	7	53.5	59.4	12
Previous acute pulmonary oedema, %	21.4	14.5	18	12.8	10.9	6
NYHA III-IV, %	70.4	43.5	56	69.5	56.7	27
Duke activity status index	12.3±8.2	26.7±15.3	117	11.2±7.6	25.9±15.4	**121**
Aortic valve area, cm^2	0.8±0.2	0.8±0.2	20	0.8±0.2	0.8±0.2	11
Mean gradient, mmHg	26.1±7.9	22.2±8.2	47	25.1±7.6	23.1±7.4	**27**
Confirmed True Severe AS, %	64.3	41.5	47	50.0	48.3	3
LVEF, %	34.8±12.5	35.7±15.4	6	34.9±11.9	33.9±15.2	8
Classical LFLG, %	75.5	74.9	1	74.9	76.9	5
Moderate mitral regurgitation	15.4	12	10	13.7	21.8	21
SPAP >35 mmHg, %	49.0	44.9	8	40.1	51.6	**23**
Ln NT-proBNP	7.9±1.1	7.4±1.5	40	7.9±1	7.9±1.6	2
EuroSCORE II, %	11.3±6.8	6±4.8	90	9.3±6.1	7.4±5.2	**33**

Values are mean ±SD and %

In bold: variables with SMD >20 i.e. insufficiently balanced

eGFR: estimated filtration rate; IPTW: inverse probability-of-treatment weighting; LFLG: low-flow, low-gradient; LVEF: left ventricular ejection fraction ; NYHA: New York Heart Association; SMD: standardized mean difference; SPAP: systolic pulmonary artery pressure

Table S6. Baseline Characteristics in Patients Undergoing Transcatheter Aortic Valve Replacement (TAVR) Compared to Patients Undergoing Surgical Aortic Valve Replacement (SAVR) Before and After Inverse Probability-of-Treatment Weighting.

	Before IPTW			After IPTW		
	TAVR (n=98)	SAVR (n=177)	SMD	TAVR (n=174)	SAVR (n=267)	SMD
year of inclusion	2011.7±2.4	2008.4±3.3	116	2011.3±2.4	2009.2±3.4	**74**
Age, y	80.3±7.5	70.9±10.4	104	77.8±9.1	74.2±10.8	**36**
Male sex, %	66.3	72.6	14	71.3	72.4	2
Body mass index, kg/m²	26.5±4.7	28.3±5.8	34	27.2±5.1	27.7±5.2	10
Diabetes, %	37.8	34.3	7	36.8	30.1	14
Hypertension, %	89.8	66.3	59	82.3	75	18
Hyperlipidemia, %	74.5	70.9	8	72.4	71.3	2
Chronic kidney disease i.e. eGFR≤60ml/min, %	48.0	22.3	56	35.6	32.0	8
Chronic obstructive pulmonary disease, %	35.7	25.7	22	28.7	23.8	11
Previous CABG, %	45.9	15.4	70	34.5	25.8	19
Previous myocardial infarction, %	37.8	26.3	25	33.3	31.9	3
Coronary artery disease, %	75.5	62.9	28	70.7	65.6	11
Previous stroke or transient ischemic attack, %	18.4	12	18	19.0	16.3	7
History of peripheral artery disease, %	18.4	1.7	58	10.9	3.5	**29**
Atrial fibrillation/flutter, %	25.5	15.4	25	19.0	15.6	9
Heart rate, bpm	69.6±10.7	72±13.2	20	69.4±10.2	71.4±12.7	18
Systolic blood pressure, mmHg	122.3±18.8	121.6±19.1	3	126.7±18.7	125.3±18.8	7
Diastolic blood pressure, mmHg	68.3±11.4	72.8±11.3	39	70.4±10.1	72.5±10.7	21
History of CHF, %	57.1	46.9	21	44.3	52.5	16
Previous acute pulmonary oedema, %	21.4	18.9	6	19.5	23.0	9
NYHA III-IV, %	70.4	60.0	22	66.9	61.1	12
Duke activity status index	12.3±8.3	22.7±14.1	90	10.7±7.7	20.9±14.1	**90**

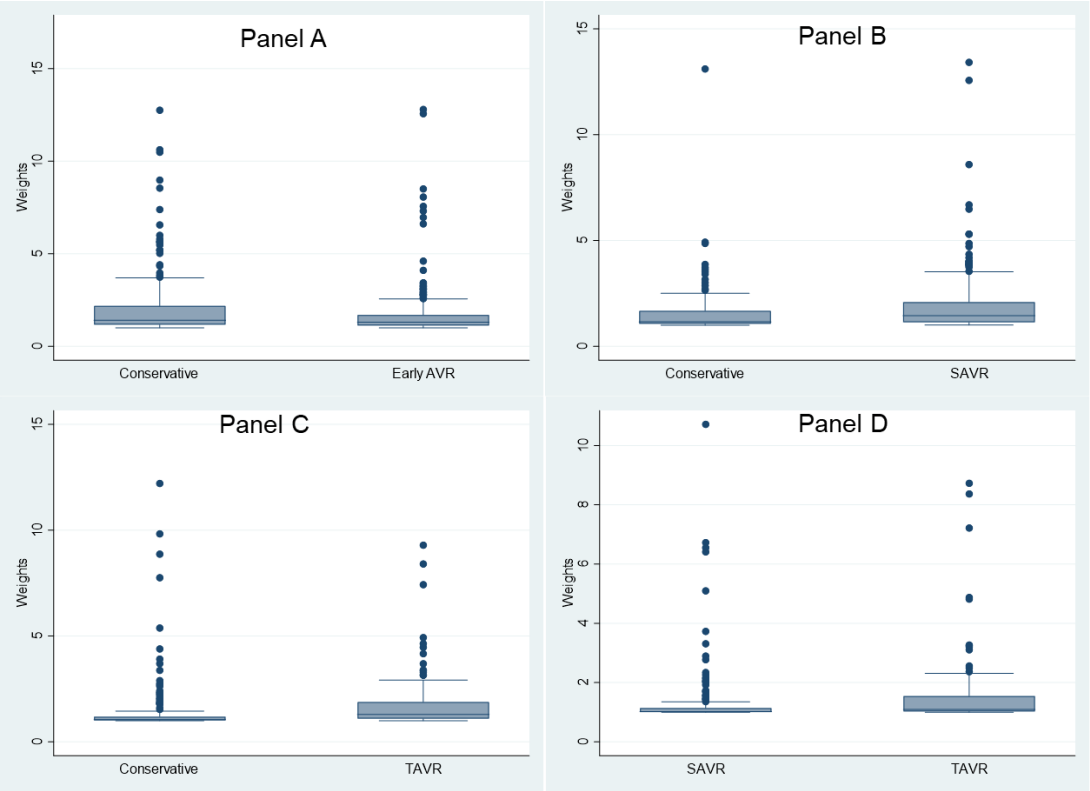
Aortic valve area, cm^2	0.8±0.2	0.8±0.2	20	0.8±0.2	0.8±0.2	11
Mean gradient, mmHg	26.1±8	27.8±7.6	21	26.5±8.7	27.6±7.3	14
Confirmed True Severe AS, %	64.3	81.7	40	64.9	74.7	**21**
LVEF, %	34.9±12.6	41.3±18.7	40	57.3±15.1	56.7±10.6	5
Classical LFLG, %	75.5	65.3	22	65.5	61.7	8
Moderate mitral regurgitation, %	15.4	10.0	16	11.2	11.2	0
SPAP >35 mmHg, %	49.0	50.6	3	46.0	52.1	12
Ln NT-proBNP	8±1.1	7.6±1.6	31	7.9±1.1	7.8±1.5	9
EuroSCORE II, %	11.4±6.8	4.7±4.5	116	9.1±6.6	6.2±5	**50**

Values are mean ±SD and %

In bold: variables with SMD >20 i.e. insufficiently balanced

eGFR: estimated filtration rate; IPTW: inverse probability-of-treatment weighting; LFLG: low-flow, low-gradient; LVEF: left ventricular ejection fraction ; NYHA: New York Heart Association; SMD: standardized mean difference; SPAP: systolic pulmonary artery pressure

Figure S1. Distribution of inverse probability-of-treatment weights stratified by the different pairs of treatment arm.



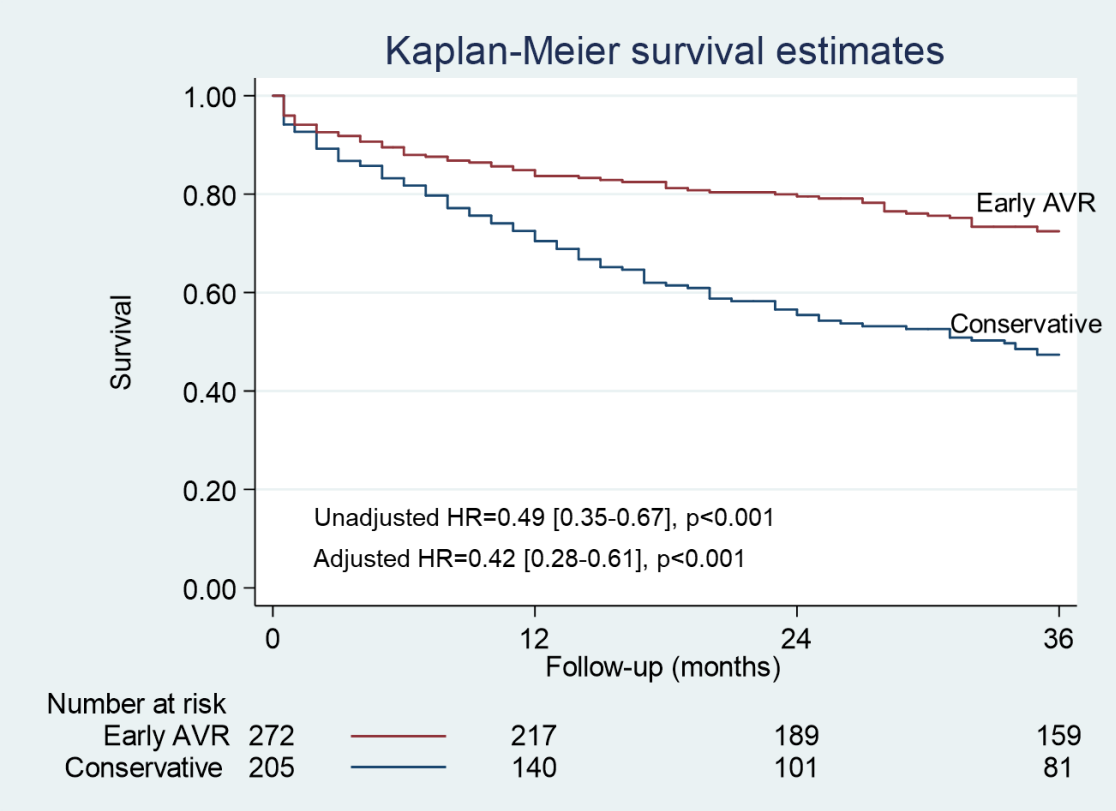
In Panel A, conservative strategy (median weight [1st-3rd quartile] 1.41 [1.16-2.19]) vs. early AVR (1.30 [1.12-1.70]);

In Panel B, conservative (1.16 [1.06-1.68]) vs. early SAVR (1.46 [1.13-2.12]);

In Panel C, conservative (1.05 [1.01-1.21]) vs. TAVR (1.30 [1.09-1.92]);

In Panel D, SAVR (1.02 [1.00-1.17]) vs. TAVR (1.10 [1.02-1.59]).

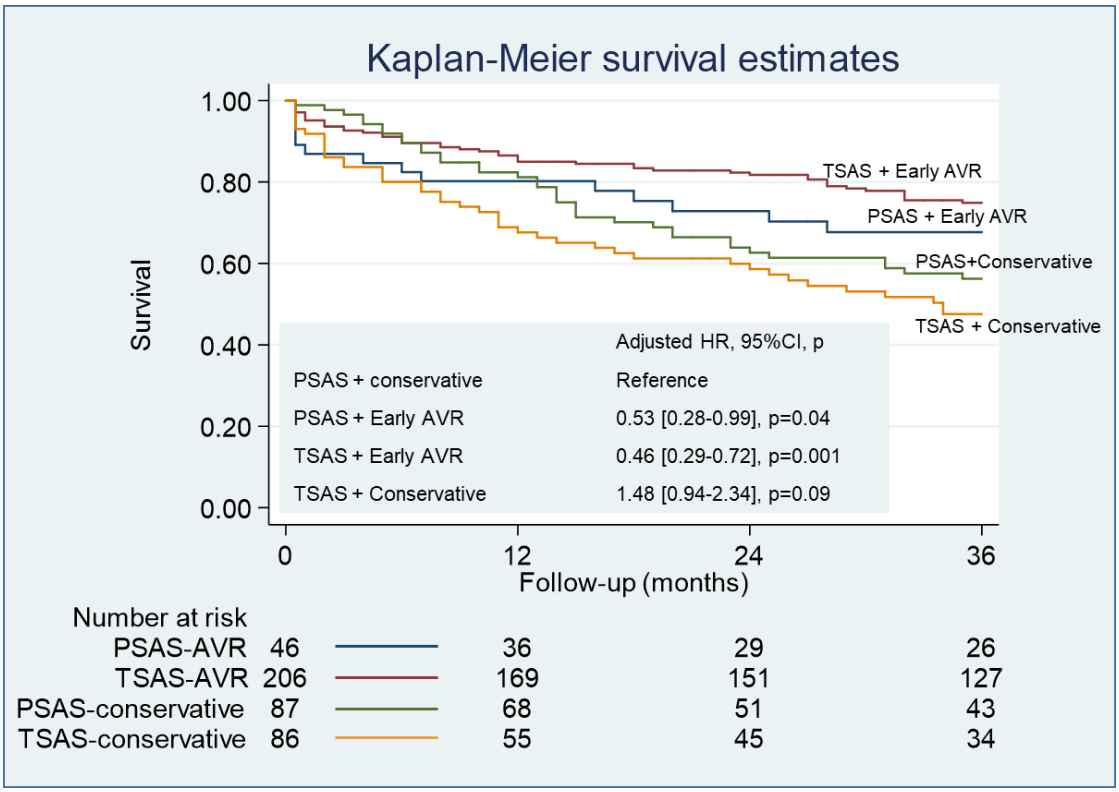
Figure S2. Survival benefit associated with aortic valve replacement (non-weighted population).



The benefit of aortic valve replacement was studied in the original population to corroborate the findings with inverse probability of treatment weighting. A multilevel, mixed effect survival model was used to account for potential clustering effect of the participating centers.

Adjusted hazard ratio (HR): see supplemental methods for details regarding multivariate analysis. AVR: aortic valve replacement.

Figure S3. Survival Benefit Associated With Aortic Valve Replacement After Stratification According to the Presence of True or Pseudo-Severe AS (Non-Weighted Population).



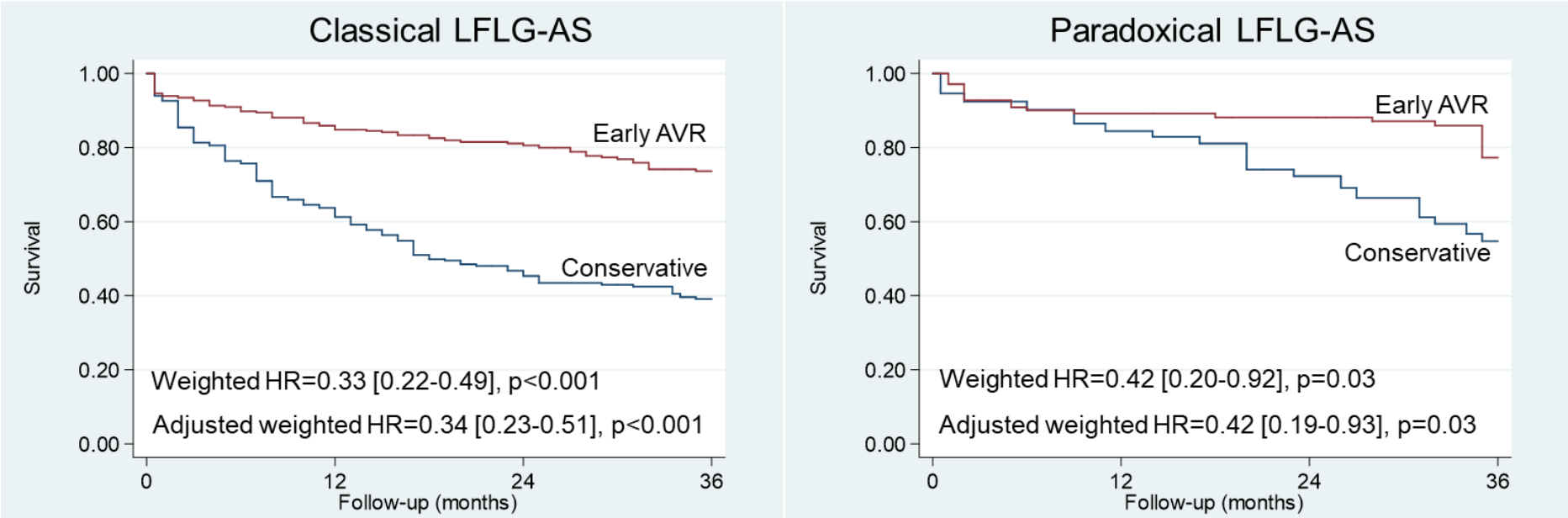
The benefit of aortic valve replacement was studied in the original population to corroborate the findings with inverse probability of treatment weighting.

Adjusted hazard ratio (HR): see supplemental methods for details regarding multivariate analysis

TSAS/PSAS: true/pseudo-severe aortic stenosis; AVR: aortic valve replacement; ConsRx: conservative management.

*Patients with indeterminate AS severity (n=56) were excluded and 3 of 425 remaining patients were lost to follow up

Figure S4. Survival Benefit Associated With Aortic Valve Replacement in Classical (Left Panel) and Paradoxical LFLG-AS (Right Panel) Using Inverse Probability-of-Treatment Weighting.



The adjusted weighted hazard ratios are adjusted for peripheral artery disease which remained significant despite IPTW (see Table S3).

AVR: aortic valve replacement.