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SGLT2-inhibitors in diabetic patients with severe aortic stenosis and cardiac damage undergoing transcatheter aortic valve implantation (TAVI)

Pasquale Paolisso[1,3†], Marta Belmonte[3,4†], Emanuele Gallinoro[1], Roberto Scarsini[5], Luca Bergamaschi[6], Leonardo Portolan[5], Matteo Armillotta[6], Giuseppe Esposito[7], Elisabetta Moscarella[8,9], Giovanni Benfari[5], Claudio Montalto[7], Monika Shumkova[3], Elayne Kelen de Oliveira[3,4], Francesco Angeli[6], Mateusz Orzalkiewicz[6], Margherita Fabroni[5], Nurcan Baydaroglu[7], Andrea Raffaele Munafò[7], Daniele Oreste D'Atri[10], Matteo Casenghi[11], Lucia Scisciola[12], Michelangela Barbieri[12], Raffaele Marfella[12], Felice Gragnano[8,9], Edoardo Conte[1,2], Dario Pellegrini[10], Alfonso Ielasi[10], Daniele Andreini[1,2], Martin Penicka[3], Jacopo Andrea Oreglia[7], Paolo Calabrò[8,9], Antonio Bartorelli[1,2], Carmine Pizzi[6], Tullio Palmerini[6], Marc Vanderheyden[3], Francesco Saia[6], Flavio Ribichini[5] and Emanuele Barbato[11,13*]

Abstract

Background A substantial number of patients with severe aortic stenosis (AS) undergoing transcatheter aortic valve implantation (TAVI) experience adverse events after TAVI, with health care expenditure. We aimed to investigate cardiac remodeling and long-term outcomes in diabetic patients with severe AS, left ventricular ejection fraction (LVEF) < 50%, and extra-valvular cardiac damage (EVCD) undergoing TAVI treated with sodium-glucose cotransporter-2 inhibitors (SGLT2i) versus other glucose-lowering strategies (no-SGLT2i users).

Methods Multicenter international registry of consecutive diabetic patients with severe AS, LVEF < 50%, and EVCD undergoing TAVI. Based on glucose-lowering therapy at hospital discharge, patients were stratified in SGLT2i versus no-SGLT2i users. The primary endpoint was a composite of all-cause death and heart failure (HF)-hospitalization (major adverse cardiovascular events, MACE) at 2-year follow-up. Secondary outcomes included all-cause death, cardiovascular death, and HF hospitalization.

Results The study population included 311 patients, among which 24% were SGLT2i users. Within 1-year after TAVI, SGLT2i users experienced a higher rate of LV recovery ($p = 0.032$), especially those with baseline LVEF ≤ 30% ($p = 0.026$), despite the lower baseline LVEF. Patients not treated with SGLT2i were more likely to progress to a worse EVCD stage

†Pasquale Paolisso and Marta Belmonte contributed equally to this work.

*Correspondence:
Emanuele Barbato
emanuele.barbato@uniroma1.it

Full list of author information is available at the end of the article

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over time ($p=0.018$). At 2-year follow-up, SGLT2i use was associated with a lower rate of MACE, all-cause death, and HF hospitalization ($p<0.01$ for all). After adjusting for confounding factors, the use of SGLT2i emerged as an independent predictor of reduced MACE (HR = 0.45; 95% CI 0.17–0.75; $p=0.007$), all-cause death (HR = 0.51; 95% CI 0.25–0.98; $p=0.042$) and HF-hospitalization (HR = 0.40; 95% CI 0.27–0.62; $p=0.004$).

Conclusions In diabetic patients with severe AS, LVEF < 50%, and EVCD undergoing TAVI, the use of SGLT2i was associated with a more favorable cardiac remodeling and a reduced risk of MACE at 2-year follow-up.

Keywords Aortic stenosis, TAVI, SGLT2i, Cardiac damage staging, Low-flow low-gradient, Cardiac remodeling, LV recovery, Heart failure, Outcomes, Prognosis

Introduction

Aortic stenosis (AS) accounts for substantial global morbidity and premature mortality, affecting more than 12% of over-75-year-old adults, with an estimated 4.5 million cases diagnosed worldwide by 2030 [1–4]. So far, aortic valve replacement (AVR), either surgical (SAVR) or transcatheter (TAVI), is the only treatment associated with improved outcomes, being recommended once symptoms or left ventricular (LV) dysfunction develop [5]. The presence, extent, and reversibility of extra-valvular (extra-aortic valve) cardiac damage (EVCD) affect the prognosis of AS patients and could even hamper the benefits of AVR [6–9]. Despite device and procedural advances, a substantial number of patients treated with TAVI experience heart failure (HF)-related hospitalizations within the first-year post-implantation, leading to a notable increase in healthcare expenditure and long-term mortality [10].

Medical therapy, albeit ineffective in slowing AS progression, could potentially play a role in EVCD recovery after TAVI [11, 12]. In large, randomized trials, SGLT2i significantly improved cardiovascular and renal outcomes in patients with type 2 diabetes mellitus (T2DM), extending benefits to non-diabetic patients with HF [13–16]. However, data on SGLT2i use in patients with severe valvular heart disease requiring intervention are lacking [13, 15, 16]. We recently demonstrated in patients with severe AS: (i) the expression of SGLT2 protein in human cardiomyocytes; (ii) the hyper-expression of SGLT2 in the subgroup of patients with reduced LV ejection fraction (LVEF < 50%), independently of glucose-metabolic control [17]. Based on these observations, we hypothesized that SGLT2i might promote favorable cardiac remodeling in T2DM patients with severe AS, LVEF < 50%, and EVCD undergoing TAVI. Thus, we investigated the impact of SGLT2i use on cardiac remodeling and long-term outcomes in T2DM patients with severe AS, LVEF < 50%, and EVCD undergoing TAVI compared to no-SGLT2i users.

Methods

Study population

In this multicenter international observational registry consecutive T2DM patients with severe AS, LVEF < 50%, and EVCD [any stage, from 1 to 4 [18]] undergoing TAVI between January 2020 and September 2023 were included. The definition of severe AS, AS phenotype, and indication for TAVI followed current guidelines (Supplementary Files—Extended Methods) [5, 19]. Based on antidiabetic therapy at hospital discharge, patients were stratified in SGLT2i users if they were discharged on SGLT2i therapy and no-SGLT2i users if they received other glucose-lowering strategies. Patients with inadequate echocardiographic data at baseline to assess EVCD and incomplete information on medical therapy at discharge were excluded. Further exclusion criteria were: glomerular filtration rate < 20 ml/min/1.73 m^2, active cancer, follow-up data unavailable or shorter than 6 months, and inability to provide informed consent. The standard transthoracic echocardiographic (TTE) protocol is described in Supplementary Files—Extended Methods. For the follow-up, a TTE performed between 6 and 12 months after TAVI was considered. The present study was conducted according to the principles of the Declaration of Helsinki. The institutional review boards approved the protocol. All patients were informed about their participation in the registry and provided informed consent for the anonymous publication of scientific data.

Extra-aortic valve cardiac damage staging

The extent of EVCD was categorized into 5 stages according to the model described by Genereux et al. [18]: (i) stage 0—no cardiac damage; (ii) stage 1—left ventricular damage, as defined by left ventricular mass index (LVMi) > 115 g/m^2 (male) or > 95 g/m^2 (female), E/E' > 14, LVEF < 50%; (iii) stage 2: left atrial or mitral damage, as defined by left atrial volume index > 34 ml/m^2, moderate to severe mitral regurgitation, atrial fibrillation; (iv) stage 3: pulmonary vasculature or tricuspid damage, as defined by pulmonary artery systolic pressure (PASP) ≥ 60 mmHg, moderate to severe tricuspid regurgitation; (v) stage 4: right ventricular damage, as defined by TAPSE < 17 mm, S' < 9.5 cm/s, and fractional

area change < 35%. Patients were hierarchically classified in one given stage (the worst one) if at least one of the criteria of that stage was met. In this study, EVCD was also dichotomized in Genereux stages 1–2 (isolated left heart dysfunction) and Genereux stages 3–4 (right heart involvement, advanced EVCD), as previously reported [20, 21].

Clinical and echocardiographic endpoints

Patients were followed over time with outpatient visits and telephone contacts using a standard questionnaire. None of the no-SGLT2i users started SGLT2i therapy during follow-up. Clinical outcomes were defined according to the current standards [22]. The primary endpoint of our study was defined as a composite of all-cause death and hospitalization for HF (major adverse cardiovascular events, MACE) at 2-year follow-up. Secondary outcomes included all-cause death, cardiovascular death, and hospitalization for HF at 2-year follow-up. The definition of the clinical endpoints is reported in the Supplementary File—Extended Methods. LV recovery was defined as an EF improvement ≥ 10% associated with a decrease ≥ 20% of LVMi and/or a decrease ≥ 20% of left ventricular end-diastolic volume (LVEDV) at short-term follow-up after TAVI [19, 23–26].

Statistical analysis

Normal distribution of continuous variables was assessed by histograms and q-plot; the Shapiro–Wilk test was used when required. Continuous variables with normal distribution were expressed as the mean ± standard deviation and non-normally distributed variables as median and interquartile range. Categorical variables were expressed as counts and percentages. Differences between groups were analyzed using the t-test or the Mann–Whitney U-test for continuous variables and the chi-square test or the Fisher's exact test for categorical variables, as appropriate. To compare paired data, a Wilcoxon signed test or a Paired sample T-test was performed as appropriate. Univariable analysis was performed to identify clinically relevant variables associated with MACE, all-cause death, and HF hospitalization. Variables showing statistical significance at the 10% level in univariable analysis were then entered into a multivariable analysis using the Cox regression model to determine the independent association of each risk factor with outcomes. The hazard ratio (HR) and the associated 95% confidence interval (CI) for each variable were determined. The final list of covariates was also determined by removing variables that caused high collinearity, as assessed by variance inflation factors. The predicted probability of MACE across continuous LVEF values was calculated based on the Cox proportional hazard regression model, where the covariate LVEF was included as a restricted cubic spline in a cubic polynomial regression model. Kaplan–Meier analysis and Log-rank test were used to compare the cumulative incidence of clinical events between groups. To account for survival bias, a 30-day and 1-year post-TAVI landmark analysis was performed. p-values < 0.05 were considered statistically significant. All analyses were performed using R statistical software version 3.5.2 (R Foundation for Statistical Computing, Vienna, Austria), Statistical Package for Social Sciences, version 28.0 (SPSS, PC version, Chicago, IL, USA), and GraphPad Prism (GraphPad Software, Inc., CA, US).

Results

Study population

The final study population consisted of 311 diabetic patients with severe AS, LVEF < 50%, and EVCD (any stage, from 1 to 4) undergoing TAVI, stratified into SGLT2i (n = 74, 23.8%) and no-SGLT2i users (n = 237) (Supplementary Fig. 1). Among SGLT2i users, 38 (51.4%) patients were prescribed dapagliflozin and 36 (48.6%) empagliflozin, with an increase in prescription rate of SGLT2i in the last 2 years of the study period (Supplementary Table 1).

Baseline and procedural characteristics

Baseline characteristics, cardiovascular risk factors, and comorbidities are reported in Table 1. The median age of the overall study population was 80 [76–84] years, and 66.9% were males. The mean T2DM duration was 14 ± 8 years, similar for both groups ($p = 0.923$). SGLT2i patients were younger, and more frequently males compared to no-SGLT2i users ($p < 0.001$ and $p = 0.016$, respectively, Table 1). At baseline, body mass index, main cardiovascular risk factors, comorbidities, and clinical presentation were similar in the two groups, except for a higher prevalence of atrial fibrillation in SGLT2i users ($p = 0.020$). The STS-PROM score, renal function, and glucose-metabolic control were also not different between the 2 study groups.

The echocardiographic data are reported in Table 2. Overall, the median LVEF was 38 [30–45]%, with a mean peak aortic jet velocity of 3.4 ± 0.5 m/s, a mean gradient of 36 ± 17 mmHg, and a mean AVA of 0.76 ± 0.19 cm^2. No differences in AS severity were observed between the 2 cohorts, even though the rate of classical low flow–low gradient (LF–LG) hemodynamic phenotype was higher among SGLT2i users ($p = 0.003$) (Table 2 and Fig. 1). Overall, SGLT2i users had significantly baseline lower LVEF compared to no-SGLT2i ones ($p = 0.002$) (Table 2). No significant differences were observed in baseline EVCD, with around 40% of patients presenting advanced EVCD with right chamber involvement in both groups (Table 2 and Fig. 1).

Table 1 Baseline characteristics and clinical presentation of the study population, stratified in SGLT2i versus no-SGLT2i users

	Total (N = 311)	SGLT2i users (N = 74)	No-SGLT2i users (N = 237)	*p*-value
Baseline characteristics				
Age, years	80 [75.6–84]	77 [73–81]	81 [77– 84]	< 0.001
Male Sex, n (%)	208 (66.9)	58 (78.4)	150 (63.3)	0.016
BMI, kg/m^2	26.3 [23.9–29.7]	27.1 [24–31.1]	25.9 [23.7–29.2]	0.307
BSA, m^2	1.85 [1.75–1.96]	1.89 [1.81–1.98]	1.83 [1.73–1.95]	0.006
Hypertension, n (%)	261 (83.9)	58 (78.4)	203 (85.7)	0.137
Dyslipidemia, n (%)	250 (80.4)	62 (83.8)	188 (79.3)	0.399
COPD, n (%)	65 (20.9)	16 (21.6)	49 (20.7)	0.861
CKD, n (%)	170 (54.7)	41 (55.4)	129 (54.4)	0.883
Cancer, n (%)	40 (12.9)	5 (6.8)	35 (14.8)	0.072
AF, n (%)	136 (43.7)	41 (55.4)	95 (40.1)	0.020
Previous HF hospitalization	114 (36.7)	25 (33.8)	89 (37.6)	0.557
CAD*, n (%)	199 (64)	53 (71.6)	146 (61.6)	0.117
Previous PCI, n (%)	132 (42.4)	28 (37.8)	104 (43.9)	0.358
Previous CABG, n (%)	57 (18.3)	14 (18.9)	43 (18.1)	0.880
Previous MV surgery, n (%)	2 (0.6)	1 (1.4)	1 (0.4)	0.383
Previous SAVR, n (%)	16 (5.1)	5 (6.8)	11 (4.6)	0.472
STS PROM score	7.3 [4.8–12.9]	7.2 [5.1–13.2]	7.4 [4.3–12.2]	0.174
Clinical presentation				
Angina, n (%)	55 (17.7)	12 (16.2)	43 (18.1)	0.704
Syncope, n (%)	18 (5.8)	8 (10.8)	10 (4.2)	0.034
Dyspnea, n (%)	308 (99)	74 (100)	234 (98.7)	0.331
NYHA ≥ 2, n (%)	303 (97.4)	71 (95.9)	232 (97.9)	0.356
Admission lab test				
Creatinine, mg/dL	1.4 ± 0.5	1.43 ± 0.6	1.39 ± 0.5	0.481
eGFR, mL/min/m^2	51 ± 21	55.6 ± 24	50 ± 19	0.097
HbA1c, mmol/mol	51 [44–58]	53 [48–58]	50 [44–58]	0.574
NT pro-BNP, ng/L	3524 [1554–7961]	3214 [1146–12026]	3688 [1804–7657]	0.769

Continuous variables are presented as mean ± SD or as median [IQR]; while categorical variables as number (%)

SGLT2i sodium/glucose cotransporter 2 inhibitors, *BMI* body mass index, *BSA* body surface area, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease with eGFR < 60 ml/min/m^2, *AF* atrial fibrillation, *HF* heart failure, *CAD* coronary artery disease, *PCI* percutaneous coronary intervention, *CABG* coronary artery bypass graft, *MV* mitral valve, *SAVR* surgical aortic valve replacement, *STS PROM* society of thoracic surgeons predicted risk of mortality, *NYHA* New York heart association, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *NT pro-BNP* N-terminal pro-B-type natriuretic peptide

*CAD was defined by the history of myocardial infarction or significant coronary artery stenosis (≥1 stenosis ≥ 50% within the major epicardial coronary arteries) on coronary angiography or history of coronary revascularization

Table 2 Baseline echocardiographic characteristics and cardiac damage staging of the study population, stratified in SGLT2i versus no-SGLT2i users

	Total (N = 311)	SGLT2i users (N = 74)	No-SGLT2i users (N = 237)	*p*-value
LVEDD, mm	54.1 ± 7.6	56.1 ± 7.7	53.4 ± 7.5	0.016
LVEDDi, mm/m^2	29.4 ± 4.6	29.4 ± 4.5	29.3 ± 4.6	0.577
LVEDV, mL	149.4 ± 54	159.1 ± 57.9	146.1 ± 52.2	0.112
LVEDVi, mm/m^2	79.8 ± 26	82.4 ± 28	78.8 ± 25.5	0.365
IVS, mm	12 [11–13]	12 [11–13]	12 [11–13]	0.890
RWT, mm	0.40 ± 0.11	0.37 ± 0.09	0.41 ± 0.11	0.006
LV Mass, g	247.3 ± 61	258.3 ± 64.6	243.5 ± 59.3	0.076
LV Mass index, g/m^2	133.4 ± 32	135 ± 33	132.7 ± 32	0.555
2D BP LVEF, %	38 [30–45]	35 [26–42]	39 [32–45]	0.002
LAVi, ml/m^2	50.2 ± 15.9	49.5 ± 17.4	50.5 ± 15	0.443
E/e' mean	18.1 ± 6.7	18.1 ± 7.1	18.2 ± 6.5	0.731
Significant MR, n (%)*	28 (9)	8 (10.8)	20 (8.4)	0.807
Significant TR, n (%)*	12 (3.9)	4 (5.4)	8 (3.4)	0.429
Significant AR, n (%)*	10 (3.2)	3 (4.1)	7 (3)	0.124
TAPSE, mm	19 [16–21]	19 [17–21]	19 [16–21]	0.986
PASP, mmHg	40 [34–52]	40 [35–50]	41 [33–54]	0.559
Peak aortic jet velocity, m/s	3.4 ± 0.5	3.3 ± 0.4	4 ± 0.2	0.053
Max AV gradient, mmHg	54 ± 18	46 ± 16	57 ± 19	< 0.001
Mean AV gradient, mmHg	36 ± 17	34 ± 22	35 ± 14	0.076
AVA, cm^2	0.76 ± 0.19	0.80 ± 0.19	0.75 ± 0.20	0.019
AVAi, cm^2/m^2	0.41 ± 0.12	0.41 ± 0.10	0.41 ± 0.13	0.218
Classical LF–LG AS, n (%)	176 (56.6)	53 (71.6)	123 (51.9)	0.003
Extra-valvular cardiac damage staging, n (%)				0.543
Stage 1	48 (15.4)	8 (10.8)	40 (16.9)	
Stage 2	135 (43.4)	34 (45.9)	101 (42.6)	
Stage 3	51 (16.4)	11 (14.9)	40 (16.9)	
Stage 4	77 (24.8)	21 (28.4)	56 (23.6)	
Left versus right chambers cardiac damage staging, n (%)				0.676
Stage 1–2	183 (58.8)	42 (56.8)	141 (59.5)	
Stage 3–4	128 (41.2)	32 (43.2)	96 (40.5)	

Continuous variables are presented as mean ± SD or as median [IQR]; while categorical variables as number (%)

SGLT2i sodium/glucose cotransporter 2 inhibitors, *LV* left ventricle, *LVEDDi* left ventricular end-diastolic diameter indexed, *LVEDVi* left ventricular end-diastolic volume indexed, *IVS* interventricular septum, *BP* biplane, *LVEF* left ventricular ejection fraction, *LAVi* left atrial volume indexed, *MR* mitral regurgitation, *TR* tricuspid regurgitation, *AR* aortic regurgitation, *TAPSE* tricuspid annular plane systolic excursion, *PASP* systolic pulmonary artery pressure, *Max* maximum, *AV* aortic valve, *AVAi* aortic valve area indexed, *LF–LG* low flow low gradient, *AS* aortic stenosis

*> moderate MR/TR

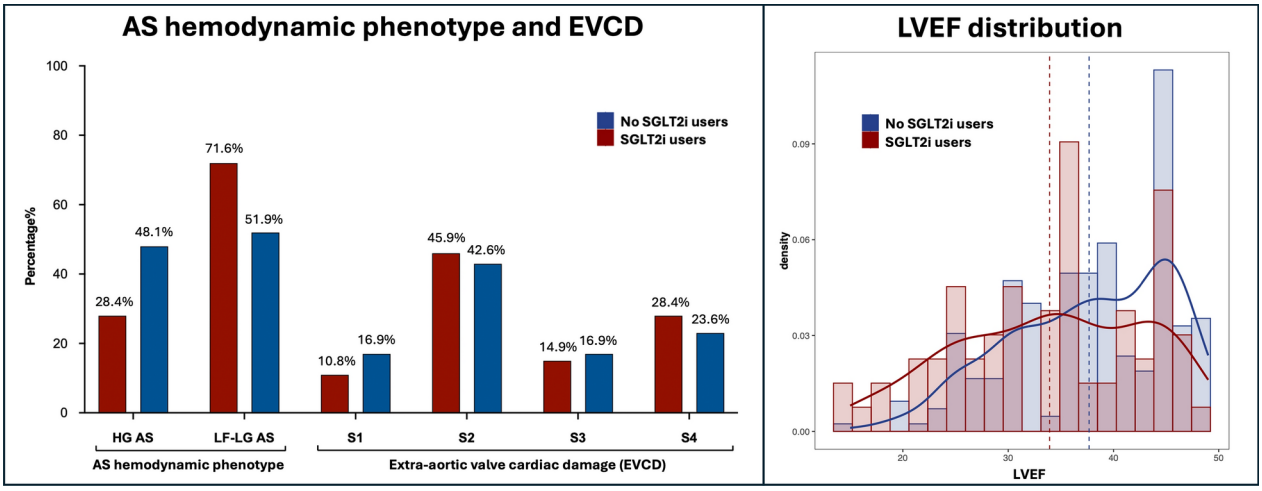

Fig. 1 Hemodynamic phenotype, extra-valvular cardiac damage staging, and left ventricle ejection fraction distribution, stratified in SGLT2i versus no-SGLT2i users. Abbreviations: *HG* high gradient; LF–LG low flow low gradient, *LVEF* left ventricle ejection fraction, *SGLT2i* sodium/glucose cotransporter 2 inhibitors, *S* stage

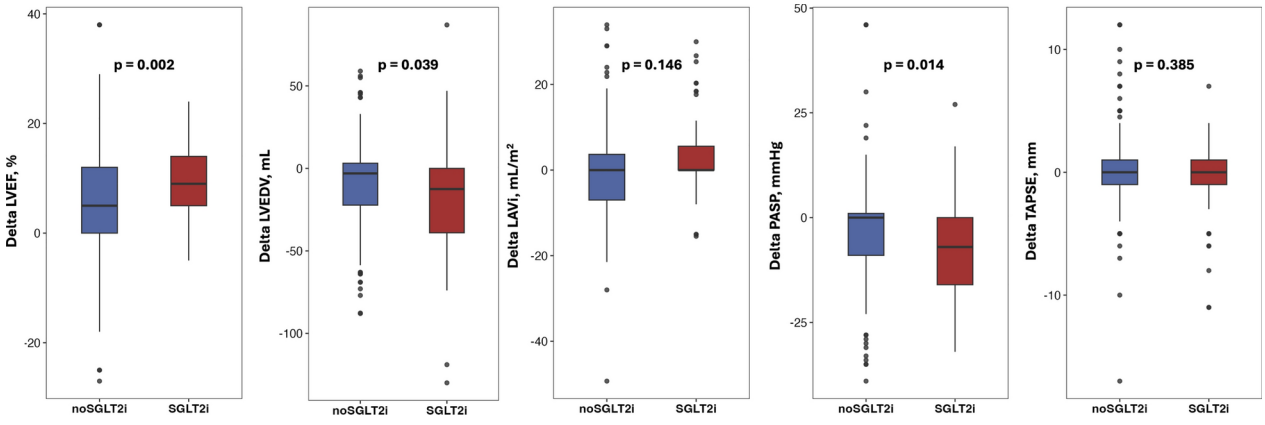

Fig. 2 Baseline versus follow-up changes in echocardiographic data (LVEF, LVEDV, LAV, TAPSE, PASP) in SGLT2i versus no-SGLT2i users. Abbreviations: *SGLT2i* sodium/glucose cotransporter 2 inhibitors, *LV* left ventricle, *LVEDV* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *LAVi* left atrial volume indexed, *PASP* systolic pulmonary artery pressure, *TAPSE* tricuspid annular plane systolic excursion

Procedural data are reported in Supplementary Table 2. Vascular access, procedural time, and contrast dose did not differ between the 2 cohorts. A similar rate of significant paravalvular leak, permanent pacemaker implantation, vascular and neurological complications, and bleeding events were observed between the 2 study groups (Supplementary Table 2). Finally, no differences were found between the two cohorts in cardiovascular and antidiabetic medical therapy at discharge (Supplementary Table 3).

Impact of SGLT2i on cardiac damage after TAVI

Comprehensive follow-up echocardiographic data were available in 224 patients (72% of the study population), among which 55 (74.3%) were in the SGLT2i group and 169 (71.3%) in the no-SGLT2i users. Baseline EVCD is reported in Table 2. The median time of follow-up echocardiographic assessment was 8 [7–11] months after TAVI, with no differences between groups ($p=0.752$). The baseline characteristics of patients with comprehensive follow-up echocardiographic data did not significantly differ from those without (Supplementary Table 4).

At follow-up, favorable reverse remodeling was observed in both cohorts, with a reduction in left ventricular end-diastolic volume (LVEDV), LV mass, and an improvement in LVEF ($p<0.020$ for all, Supplementary Table 5 and Supplementary Fig. 2). TTE-derived pulmonary artery systolic pressure (PASP) also decreased in both groups ($p\leq0.010$ for both) (Supplementary Table 5 and Supplementary Fig. 2). However, compared to baseline, patients treated with SGLT2i experienced a more pronounced increase of LVEF ($p=0.002$), and reduction of LVEDV ($p=0.039$), and PASP ($p=0.014$) (Figs. 2 and 3). Interestingly, compared to no-SGLT2i users, patients treated with SGLT2i experienced a higher rate of LV recovery ($p=0.032$), especially in those with baseline

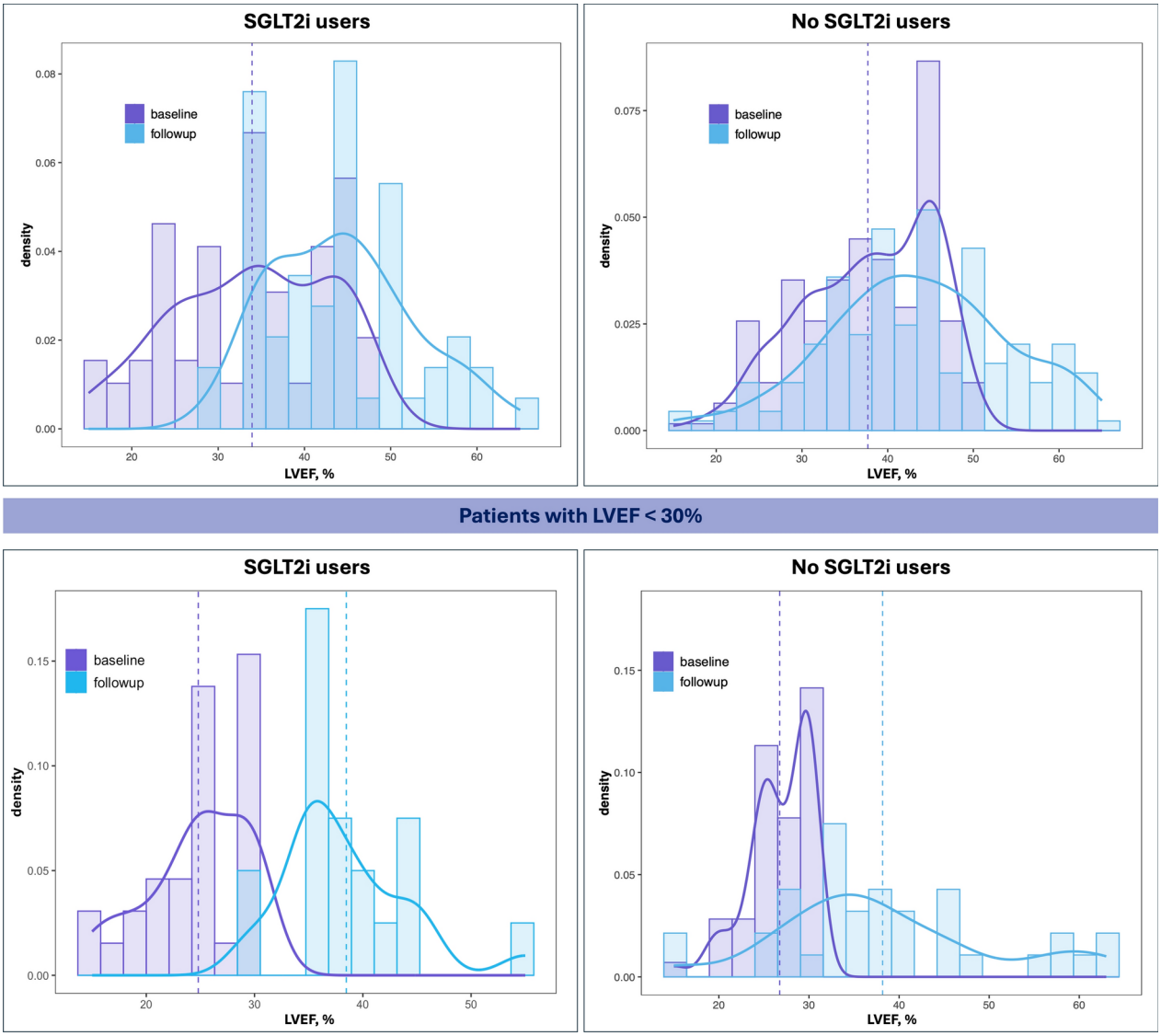

Fig. 3 Baseline versus follow-up LVEF distribution, stratified in SGLT2i versus no-SGLT2i users, in the overall study population and in the sub-groups of patients with LVEF ≤ 30%. Abbreviations: *SGLT2i* sodium/glucose cotransporter 2 inhibitors, *LVEF* left ventricular ejection fraction

LVEF ≤ 30% ($p=0.026$), despite the lower LVEF at baseline and the higher prevalence of LF–LG AS phenotype in the SGLT2i sub-group (Supplementary Table 6 and Figs. 3 and 4).

Regarding the EVCD at follow-up, a small percentage of patients (2% among no-SGLT2i users and 5% among SGLT2i users) reverted to Stage 0. Interestingly, when comparing the EVCD pre- and post-TAVI between the two groups, a significantly higher number of SGLT2i users (92.7%) presented a stable or improved stage compared to no-SGLT2i users, who conversely tended to progress to a worse stage over time (21.3% of cases, $p=0.018$, Supplementary Table 6 and Fig. 4).

Impact of SGLT2i on clinical endpoints

Overall, the median follow-up of the study population (N = 311) was 24 [14–36] months. Over this period, 123 (39.5%) experienced the composite endpoint (MACE), with 99 (31.8%) deaths, among which 19% were related to cardiovascular causes. Sixty-six (21.2%) patients had HF hospitalization, and 20 (6.4%) had coronary revascularization (Supplementary Table 7). Kaplan–Meier estimates at 2-year follow-up are shown in Fig. 5. The primary composite endpoint (MACE) and the single components of all-cause death and HF hospitalization occurred more frequently in no-SGLT2i patients compared to SGLT2i users ($p<0.001$, $p<0.001$, $p=0.009$, respectively, Fig. 5). These results were confirmed at sensitivity analysis excluding diabetic patients treated with diet and lifestyle alone (Supplementary Fig. 3).

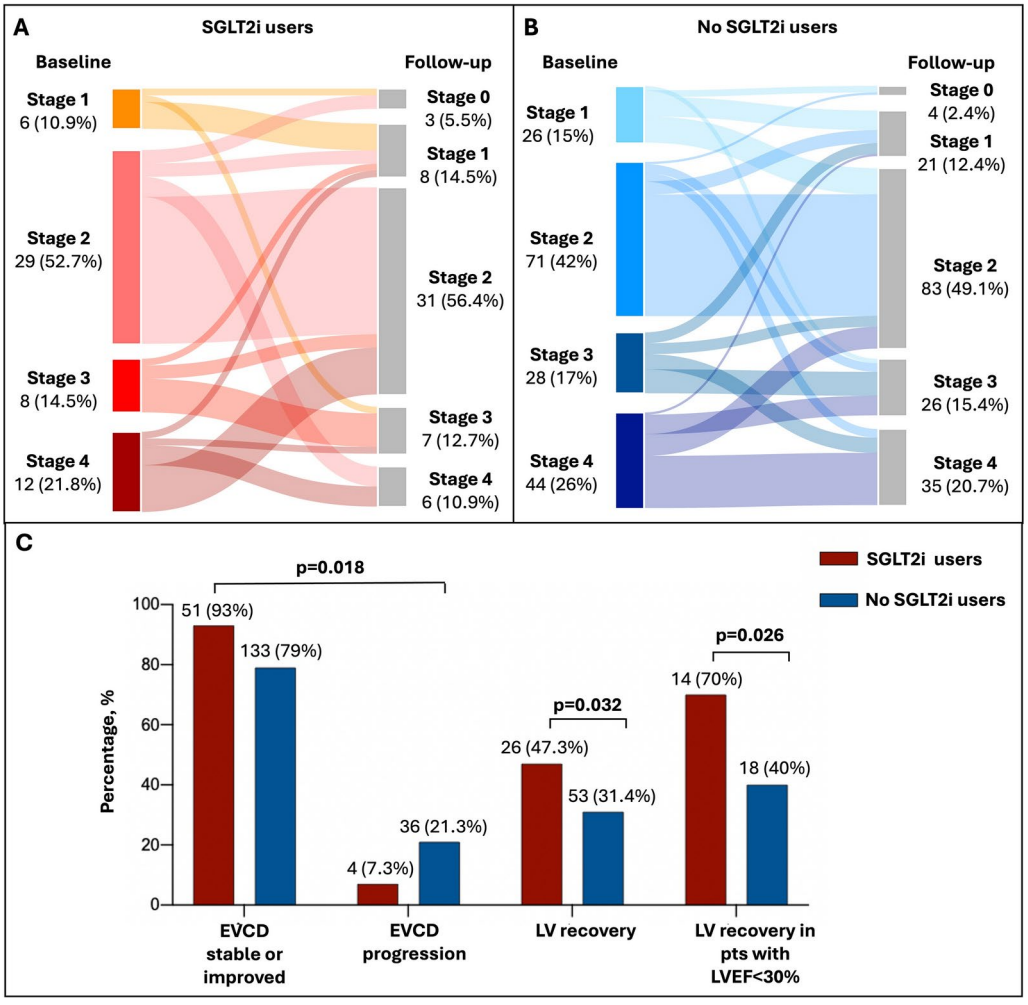

Fig. 4 Sankey diagram showing the transition of cardiac damage from baseline up to 1 year after TAVI in SGLT2i-treated versus no-SGLT2i-treated patients with comprehensive follow-up echocardiographic assessment (N = 224) (median time 8 [7–11] months, with no differences between groups) (Panel **A**). Rate of extra-valvular cardiac damage staging progression and LVEF recovery in SGLT2i versus no-SGLT2i users (Panel **B**) (median follow-up time 24 [14–35] months). Abbreviations: *SGLT2i* sodium/glucose cotransporter 2 inhibitors, *LV* left ventricle, *LVEF* left ventricular ejection fraction, *EVCD* extra-valvular cardiac damage

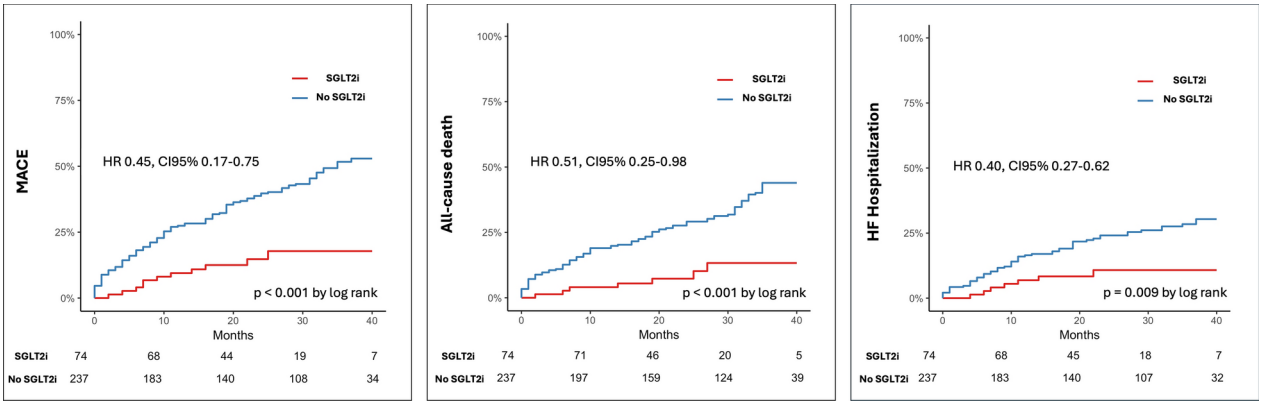

Fig. 5 Kaplan–Meier survival curves of SGLT2i (red curve) versus no-SGLT2i users (blue curve). Panel **A**: MACE. Panel **B**: all-cause death; Panel **C**: hospitalization due to heart failure. Abbreviations: *SGLT2i* sodium-glucose co-transporter 2 inhibitors, *MACE* major adverse cardiovascular event, *HF* heart failure

In the multivariable Cox regression model, after adjusting for potential confounding factors, the use of SGLT2i was identified as an independent predictor of lower MACE rate (HR=0.45; 95% CI 0.17–0.75; p=0.007), while creatinine values at baseline and advanced EVCD were independently associated with a higher risk of MACE (Table 3). Similarly, SGLT2i therapy appeared to be an independent predictor of reduced all-cause death (HR=0.51; 95% CI 0.25–0.98; p=0.042) and HF hospitalization (HR=0.40; 95% CI 0.27–0.62; p=0.004), together with less advanced EVCD staging (Table 3).

The landmark analysis at 30 days post-TAVI confirmed that the significant outcomes benefit for SGLT2i users arise after the first month, with no statistically significant differences between the two groups during the initial 30 days (Supplementary Fig. 4, Panels A–C). At 1-year follow-up landmark analysis, a lower event rate for MACE, all-cause death, and HF hospitalization was observed in SGLT2i users within the first year (p=0.002, p=0.002, p=0.049, respectively, Supplementary Fig. 4, Panels D–F). These results were confirmed at multivariable Cox regression analysis after adjusting for potential confounding factors (Supplementary Table 8).

To further support a pathophysiological association between echocardiographic findings at follow-up and outcomes benefit, a numerically lower event rate (albeit not statistically significant) was observed in patients who underwent LV recovery at follow-up compared to patients who did not (Supplementary Table 9).

Interestingly, when comparing the risk of MACE of SGLT2i versus no-SGLT2i users, using LVEF at baseline as a continuous variable, SGLT2i users showed a lower probability of MACE across the whole spectrum of LVEF. Moreover, in the case of baseline LVEF ≤ 30%, there was a steep increase in the risk of MACE for no-SGLT2i users compared to SGLT2i users, in line with the higher rate of LV recovery after TAVI observed for the latter (Supplementary Fig. 5).

Discussion

Our study is the first to investigate the impact of SGLT2i on cardiac remodeling and long-term outcomes of diabetic patients with severe AS, LVEF < 50%, and EVCD undergoing TAVI. The main findings were: (i) SGLT2i were prescribed in 23.8% of the study population; (ii) SGLT2i users had a lower LVEF at baseline and more frequently presented LF–LG AS phenotype; (iii) after TAVI, 92.7% of SGLT2i users had a stable or improved EVCD staging compared to no-SGLT2i group, who conversely tended to progress to a worse stage in 21.3% of the cases; (iv) after TAVI, patients treated with SGLT2i experienced a higher rate of LV recovery, especially those with baseline LVEF ≤ 30%; (v) at a median of 24-month follow-up, use of SGLT2i was associated with a lower rate of the composite endpoint (MACE), all-cause death, and HF-hospitalization compared to no-SGLT2i therapy; vi) after adjusting for potential confounding factors, the use of SGLT2i was identified as an independent predictor of reduced MACE rate, all-cause death, and HF-hospitalization after TAVI.

Recently, there has been a clear paradigm shift in the conception of AS, as a pathology of both the valve and myocardium rather than an isolated disease of the aortic valvular apparatus [18, 19, 27]. From this perspective, the assessment of the EVCD is crucial for risk stratification and the prognosis of patients with AS [8, 18, 28]. Remarkably, the residual or new-onset EVCD post-TAVI is emerging to be even more clinically relevant, being associated with poor prognosis despite TAVI [7, 21, 29]. In this view, technological advances in TAVI devices and procedures and operators' expertise seem to be not enough to lower the residual EVCD risk. Indeed, an unmet clinical need consists in the identification of medical strategies targeting the "myocardium" which, combined with TAVI, could promote favorable cardiac remodeling, thus improving prognosis. Medical therapy, albeit ineffective in slowing AS progression, could potentially play a role in EVCD recovery after TAVI [11, 12]. So far, no data are available to guide the management and treatment of EVCD, pre- and post-TAVI. This is an important clinical issue, considering the exponential increase in TAVI procedures and increasingly younger patients treated by TAVI. In our prior study, we demonstrated the hyper-expression of the SGLT2 gene with consequently high protein levels in patients with AS and reduced LVEF and their correlation with plasma and tissue biomarkers related to fibrosis, inflammation, and oxidative stress [17]. This highlighted the potential molecular involvement of SGLT2 in cardiac remodeling, thus emerging as a potential therapeutic target, especially among patients with reduced LVEF (LVEF < 50%) [17, 30].

A recent study by Witberg et al., reported the outcomes of the largest cohort of patients with severe LV dysfunction undergoing TAVI. The study introduced a model of LVEF spectrum in AS patients, with advanced myocardial damage and severely depressed LVEF at one end, and pure "valvular" cardiomyopathy at the other end. The authors hypothesized that the closer the patient is to severe LV dysfunction, the less likely they are to benefit from TAVI and experience LV recovery [23]. However, the authors did not explore the role of medical therapy in LV recovery. Thus, it could be hypothesized that SGLT2i might sustain and enhance the "mechanical" pressure unloading after TAVI by a "biological" effect on the dysregulated molecular pathways related to cardiac metabolism, oxidative stress, inflammation, and fibrosis [17]. The clinical benefits observed in our study population may therefore result from both the direct pleiotropic

Table 3 Univariable and multivariable analysis testing predictors of MACE, all-cause death, and HF hospitalization

Variables	MACE						All-cause death						HF hospitalization					
	Univariable analysis			Multivariable analysis			Univariable analysis			Multivariable analysis			Univariable analysis			Multivariable analysis		
	HR	95%CI	*p*-value	HR	95%CI	*p*-value	HR	95%CI	*p*-value	HR	95% CI	*p*-value	HR	95%CI	*p*-value	HR	95% CI	*p*-value
Age	1.02	1.01–1.05	0.043	0.99	0.95–1.04	0.909	1.03	1.01–1.07	0.048	1.02	0.96–1.07	0.568	1.01	0.97–1.06	0.583	–	–	–
Gender, male	1.25	0.87–1.79	0.218	–	–	–	1.20	0.80–1.81	0.383	–	–	–	1.16	0.70–1.93	0.562	–	–	–
BMI	1.03	0.99–1.06	0.109	–	–	–	1.02	0.98–1.06	0.358	–	–	–	1.03	0.98–1.08	0.276	–	–	–
Hypertension	1.09	0.68–1.76	0.717	–	–	–	1.36	0.76–2.44	0.303	–	–	–	1.16	0.59–2.27	0.671	–	–	–
Dyslipidemia	0.87	0.57–1.33	0.517	–	–	–	0.77	0.48–1.22	0.263	–	–	–	1.04	0.56–1.94	0.904	–	–	–
COPD	1.04	0.68–1.60	0.843	–	–	–	1.19	0.74–1.92	0.469	–	–	–	0.94	0.51–1.73	0.851	–	–	–
CKD	1.59	1.11–2.28	0.011	0.97	0.55–1.73	0.924	1.62	1.08–2.44	0.020	1.15	0.59–2.23	0.683	1.58	0.96–2.60	0.072	1.03	0.51–2.10	0.925
AF	1.08	0.76–1.53	0.672	–	–	–	0.95	0.63–1.41	0.783	–	–	–	1.37	0.84–2.22	0.206	–	–	–
CAD	0.98	0.68–1.41	0.919	–	–	–	1.19	0.78–1.83	0.413	–	–	–	1.22	0.72–2.06	0.466	–	–	–
Creatinine	1.85	1.36–2.52	< 0.001	1.85	1.12–3.04	0.016	1.68	1.19–2.39	0.003	1.52	0.86–2.68	0.148	1.73	1.13–2.65	0.011	1.41	0.73–2.70	0.308
HbA1c	1.01	0.98–1.02	0.830	–	–	–	1.01	0.99–1.03	0.468	–	–	–	1.01	0.98–1.03	0.724	–	–	–
LF–LG AS Phenotype	1.23	0.86–1.75	0.253	–	–	–	0.91	0.61–1.35	0.641	–	–	–	2.26	1.31–3.88	0.003	2.04	1.08–3.85	0.028
EVCD Staging 3–4	2.10	1.48–2.97	< 0.001	1.66	1.01–2.89	0.048	1.89	1.27–2.81	0.001	1.67	1.09–2.96	0.031	3.34	2.00–5.57	< 0.001	2.03	1.00–4.18	0.050
TAPSE	0.97	0.92– 1.02	0.267	–	–	–	0.98	0.92–1.04	0.493	–	–	–	0.96	0.89–1.02	0.204	–	–	–
PASP	1.02	1.01–1.04	0.004	1.02	0.99–1.03	0.080	1.02	1.01–1.03	0.043	1.01	0.99–1.03	0.380	1.03	1.01–1.05	0.007	1.01	0.99–1.03	0.547
LV recovery	0.51	0.31– 0.81	0.005	0.66	0.40–1.08	0.093	0.58	0.33–1.01	0.055	0.72	0.40–1.27	0.244	0.55	0.30–1.02	0.056	0.73	0.39–1.37	0.323
Significant MR	1.46	0.98–2.18	0.061	0.35	0.18–1.34	0.120	1.39	0.87–2.20	0.165	–	–	–	1.55	0.91–2.67	0.114	–	–	–
Significant TR	1.50	0.99–2.26	0.057	2.21	0.54–5.93	0.268	1.31	0.81–2.12	0.275	–	–	–	2.29	1.36–3.84	0.002	0.94	0.44–2.01	0.865
Balloon Expandable	1.32	0.93–1.87	0.122	–	–	–	1.26	0.85–1.88	0.245	–	–	–	1.20	0.74–1.96	0.462	–	–	–
MRA	1.11	0.78–1.58	0.560	–	–	–	1.14	0.76–1.69	0.533	–	–	–	1.26	0.78–2.05	0.350	–	–	–
B-blockers	0.96	0.66–1.36	0.761	–	–	–	1.23	0.80–1.87	0.344	–	–	–	0.78	0.48–1.27	0.315	–	–	–
RAASi	0.89	0.63–1.26	0.503	–	–	–	0.87	0.58–1.29	0.476	–	–	–	0.99	0.61–1.61	0.964	–	–	–
ARNI	0.78	0.40–1.51	0.446	–	–	–	0.56	0.23–1.34	0.187	–	–	–	0.83	0.33–2.06	0.682	–	–	–
SGLT2-I	0.42	0.21–0.67	< 0.001	0.45	0.17–0.75	0.007	0.35	0.18–0.59	0.001	0.51	0.25–0.98	0.042	0.39	0.17–0.81	0.013	0.40	0.27–0.62	0.004

MACE major adverse cardiovascular events, *HF* heart failure, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *CKD* chronic kidney disease, *AF* atrial fibrillation, *CAD* coronary artery disease, *HbA1c* glycated hemoglobin, *LF–LG* low flow low gradient, *EVCD* extra-valvular cardiac damage, *TAPSE* tricuspid annular plane systolic excursion, *PASP* systolic pulmonary artery pressure, *MR* mitral regurgitation, *TR* tricuspid regurgitation, *MRA* mineralocorticoid receptor antagonists, *ARNI* angiotensin receptor/neprilysin inhibitor, *SGLT2i* sodium/glucose cotransporter 2 inhibitors

metabolic and cardiovascular effects of SGLT2i, as well as indirectly from the LV reverse remodeling promoted by SGLT2i therapy. This was also demonstrated by the significant association of LV recovery with the primary composite endpoint at univariate analysis but not at multivariable analysis. Moreover, recent evidence showed that in patients with severe AS and HF, coronary microvascular dysfunction might be involved in the LV remodeling mechanisms, influencing the likelihood of LV recovery at follow-up [31, 32]. The potential impact of SGLT2 inhibitors on cardiac fibrosis and microvascular dysfunction, proved so far in murine models, might favor LV recovery following TAVI [33].

In this study, we provided the first data about the outcome benefit of a medical therapy acting EVCD (i.e. SGLT2i), beyond the "mechanical therapy" of the aortic valve represented by TAVI. If treated with SGLT2i, patients with LV dysfunction (LVEF < 50%) experienced a 47% rate of LV recovery, which was even higher in those with baseline LVEF ≤ 30%. The benefit of SGLT2i is not limited to LV recovery but extends to the overall EVCD. Indeed, at follow-up, SGLT2i users experienced a more marked decrease in LVEDV and PASP, with overall 92.7% of patients having stable or improved EVCD compared to the no-SGLT2i group. This might also contribute to the prognostic benefit of SGLT2i users, being both EVCD and PASP prognostic predictors in patients with AS [6, 8, 29, 34]. Remarkably, we collected comprehensive follow-up TTE data after at 8 [7–11] months post-TAVI, thus removing potential bias related to the hemodynamic effect of the procedure itself on EVCD.

Our study showed that, among T2DM patients with severe AS, LVEF < 50%, and EVCD undergoing TAVI, SGLT2i use was associated with a reduced risk of the composite endpoint (MACE), all-cause death, and HF-related hospitalization at a median of 24-month follow-up, compared to no-SGLT2i users. Accounting for potential procedural-related biases, the landmark analysis at 30-day and 1-year post-TAVI showed an outcome benefit of SGLT2i use between 30 days and 1 year after TAVI, with no statistically significant difference between the two groups within the initial 30 days. This is in line with the follow-up echocardiographic findings, which were obtained between 6 and 12 months after TAVI, suggesting a pathophysiological association between LV recovery and clinical outcomes. To further support this observation, a numerically lower event rate (even though not statistically significant) was observed in patients who underwent LV recovery compared to patients who did not.

Moreover, compared to no-SGLT2i users, SGLT2i-treated patients showed a lower probability of MACE across the whole spectrum of LVEF, especially those with baseline LVEF ≤ 30%. Indeed, for the latter, there was a steep increase in MACE risk among no-SGLT2i users, unlike SGLT2i ones, who consistently exhibited a lower risk. This might be related to the higher rate of LV recovery and an overall higher rate of stable or improved EVCD at follow-up.

Although future studies will be necessary to demonstrate a cause-effect relationship and extend the outcome benefit to non-diabetic patients, our data showed that SGLT2i might improve outcomes in T2DM patients with severe AS, LVEF < 50%, and EVCD undergoing TAVI, being associated with favorable cardiac remodeling. Further insights will be provided by the ongoing randomized clinical trial DapaTAVI (NCT04696185) [35].

Study limitations

Our results should be interpreted considering some limitations. First, the sample size was powered to evaluate only a "class effect" but not a "drug effect". However, an analysis of a nationwide real-world dataset suggested that the risk of cardiovascular events including HF, MI, stroke, and AF would be comparable between different SGLT2 inhibitors, supporting our hypothesis of a "class effect" [36]. Second, the present analysis is an observational international multicenter study with inherent limitations. It cannot be excluded that baseline characteristics of our study groups might have influenced the results, although most cardiovascular risk factors, comorbidities, and baseline characteristics were similar between SGLT2i and no-SGLT2i users. Third, comprehensive follow-up echocardiographic data were available in 224 patients (72% of the study population), among which 55 (74.3%) were in the SGLT2i group and 169 (71.3%) in the no-SGLT2i users. The missing echocardiogram data was mainly attributed to the following reasons: either the echocardiograms conducted were incomplete and lacked essential measurements necessary to evaluate reverse remodeling and assess EVCD at follow-up, or they were from patients who were referred to the centers for the procedures but subsequently followed up externally. Lastly, it should be acknowledged that our study was not powered for sub-group analysis.

Conclusions

In T2DM patients with severe AS, LVEF < 50%, and EVCD undergoing TAVI, the use of SGLT2i was associated with a more favorable cardiac remodeling and improved cardiovascular outcomes at a median of 24-month follow-up compared to no-SGLT2i users. Our findings provide new insights into the beneficial effect of SGLT2i, pointing out their clinical impact in improving cardiac remodeling and cardiovascular outcomes after TAVI.

Abbreviations

AS	Aortic stenosis
AVR	Aortic valve replacement
EVCD	Extra-valvular cardiac damage
HF	Heart failure
LAVi	Left atrial volume indexed
LF–LG	Low flow–low gradient
LV	Left ventricle
LVEDDi	Left ventricular end-diastolic diameter indexed
LVEDVi	Left ventricular end-diastolic volume indexed
LVEF	Left ventricular ejection fraction
SGLT2i	Sodium-glucose cotransporter 2 inhibitors
TAVI	Transcatheter aortic valve implantation
T2DM	Type 2 diabetes mellitus

Supplementary Information

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Supplementary Material 1.

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Author contributions
PP, MB, EG contributed to the conception and design of the study; PP, MB, EG, RS, LB, LP, MA, GE, EM, GB, CM, MS, EKDO, FA, MO, MF, LB, ARM, DOA, MA, DA, AI organized the database and collected data; PP, MB, EG and LB performed the statistical analysis; PP and MB wrote the first draft of the manuscript. LS, MB, RM, EC, DA, MP, JAO, PC, AB, CP, TP, MVDH, FS, FR, and EB revised the article and approved the final version of the manuscript. All authors contributed to the manuscript revision and read and approved the submitted version.

Statement of guarantor
EB and PP are the guarantors of the research and, as such, have full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Data were collected as part of an approved international multicenter observational study. The present study was conducted according to the principles of the Declaration of Helsinki; all patients were informed about their participation in the registry and provided informed consent for the anonymous publication of scientific data.

Consent for publication
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Competing interests
The authors declare no competing interests.

Author details
[1]Clinical Cardiology and Cardiovascular Imaging Unit, IRCCS Galeazzi-Sant'Ambrogio Hospital, Milan, Italy
[2]Department of Biomedical and Clinical Sciences, University of Milan, Milan, Italy
[3]Cardiovascular Center Aalst, OLV-Clinic, Aalst, Belgium
[4]Department of Advanced Biomedical Sciences, University Federico II, Naples, Italy
[5]Cardiovascular Department, Azienda Ospedaliero Universitaria Integrata di Verona, Verona, Italy
[6]Unit of Cardiology, Department of Medical and Surgical Sciences (DIMEC), Sant'Orsola-Malpighi Hospital, IRCCS, University of Bologna, Bologna, Italy
[7]Interventional Cardiology Unit, De Gasperis Cardio Center, Niguarda Hospital, Milan, Italy
[8]Division of Cardiology, A.O.R.N. "Sant'Anna e San Sebastiano", Caserta, Italy
[9]Department of Translational Medical Sciences, University of Campania 'Luigi Vanvitelli', Naples, Italy
[10]Cardiology Division, IRCCS Galeazzi-Sant'Ambrogio Hospital, Milan, Italy
[11]Division of Cardiology, Sant'Andrea Hospital, Rome, Italy
[12]Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Naples, Italy
[13]Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy

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