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ORIGINAL ARTICLE
Aortic valvular heart disease

TAVR versus surveillance in patients with moderate aortic stenosis and heart failure: a conversion-censored analysis of the TAVR UNLOAD trial

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Abstract

Background The neutral TAVR UNLOAD trial randomized patients with heart failure with reduced ejection fraction and moderate aortic stenosis (AS) to transcatheter aortic valve replacement (TAVR) or clinical AS surveillance (CASS). Frequent conversion from CASS to TAVR, primarily due to AS progression, potentially reduced the benefit of TAVR vs CASS.

Aims To identify conversion predictors and evaluate outcomes censoring CASS patients at conversion.

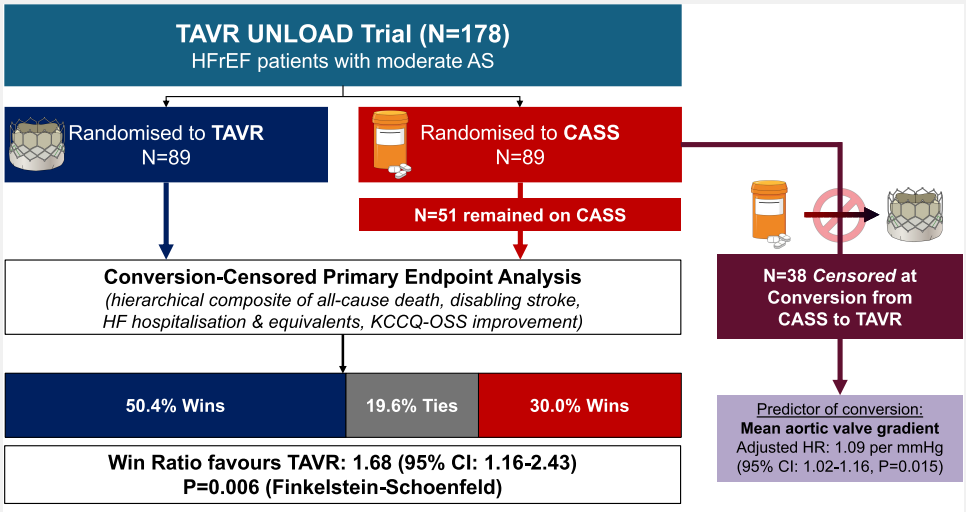
Methods and results Patients eligible for balloon-expandable transfemoral TAVR were 1:1 randomized to TAVR or CASS. The hierarchical primary endpoint comprised all-cause death, disabling stroke, heart failure hospitalization/equivalents, and quality of life change. Analyses were performed to longest follow-up, censoring CASS patients at TAVR. Baseline predictors of conversion were identified using cause-specific multivariable Cox regression. Between 2017 and 2022, 178 patients (77 ± 9 years; 21% female; 56% New York Heart Association ≥ III) were randomized (TAVR *n* ampa#thinsp;89; CASS *n* ampa#thinsp;89). During a median follow-up of 690 days, 38 CASS patients (43%) underwent TAVR after a median of 366 days. After censoring, the primary endpoint favoured TAVR over CASS [50% vs 30% wins; 20% ties; win ratio: 1.68 (95% CI: 1.16–2.43); $P = .006$]. Adjusting for age, sex, atrial fibrillation, and left ventricular ejection fraction, the mean aortic valve gradient was the only independent conversion predictor [HR per mmHg: 1.09 (95% CI: 1.02–1.16); $P = .015$].

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Conclusions In patients with heart failure with reduced ejection fraction and moderate AS, TAVR conferred benefit over CASS when censoring CASS patients at conversion. Although caution is warranted given the observational nature of the comparison, these findings suggest that these patients may derive clinical benefit from TAVR, warranting confirmation in a larger trial.

Graphical abstract



Study design and key outcomes of this exploratory conversion-censored analysis of the TAVR UNLOAD trial. A total of 178 patients with HFrEF and moderate AS were randomized to TAVR ($n = 89$) or CASS ($n = 89$). During follow-up, 38 patients (43%) initially assigned to CASS converted to TAVR, whereas 51 remained under surveillance. Mean aortic valve gradient was the strongest predictor of conversion. In the conversion-censored hierarchical composite primary endpoint analysis, TAVR achieved more wins than CASS. AS, aortic stenosis; CASS, conservative aortic stenosis surveillance; CI, confidence interval; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; TAVR, transcatheter aortic valve replacement.

Keywords Moderate aortic stenosis • Heart failure • HFrEF • TAVR • Surveillance • Conservative

Introduction

Transcatheter aortic valve replacement (TAVR) is a safe, effective, and guideline-endorsed therapy for patients with severe aortic stenosis (AS).[1,2] In contrast, no formal recommendation exists for TAVR in moderate AS, although untreated moderate AS is associated with excess mortality and affects ~2% of the population, with prevalence increasing with age.[3–5] Patients with heart failure with reduced ejection fraction (HFrEF) represent a particularly vulnerable population, burdened by high mortality and heart failure (HF) hospitalizations.[6,7] In fact, in a recently published analysis including over 400 000 patients, those with moderate AS and HFrEF had a 10-year survival rate of only 15.5%, compared with 37.3% in patients with no or mild AS, corresponding to a significant lifetime loss of 1.9 years.[7]

Transcatheter aortic valve replacement for moderate AS in the context of HFrEF is a compelling complementary target for afterload reduction and was studied in the Transcatheter Aortic Valve Replacement to UNload the Left ventricle in patients with ADvanced heart failure (TAVR UNLOAD) trial (NCT02661451).[8] The trial, which was terminated prematurely, did not demonstrate superiority of TAVR compared with clinical AS surveillance (CASS) in patients with HFrEF.[8] However, during follow-up, a substantial proportion of CASS patients underwent TAVR, primarily due to progression to severe AS. Therefore, the present study sought to identify baseline predictors of conversion from CASS to TAVR and to assess outcomes when censoring CASS patients at the time of TAVR.

Methods

Study design and patient population

The TAVR UNLOAD trial design, methodology, and protocol modifications have been reported previously.[8,9] Importantly, the trial was terminated prematurely due to funding constraints and slower-than-anticipated enrolment.[8] In brief, TAVR UNLOAD was an investigator-initiated, international, randomized controlled, open label, superiority trial comparing transfemoral TAVR with CASS in patients with HFrEF and moderate AS who remained symptomatic (New York Heart Association functional class II–IV) despite ≥1-month stable guideline-directed medical therapy (GDMT), including cardiac resynchronization therapy as appropriate. Eligible patients had a left ventricular ejection fraction (LVEF) between 20% and 50% and moderate AS, which was defined by an aortic valve area (AVA) > 1.0 and ≤1.5 cm^2 on resting echocardiography. In cases of low-flow physiology, dobutamine stress echocardiography was performed. Patients with AVA <1.0 cm^2 but indexed AVA >0.6 cm^2/m^2, or AVA >1.5 cm^2 but indexed AVA <0.9 cm^2/m^2, were also classified as moderate AS. Additional inclusion and exclusion criteria were reported previously.[8,9] Patients were randomized in a 1:1 fashion to transfemoral TAVR with a balloon-expandable valve (BEV; SAPIEN 3 family, Edwards Lifesciences) or to CASS. For patients randomized to CASS, by

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protocol, conversion to TAVR was allowed, only upon progression to severe AS, as determined by echocardiography.[8]

Study endpoints and follow-up

For this analysis, CASS patients who were converted to TAVR were censored at the time they received TAVR. The primary study endpoint was a hierarchical composite of (1) all-cause death, (2) disabling stroke, (3) disease-related hospitalizations and HF hospitalization equivalents, and (4) change from baseline in the Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS). Disease-related hospitalizations were defined as admissions for HF, symptomatic aortic valve disease, or non-disabling stroke. HF hospitalization equivalents included urgent visits to the emergency department or outpatient clinics, as well as the intensification of HF therapy. The hospitalization for TAVR was not counted as a valve-related hospitalization in both patients randomized to TAVR and CASS. In contrast to our prior publication, prolonged hospital stays >5 days during the TAVR admission were not counted as a valve-related hospitalization. This was applied to both treatment arms, as prolonged post-procedural stays were almost always related to procedural complications or logistical reasons rather than HF.[1,8] Change in KCCQ-OSS from baseline was categorized as an improvement ≥10 points, an improvement of ≥5 to <10 points, a change of <5 points, a worsening of ≥5 to <10 points, or a worsening of ≥10 points.

Key secondary endpoints included (1) the hierarchical composite of all-cause death, disabling stroke, or disease-related hospitalizations and their equivalents, (2) time to first occurrence of all-cause death, disabling stroke, or hospitalization for HF or aortic valve disease, including HF hospitalization equivalents (major adverse cardiovascular and cerebrovascular events, MACCE), (3) time to all-cause death, and (4) change in KCCQ-OSS. Sensitivity analyses were performed by censoring follow-up at 1 year. Additionally, outcomes were evaluated among CASS patients who converted to TAVR, using a landmark at the time of TAVR.

All clinical events were adjudicated by an independent clinical events committee. Echocardiograms were evaluated by dedicated core laboratories (Quebec Heart and Lung Institute Echo Core Laboratory, Quebec, Canada; Cardiovascular Research Foundation, New York, USA). Further methodological details have been reported previously.[8]

Statistical analysis

Continuous variables are presented as mean ± standard deviation or as median with interquartile range, according to distribution, and compared using the unpaired Student's *t*-test or the Mann–Whitney *U* test, as appropriate. Normality was assessed using the Shapiro–Wilk test. Categorical variables are expressed as counts and proportions (*n*/*N*, %) and were compared with the chi-square test or Fisher's exact test.

All outcome analyses censored CASS patients at the time of TAVR, unless otherwise specified. For the primary endpoint, patients in the TAVR and CASS cohorts were compared across all possible patient pairs. For each pair, a win was assigned to TAVR, to CASS, or scored as a tie, according to the hierarchical occurrence of the primary endpoint assessed at the longest common follow-up. The win ratio was calculated as the number of wins for TAVR divided by those for CASS, with 95% confidence intervals (CIs) obtained by bootstrapping and two-sided *P*-value estimated using the Finkelstein–Schoenfeld method. For time-to-first-event analyses, hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards models. The proportional hazards assumption was evaluated with Schoenfeld residuals. Event probabilities are displayed using Kaplan–Meier curves and compared with the log-rank test. Recurrent HF hospitalization or equivalent events were analysed with Andersen–Gill models using cluster-robust standard errors, with all-cause death treated as a terminal event and CASS patients censored at TAVR. In CASS patients who underwent TAVR, event rates before and after conversion to TAVR were compared using Poisson regression models with patient-level fixed effects, post-conversion follow-up was censored at death.

Predictors of conversion from CASS to TAVR were evaluated using cause-specific Cox models, treating all-cause death as a competing risk. Missing baseline data were handled with multiple imputations by chained equations (20 imputed datasets, predictive mean matching for continuous variables and logistic regression for categorical variables). Variables with >20% missingness were excluded. Variables with $P < .10$ in univariable analyses were entered into multivariable models together with age, sex, atrial fibrillation, and LVEF. HRs with 95% CIs were reported from pooled estimates across imputations.

Analysis of covariance (adjusted for baseline values) was performed to compare mean changes in KCCQ-OSS at longest available and 1-year follow-up, with CASS patients censored at conversion to TAVR. Least-squares mean differences (TAVR minus CASS) with 95% CIs are reported. All analyses included clinical endpoints and, when applicable, KCCQ-OSS outcomes occurring between randomization and the censoring date of the current analysis, defined as 31 December 2023, 1 year or 5 years after randomization, or the latest date of known endpoint status, whichever was applicable. Two-sided *P*-values <.05 were considered statistically significant without correction for multiple comparisons. All analyses were performed using R version 4.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient population and conversion to TAVR

From January 2017 to December 2022, a total of 178 patients were randomized 1:1 to TAVR (*N* ampa#thinsp;89) or CASS (*N* ampa#thinsp;89) across 66 institutions in the United States, the Netherlands, and Austria. Among patients assigned to CASS, 38 (42.7%) underwent TAVR after a median of 366 days (Q1–Q3: 179–576), whereas 51 (57.3%) remained on CASS. Most CASS patients undergoing TAVR (28 out of 38, 73.7%) received TAVR during the first 18 months of follow-up. The timing of conversion is depicted in *Figure 1*. Of the 38 CASS patients who underwent TAVR, 35 (92.1%) had progression to severe AS. One additional patient who declined TAVR underwent balloon aortic valvuloplasty after experiencing several episodes of hospitalization for HF.

Baseline clinical and echocardiographic characteristics

Baseline clinical and echocardiographic characteristics are summarized in *Tables 1* and *2*. Baseline characteristics were similar between CASS patients who remained on surveillance and those who later underwent TAVR. However, CASS patients who converted to TAVR tended to have lower STS scores and higher KCCQ-OSS at the time of enrolment. Echocardiographically, these patients exhibited higher mean aortic valve gradients, lower dimensionless valve indices, and lower right ventricular systolic pressure.

Predictors of conversion to TAVR

Univariable predictors of conversion to TAVR among CASS patients are reported in Supplementary Table S1. The only statistically significant predictor was the baseline mean aortic valve gradient. This association remained significant after forcing age, sex, atrial fibrillation, and left ventricular ejection fraction into the model [$HR_{adjusted}$: 1.09 (95% CI: 1.02–1.16); *P* ampa#thinsp;.015, *Table 3*].

During the pre-conversion period, annualized HF or equivalent hospitalization rates were 65.3 per 100 patient-years in CASS patients who subsequently converted to TAVR (27 events) and 47.3 per 100 patient-years in CASS patients who did not convert throughout the entire follow-up (36 events), with no significant difference between groups [HR: 1.34 (95% CI: 0.70–2.58); $P = .382$].

Clinical outcomes

Primary and secondary endpoints

At longest follow-up, the hierarchical primary composite endpoint favoured TAVR over CASS when censoring CASS patients at the time of conversion, with 50% wins for TAVR, 30% wins for CASS and

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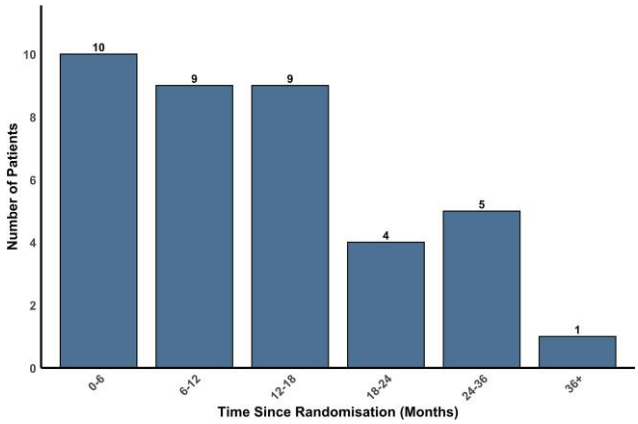


Figure 1 Timing of TAVR in the CASS arm. CASS, clinical aortic stenosis surveillance; TAVR, AVRtranscatheter aortic valve replacement

20% ties [win ratio: 1.68 (95% CI: 1.16–2.43); $P = .006$]. The hierarchical secondary endpoint, composed of the same components except for KCCQ-OSS, numerically favoured TAVR, but did not reach statistical significance with 36% wins for TAVR, 23% wins for CASS, and 42% ties [win ratio: 1.59 (95% CI: 0.99–2.52); $P = .052$, *Figure 2*]. Results were consistent in a sensitivity analysis that was limited to 1-year follow-up (Supplementary Figure S1).

Time-to-event analyses demonstrated a significantly higher MACCE rate among CASS compared to TAVR patients (*Figure 3*), which was directionally aligned in the 1-year sensitivity analysis (Supplementary Figure S2). No significant difference in all-cause mortality was observed, either at longest follow-up (*Figure 3*) or at 1 year (Supplementary Figure S2).

Changes in KCCQ

At longest available follow-up, KCCQ-OSS was obtained in 85 patients randomized to TAVR and 73 randomized to CASS, of whom 33 were censored at conversion to TAVR. In the TAVR group, mean KCCQ-OSS increased from 57.1 ± 24.4 to 67.9 ± 24.8, corresponding to a mean change of 10.8 ± 21.9 points. In the CASS group, censored at conversion to TAVR, mean KCCQ-OSS increased from 54.5 ± 22.3 to 58.0 ± 26.4, a mean change of 3.5 ± 24.5 points. In analysis of covariance adjusted for baseline, follow-up KCCQ-OSS was higher with TAVR compared with CASS [least-squares mean difference: 8.3 points (95% CI: 1.5–15.0); $P = .016$]. At 1 year, mean KCCQ-OSS increased to 69.7 ± 24.7 in TAVR patients (mean change from baseline 12.6 ± 22.8) and to 57.4 ± 26.0 in CASS (mean change from baseline of 2.9 ± 23.2), resulting in higher follow-up KCCQ-OSS with TAVR compared to CASS [least-squares mean difference: 10.9 points (95% CI: 4.1–17.5; *P* ampa#thinsp;.002)]. Consistent with these findings, a ≥5 point improvement in KCCQ-OSS was observed in 61.2% of TAVR vs 43.8% of CASS patients at longest follow-up prior to TAVR conversion (*P* ampa#thinsp;.044). At 1 year, after censoring 15 CASS patients at conversion to TAVR, the proportions were 67.1% vs 43.8% (*P* ampa#thinsp;.006).

Outcomes after conversion to TAVR

The median follow-up after conversion in the CASS arm was 444 days (Q1–Q3: 230–952). Following TAVR, event rate for HF hospitalizations or equivalents declined to 25.5 per 100 patient-years in patients randomized to CASS [relative risk: 0.34 (95% CI 0.15–0.75); $P = .008$], with a total of 16 events after conversion. A total of 14 deaths occurred after TAVR among CASS patients (Supplementary Figure S3).

Among 28 CASS patients who converted to TAVR and had KCCQ-OSS data available at the last assessment before and the first assessment after conversion, KCCQ-OSS increased from 54.5 ± 25.7 to 63.5 ± 20.0 points, corresponding to a mean change of 9.0 ± 27.2 points.

Discussion

In this exploratory analysis of the TAVR UNLOAD trial, we assessed baseline predictors of conversion from CASS to TAVR and outcomes when censoring CASS patients at the time of conversion to TAVR. The following principal findings were observed: first, conversion occurred in nearly half of the patients with HFrEF and moderate AS assigned to CASS and occurred predominantly within the first 18 months after randomization. Second, the only independent baseline predictor of conversion was the mean aortic valve gradient. Third, when censoring patients at the time of conversion, TAVR was associated with a significant benefit in the hierarchical primary endpoint, which was confirmed for the time-to-event MACCE analyses, but not for all-cause mortality. After conversion, patients experienced fewer HF hospitalizations than before conversion; yet, all-cause mortality remained high. Fourth, KCCQ-OSS improvement was significantly greater in patients undergoing TAVR compared with patients assigned to CASS and censored at the time of TAVR.

The observation that nearly half of the patients assigned to CASS crossed over to TAVR, primarily because of progression to severe AS, is an interesting signal requiring attention. In clinical practice, we usually anticipate slower rates of AS progression, with a mean decrease of aortic valve area of 0.1 cm^2 per year or an increase of mean aortic valve gradients of ~8 mmHg per year.[10] However, several studies have suggested that patients with AS can be categorized as those with slow or rapid AS progression.[10,11] In this context, Peter *et al.*[12] identified greater age and the presence of coronary artery disease as factors associated with rapid AS progression. With a mean age of ~77 years and ~80% of patients with coronary artery disease, patients enrolled in the TAVR UNLOAD trial certainly might fall into to the category of patients who are prone to more rapid AS progression.[11] Within this population, the only independent predictor of conversion from CASS to TAVR was the mean aortic valve gradient at baseline, emphasizing the necessity of close surveillance (≤6 months rather

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Table 1 Clinical characteristics of the patients at baseline

	TAVR (N = 89)	CASS (N = 51)	$CASS_{TAVR}$ (N = 38)	*P*-value[a]
Age, y	76.6 ± 7.7	77.4 ± 7.2	79.4 ± 5.5	.135
Sex, female	16/89 (18.0)	11/51 (21.6)	10/38 (26.3)	.788
Body mass index, kg/m^2	28.8 (25.2–33.2) (N = 88)	26.9 (25.1–31.6) (N = 50)	28.1 (25.5–32.7) (N = 38)	.379
STS PROM score, %[b]	3.0 (2.1–5.0) (N = 85)	4.0 (2.4–6.3) (N = 50)	3.2 (2.1–5.2)	.180
NYHA functional class				.235
I	1/89 (1.1)	0/51 (0.0)	1/51 (2.6)	
II	34/89 (38.2)	26/51 (51.0)	17/51 (44.7)	
III	51/89 (57.3)	22/51 (43.1)	20/51 (52.6)	
IV	3/89 (3.4)	3/51 (5.9)	0/51 (0.0)	
KCCQ-OSS	57.1 ± 24.4 (N = 87)	51.0 ± 20.0 (N = 48)	59.4 ± 23.5 (N = 34)	.097
6-min walk distance, m	235 (118–347) (N = 85)	221 (110–304) (N = 47)	216 (123–369) (N = 34)	.452
Comorbidities				
Any HFH during the past 12 mo	37/88 (42.0)	26/50 (52.0)	16/38 (42.1)	.481
Coronary artery disease	66/89 (74.2)	41/51 (80.4)	29/38 (76.3)	.839
Previous myocardial infarction	40/89 (44.9)	25/51 (49.0)	15/38 (39.5)	.496
Previous coronary revascularisation	61/89 (68.5)	39/51 (76.5)	26/38 (68.4)	.545
Previous stroke	8/89 (9.0)	5/51 (9.8)	3/38 (7.9)	>.999
Pre-existing implantable devices				
Pacemaker	11/89 (12.4)	2/51 (3.9)	4/38 (10.5)	.395
ICD	31/89 (34.8)	19/51 (37.3)	12/38 (31.6)	.741
CRT	10/89 (11.2)	0/51 (0.0)	0/38 (0.0)	N/A
Peripheral vascular disease	19/89 (21.3)	14/50 (28.0)	6/38 (15.8)	.273
Chronic obstructive pulmonary disease	14/89 (15.7)	14/51 (27.5)	6/38 (15.8)	.295
Creatinine >2 mg/dL	7/85 (8.2)	2/49 (4.1)	2/37 (5.4)	>.999
Atrial fibrillation	40/88 (45.5)	25/50 (50.0)	25/38 (65.8)	.206
Frailty condition[c]	17/56 (30.4)	9/32 (28.1)	7/25 (28.0)	>.999
Diabetes mellitus	37/89 (41.6)	24/51 (47.1)	16/38 (42.1)	.803
Heart failure medications				
ACE inhibitors, ARB, or ARNI	63/87 (72.4)	36/50 (72.0)	27/38 (71.1)	>.999
Beta-blockers	77/87 (88.5)	43/51 (84.3)	32/38 (84.2)	>.999
Mineralocorticoid receptor antagonists	46/87 (52.9)	23/50 (46.0)	13/36 (36.1)	.487
Diuretics	70/88 (79.5)	44/51 (86.3)	33/38 (86.8)	>.999
Cardiac glycosides	12/86 (14.0)	6/50 (12.0)	5/37 (13.5)	>.999

Values are n/N (%), median (Q1–Q3), or mean ± SD.

ACE, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CASS, conservative aortic stenosis surveillance; CRT, cardiac resynchronization therapy; HFH, heart failure hospitalization; ICD, implantable cardioverter-defibrillator; KCCQ-OSS, Kansas City Cardiomyopathy Questionnaire Overall Summary Score; NYHA, New York Heart Association; PROM, predicted risk of mortality; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.

[a]Statistical comparisons were performed between the two CASS subgroups.

[b]STS-PROM ranges from 0% to 100%, higher values reflect an increased risk of 30-day mortality after the procedure.

[c]Frailty was defined as the presence of ≥3 of the following: grip strength <18 kg, 5-meter walk-test time >6 s, serum albumin <3.5 g/dL, or a Katz Index of Independence in Activities of Daily Living ≤4 (scale 0–6, with higher values indicating greater independence).

than 1 year) of this vulnerable and diagnostically challenging patient population.

The frequent and rapid progression to severe AS in our population may also indicate how challenging echocardiographic evaluation may be in HFrEF and low-flow situations. In the TAVR UNLOAD trial, only 44.9% (80 of 178) of patients underwent dobutamine stress echocardiography, raising the possibility that a substantial proportion of the remaining patients may already have had severe, or at least moderate-to-severe, AS at baseline. These observations highlight the importance of multimodality imaging, including dobutamine stress echocardiography and multislice computed

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Table 2 Echocardiographic characteristics of the patients at baseline

	TAVR (N = 89)	CASS (N = 51)	$CASS_{TAVR}$ (N = 38)	*P*-value[a]
Aortic valve				
Aortic valve peak gradient, mmHg	34.0 ± 15.8	30.1 ± 10.2	33.1 ± 9.9 (N = 37)	.175
Aortic valve mean gradient, mmHg	19.1 ± 6.0	17.5 ± 5.7	20.0 ± 5.9 (N = 37)	**.046**
Aortic valve area, cm^2	1.14 ± 0.24 (N = 88)	1.22 ± 0.21 (N = 50)	1.15 ± 0.16 (N = 37)	.080
Dimensionless valve index	0.26 (0.22–0.30) (N = 88)	0.28 (0.26–0.31) (N = 50)	0.26 (0.24–0.30) (N = 36)	**.034**
Left atrium and ventricle				
Left atrial volume, mL	84 (72–101) (N = 87)	88 (69–108) (N = 49)	99 (73–117) (N = 36)	.199
Left ventricular ejection fraction, %	38 (33–44) (N = 88)	38 (31–44)	39 (33–42) (N = 37)	.386
Left ventricular end-diastolic volume, mL	172 (145–209) (N = 88)	170 (145–214)	174 (160–208) (N = 37)	.568
Left ventricular end-diastolic diameter, cm	5.9 (5.40–6.2)	5.9 (5.4–6.2) (N = 50)	5.8 (5.3–6.1) (N = 36)	.636
Right ventricle				
Tricuspid annular plane systolic excursion, cm	1.66 (1.37–2.00) (N = 80)	1.58 (1.37–1.77) (N = 46)	1.67 (1.4–2.17) (N = 36)	.194
Right ventricular systolic pressure, mmHg	28 (22–34) (N = 59)	26 (18–33) (N = 41)	33 (22–38) (N = 32)	.090
Moderate or moderate-to-severe regurgitation[b]				
Aortic	3/87 (3.4)	2/49 (4.1)	0/36 (0.0)	.506
Mitral	6/87 (6.9)	4/47 (8.5)	2/36 (5.6)	.693
Tricuspid	12/80 (15.0)	5/46 (10.9)	7/34 (20.6)	.375

Values are n (%), median (Q1–Q3), or mean ± SD. Bold values indicate statistical significance.
CASS, conservative aortic stenosis surveillance; TAVR, transcatheter aortic valve replacement.
[a]Statistical comparisons were performed between the two CASS subgroups.
[b]There were no cases of severe mitral regurgitation, aortic regurgitation, or tricuspid regurgitation at baseline.

Table 3 Baseline multivariable predictors of conversion from conservative aortic stenosis surveillance to conservative aortic stenosis surveillance

Variable	HR	95% CI	*P*-value
Aortic valve mean gradient per mmHg increase	1.09	1.02–1.16	**.015**
Age per year	1.05	0.99–1.10	.082
Atrial fibrillation	2.01	0.91–4.44	.084
Female vs male	1.05	0.48–2.26	.906
Left ventricular ejection fraction per % increase	1.00	0.95–1.06	.947

Bold values indicate statistical significance.
CASS, conservative aortic stenosis surveillance; CI, confidence interval; HR, hazard ratio; TAVR, transcatheter aortic valve replacement.

tomography in the evaluation of patients with low-flow AS. At the same time, they argue against reliance on formal echocardiographic Doppler cut-offs for risk stratification and therapeutic decision-making to treat AS, as AS represents a disease continuum rather than a binary disease.

The concept of AS as a continuum is further supported by recent findings from Jacquemyn *et al.*[7], who demonstrated that even within moderate AS, lower AVA values correlate with higher mortality independent of gradients, suggesting current severity thresholds may need reconsideration in high-risk populations like HFrEF. This aligns with our finding that baseline mean gradient predicted conversion to TAVR, indicating that some patients classified as moderate AS might benefit from earlier TAVR rather than awaiting traditional severe AS criteria.

Censoring CASS patients at the time of conversion demonstrated significant benefit in the hierarchical primary endpoint, driven by more wins on HF hospitalizations and equivalents, as well as greater improvements in quality of life. On the other hand, however, no significant impact of TAVR was observed on all-cause death or disabling stroke. Aligning with the findings form the hierarchical primary endpoint, patients treated with TAVR experienced a greater and clinically meaningful improvement in health status as assessed by the KCCQ-OSS, both at longest follow-up and 1 year. It should be acknowledged that the KCCQ-OSS analysis involves some heterogeneity in follow-up duration; yet, the 1-year results consistently support these findings. Overall, these findings reinforce the notion that, in the setting of moderate AS and HFrEF, GDMT alone does not substantially improve quality of life, whereas TAVR seems to demonstrate a symptomatic benefit.

The hierarchical secondary endpoint, excluding improvements in quality of life, was directionally aligned with the primary endpoint, and was driven by more wins regarding HF hospitalizations and equivalents—a finding that was replicated in the time-to-event MACCE analyses. These findings need to be interpreted against the background of an underpowered and neutral trial. However, the finding that censoring at conversion to TAVR shifted the composite outcomes significantly in favour of TAVR suggests that the neutral overall result of the TAVR UNLOAD trial was partly driven by the high frequency of TAVR in the surveillance arm. In this regard, our analysis aligns with the concept that earlier afterload reduction may improve outcomes, reinforcing the clinically held notion that patients with HFrEF with moderate AS could

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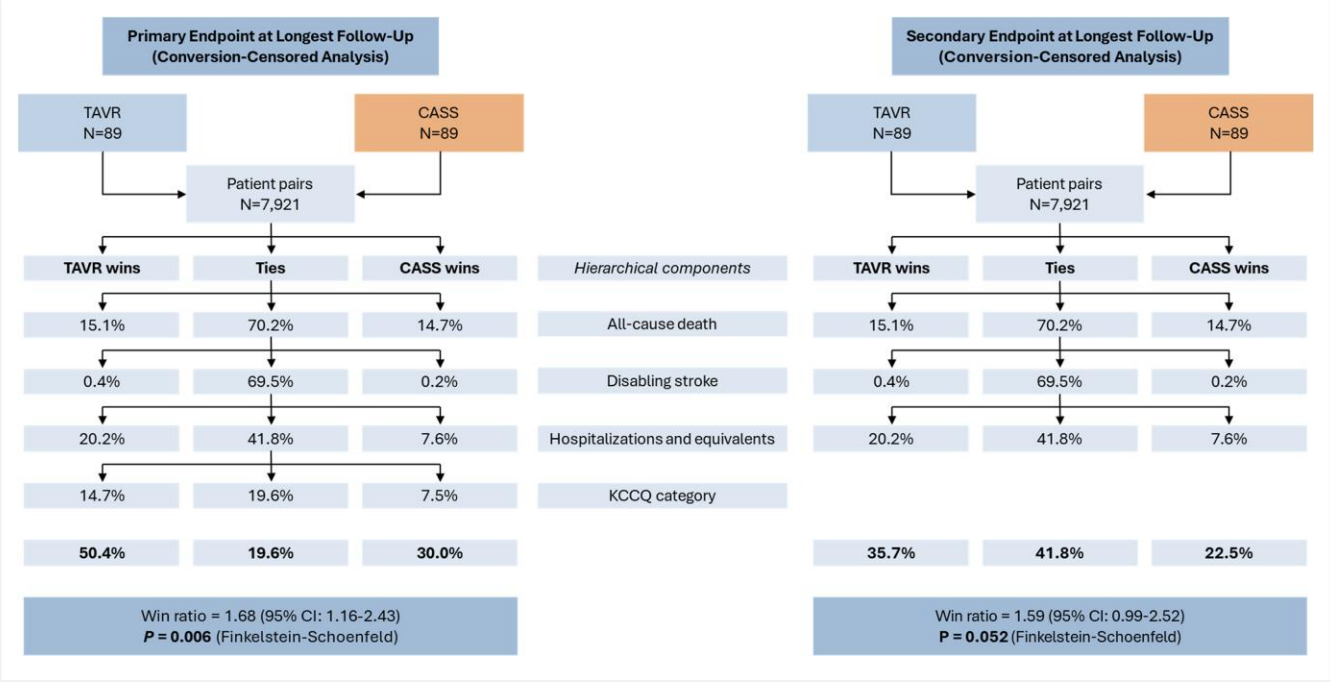


Figure 2 CASS–censored primary and secondary hierarchical endpoints. Hierarchical analysis of the composite primary and secondary endpoints, censoring patients in the CASSarm at the time of TAVR. CASS, clinical aortic stenosis surveillance; CI, confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; TAVR, transcatheter aortic valve replacement

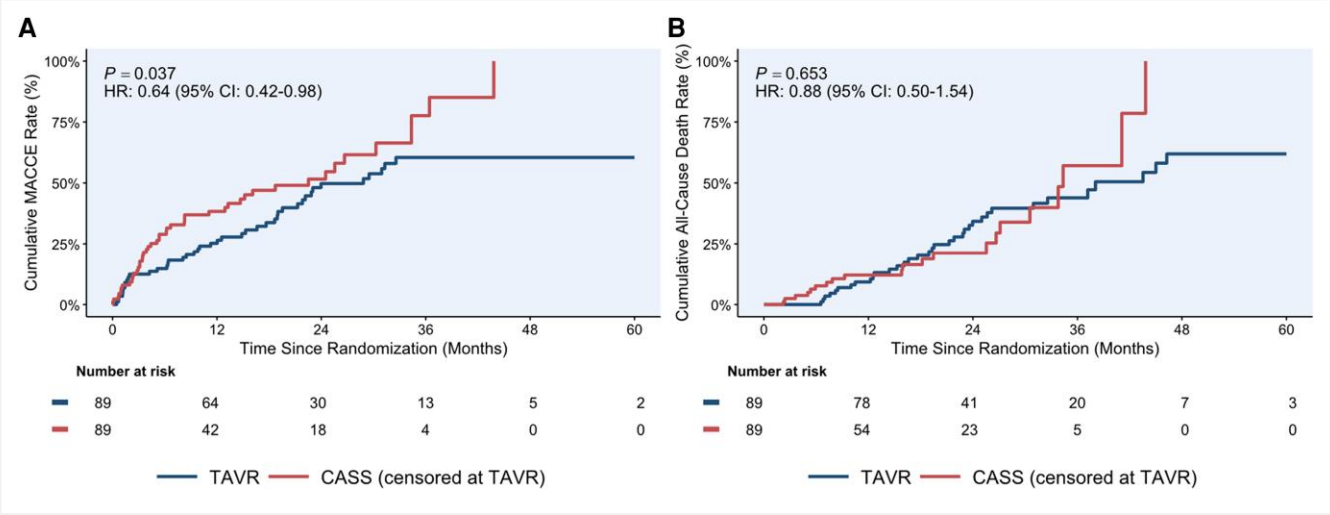


Figure 3 CASS–censored secondary time-to-event endpoints. Kaplan–Meier curves with censoring of CASS patients at the time of TAVR. (*A*) Time to first occurrence of the major adverse cardiovascular and cerebrovascular event composite endpoint, comprised of all-cause death, disabling stroke, or hospitalization for heart failure or aortic valve disease, including heart failure hospitalization equivalents. At longest follow-up, the cumulative event rate was 64.6% (95% CI: 49.7–75.0%) in the TAVR arm and 100% (95% CI: NA) in the CASS arm. (*B*) All-cause death, with rates at longest follow-up of 61.9% (95% CI: 42.7–74.7%) in the TAVR arm vs 100% (95% CI: NA) in the CASS arm. CASS, clinical aortic stenosis surveillance; CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular event; TAVR, transcatheter aortic valve replacement

benefit from TAVR. This is highlighted by the observation that after conversion, patients experienced a marked reduction in HF hospitalizations or equivalents, indicating symptomatic and functional benefit even when the procedure was deferred. However, mortality after conversion remained substantial, consistent with the advanced clinical profile of patients enrolled in the TAVR UNLOAD trial. These observations

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suggest that delaying intervention until progression to severe AS may limit the potential for improvements in quality of life and morbidity. At the same time, these findings might challenge current dogmatic guideline recommendations for intervention in patients with AS.[1] As mentioned above, AS might be more of a continuum that requires integration of more factors into its assessment, as opposed to a variable that warrants a dichotomous cut-off value, particularly when diagnostics becomes more challenging, e.g. in the presence of HFrEF.

Taken together, these findings refine the lessons from TAVR UNLOAD. While the trial did not demonstrate superiority of TAVR for HFrEF with moderate AS, our analysis indicates that progression to severe AS is common and suggests that subsequent TAVR has the potential to alleviate the burden of recurrent HF hospitalizations and improves health status. Future, adequately powered, trials are warranted to clarify the value and optimal timing of valve intervention in HFrEF patients with moderate AS. Based on the challenges observed in the TAVR UNLOAD trial, possible steps forward might be to further raise awareness for moderate AS in the context of HFrEF. Moreover, pooling HFrEF patients with moderate AS from multiple randomized controlled trials, including TAVR UNLOAD, and the ongoing PROGRESS (NCT04889872), and Evolut™ EXPAND TAVR II (NCT05149755) trials might provide a more robust database for future analyses. Until then, close surveillance with timely referral for TAVR upon AS progression remains the most prudent strategy.

Limitations

The TAVR UNLOAD trial is the largest randomized trial on TAVR compared with surveillance for patients with HFrEF with moderate AS. Nevertheless, several aspects require careful interpretation. First, premature trial termination limited statistical power and restricted the number of events, thereby limiting the precision of effect estimates. Second, censoring CASS patients at the time of conversion, while informative, inevitably introduces bias. The surveillance cohort remaining after censoring consisted of patients whose AS did not progress or did not clinically require TAVR, therefore, representing a clinically more stable subset. Consequently, the randomized comparison shifts towards patients randomized to TAVR vs a selected group of patients with a more favourable natural history, which may attenuate the observed treatment effect of TAVR. Third, mortality remained substantial in both arms, indicating that TAVR addresses only one component of the multifaceted disease burden in advanced HFrEF. Fourth, background GDMT has evolved since trial enrolment, as angiotensin receptor–neprilysin inhibitors and sodium–glucose cotransporter-2 inhibitors were not yet established as standard therapies at that time. Finally, the trial population was modest in size, enrolled at specialized centres, and restricted to treatment with a single balloon-expandable platform, which may limit the generalisability of these findings.

Conclusions

In TAVR UNLOAD, TAVR was associated with a significant benefit over CASS in HFrEF patients with moderate AS, when CASS patients were censored at conversion. Nearly half of CASS patients ultimately underwent TAVR, with mean aortic valve gradient emerging as the only independent factor predicting TAVR in CASS patients. These findings suggest that patients with moderate AS and HFrEF may derive clinical benefit from TAVR; however, a larger confirmatory trial is needed to establish its role in this population.

Supplementary data

Supplementary data are available at *European Heart Journal – Valvular and Structural Heart Disease* online.

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Declarations

Data Availability

The data underlying this article may be shared upon reasonable request to the corresponding author, subject to approval by the TAVR UNLOAD trial steering committee and in accordance with participant consent and applicable ethical requirements. Requests should be directed to n.vanmieghem@gmail.com.

Disclosure of Interest

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Pre-registered Clinical Trial Number

Trial Name: Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure (TAVR UNLOAD).

ClinialTrials.gov Identifier: NCT02661451

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