Cardiovascular Diabetology

RESEARCH

Open Access

Impact of SGLT2-inhibitors on acute kidney injury in diabetic patients with severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI)

Pasquale Paolisso[1†], Marta Belmonte[1,2†], Emanuele Gallinoro[1], Roberto Scarsini[3], Luca Bergamaschi[4,5], Leonardo Portolan[3], Matteo Armillotta[4,5], Giuseppe Esposito[6], Elisabetta Moscarella[7,8], Claudio Montalto[6,9], Elayne Kelen de Oliveira[2,10], Francesco Angeli[4,5], Mateusz Orzalkiewicz[4], Margherita Fabroni[3], Verdiana Galli[3], Nurcan Baydaroglu[6], Francesca Di Lenarda[11], Pasquale Policastro[1], Carlo Terrone[1], Davide Ausiello[1], Giose Vincelli[1], Matteo Casenghi[1], Lucia Scisciola[12], Raffaele Marfella[12], Felice Gragnano[7,8], Edoardo Conte[11], Dario Pellegrini[13], Alfonso Ielasi[13], Daniele Andreini[11,14], Jacopo Andrea Oreglia[6], Paolo Calabrò[7,8], Antonio L. Bartorelli[11,14], Tullio Palmerini[4], Francesco Saia[4], Flavio Ribichini[3], Michelangela Barbieri[12], Marc Vanderheyden[10], Carmine Pizzi[4,5] and Emanuele Barbato[1,15*]

Abstract

Background Acute kidney injury (AKI) following transcatheter aortic valve implantation (TAVI) is associated with significantly worse outcomes, leading to increased short- and long-term mortality. We sought to evaluate the impact of sodium-glucose cotransporter 2 inhibitors (SGLT2i) on the risk of AKI in patients with type 2 diabetes mellitus (T2DM) and severe aortic stenosis (AS) undergoing TAVI.

Methods Multicenter international registry of consecutive T2DM patients with severe AS undergoing TAVI between 2021 and 2024. The study population was stratified by the presence of chronic kidney disease (CKD), defined according to the KDIGO guideline, and anti-diabetic therapy at hospital admission (SGLT2i versus no-SGLT2i users). AKI was defined according to the Valve Academy Research Consortium 3 (VARC-3) criteria.

Results The study population consisted of 514 patients stratified into those without CKD (n = 226, 44%), of whom 43 (19%) were treated with SGLT2i, and 288 (56%) with CKD, of whom 71 (24.7%) were on SGLT2i treatment. The median age was 81 [77–84] years, and 60.1% were males. SGLT2i use did not impact renal function in patients without CKD, with AKI occurring in 7.1% of the cases, regardless of SGLT2i use. Among CKD patients, AKI occurred more frequently

†Pasquale Paolisso and Marta Belmonte have 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

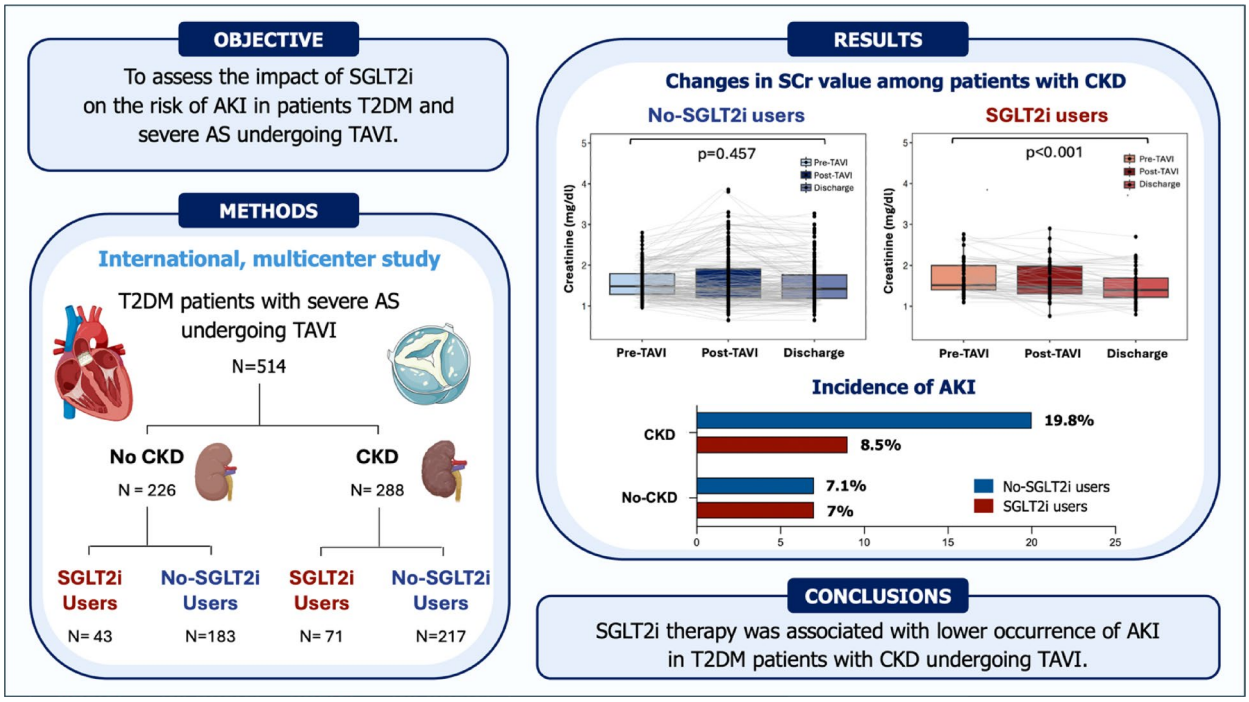
in no-SGLT2i users compared to those receiving SGLT2i (19.8% versus 8.5%, $p=0.027$), with a significant increase in post-TAVI and discharge serum creatinine values for no-SGLT2i users ($p=0.001$ after TAVI and $p<0.001$ at hospital discharge). Only in the CKD group, the use of SGLT2i was identified as an independent predictor of a lower rate of AKI (OR 0.70, 95%CI 0.42–0.91, $p=0.014$). Patients who developed AKI had a higher incidence of major adverse cardiovascular events during follow-up, regardless of CKD ($p<0.025$ for both groups).

Conclusion In diabetic patients with CKD undergoing TAVI, SGLT2i therapy was associated with a lower occurrence of AKI compared to those not treated with SGLT2i, suggesting a potential nephroprotective effect in this high-risk population.

Keywords SGLT2i, Transcatheter aortic valve implantation (TAVI), Acute kidney injury, Chronic kidney disease, Aortic stenosis

Graphical abstract

Summary of the main findings of the study.



Introduction

Sodium-glucose cotransporter 2 inhibitors (SGLT2i, gliflozins) have been shown to improve kidney and cardiovascular outcomes in patients with type 2 diabetes mellitus (T2DM) [1–3]. Recent evidence also highlights their nephroprotective effects in chronic kidney disease (CKD), even in patients without T2DM [4, 5]. The demonstrated benefits of SGLT2i and the growing body of supporting evidence have heightened interest in expanding their use as a potential therapeutic option for patients with aortic stenosis (AS) [6–8]. A recent retrospective, observational study suggested that SGLT2i might slow the progression of non-severe AS [8]. Furthermore, an observational multicenter study revealed that in T2DM patients with severe AS and extra-valvular cardiac damage (EVCD) undergoing transcatheter aortic valve implantation (TAVI), SGLT2i use was associated with more favorable cardiac remodeling and a reduced risk of major adverse cardiovascular events (MACE) at 2-year follow-up [7]. However, the underlying pathophysiological mechanisms remain to be fully elucidated.

Acute kidney injury (AKI) in patients undergoing TAVI has been shown to significantly worsen outcomes, increasing both short- and long-term mortality. Moreover, AKI is associated with prolonged hospitalizations and a higher risk of further renal impairment, establishing it as a critical prognostic marker in this high-risk population [9–12].

Currently, the impact of SGLT2i on AKI occurrence in diabetic patients with severe AS undergoing TAVI remains unexplored, especially in patients with CKD [13]. Thus, this study aimed to investigate the risk of AKI

after TAVI in T2DM patients with or without CKD, comparing those treated with SGLT2i (SGLT2i users) versus those receiving other anti-diabetic agents (no-SGLT2i users).

Methods

Study population

This international observational registry included consecutive T2DM patients with severe AS undergoing TAVI between January 2021 and June 2024. Patients with incomplete information on medical therapy at hospital admission and incomplete determinations of serum creatinine (SCr) at the time-points required for the assessment of AKI (baseline, within 48 h after TAVI, and at discharge) were excluded. Further exclusion criteria were: estimated glomerular filtration rate (eGFR) < 20 ml/min/1.73 m^2, 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. The definition of severe AS, AS phenotype, and indication for TAVI followed current guidelines (Supplementary Files– Extended Methods) [14, 15]. The extent of extra-valvular cardiac damage (EVCD) was classified into five stages based on a model proposed by Genereux et al. [16], with detailed descriptions of each stage provided in the Supplementary Files—Extended Methods. All patients with CKD underwent a pre-procedural hydration protocol before TAVI, according to local institutional practices. All TAVI procedures were performed under conscious sedation as per standard of care. The technical success and procedural safety of TAVI were defined according to the Valve Academy Research Consortium 3 (VARC-3) criteria [11]. The study population was stratified by the presence of CKD, defined as eGFR < 60 ml/min/m^2, according to the Kidney Disease Improving Global Outcomes (KDIGO) guideline [17]. Based on anti-diabetic therapy at hospital admission, each group was further divided into SGLT2i users, if the patients were admitted on SGLT2i therapy (started at least 1 month before hospitalization), and no-SGLT2i users, if they received other antidiabetic drugs. 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.

Study objectives

The SCr concentration was measured in all patients at least at hospital admission, within 48 h after TAVI, and at hospital discharge. The highest SCr level within 48 h after TAVI was used to diagnose AKI. The latter was defined as an increase of ≥ 0.3 mg/dL (≥ 26.4 mmol/L) within 48 h after TAVI or an increase in SCr ≥ 150–200% (≥ 1.5–2.0 increase) within hospital discharge compared with baseline, according to the Valve Academy Research Consortium 3 (VARC-3) criteria [11].

The primary objective was to compare the occurrence of AKI among T2DM patients undergoing TAVI treated with SGLT2i therapy versus no-SGLT2i users, both in patients with and without CKD. Secondary objectives included all-cause death, cardiovascular death, and hospitalization for heart failure (HF) at 2-year follow-up. MACEs were defined as a composite of all-cause death and HF hospitalization at 2-year follow-up. The definitions of each clinical outcome followed current standards and are specified in the Supplementary Files [18].

Statistical analysis

The 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. Normal ranges were presented as the 5th and 95th percentiles. 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 Fisher's exact test for categorical variables, as appropriate. To compare paired data, a Wilcoxon signed test, a paired sample T-test, or the Friedman test were performed as appropriate. Univariable analysis was performed to identify clinically relevant variables associated with AKI in patients with and without CKD. Variables showing statistical significance at the 5% level in univariable analysis were then entered into a multivariable logistic regression analysis to identify independent predictors of AKI. The odds ratio (OR) and the associated 95% confidence interval (CI) for each variable were determined. Kaplan–Meier analysis and Log-rank test were used to compare the cumulative incidence of clinical events between groups. A p-value < 0.05 was 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 study population consisted of 514 diabetic patients with severe AS undergoing TAVI, stratified into those without CKD (n = 226, 44%), of whom 43 (19%) were treated with SGLT2i, and those with CKD (n = 288, 56%),

of whom 71 (24.7%) were on SGLT2i therapy. The study flowchart is shown in Supplementary Fig. 1. The median age of the overall study population was 81 [77–84] years, and 60.1% were males. All patients were hemodynamically stable. Among SGLT2i users (n = 114, 22.2%), 60 (52.6%) patients were prescribed dapagliflozin and 54 (47.4%) empagliflozin. In this cohort, all patients continued SGLT2i therapy throughout the hospitalization for the TAVI procedure, with no interruptions either before or after the intervention. No patient had to discontinue SGLT2i for hypoglycemic episodes or ketoacidosis occurring during hospitalization.

Patients without CKD: SGLT2i versus no-SGLT2i users

Among patients without CKD, SGLT2i users were significantly younger compared to no-SGLT2i ones ($p = 0.024$), with no sex differences. The prevalence of cardiovascular risk factors, comorbidities, and clinical presentation was similar in both cohorts (Table 1). The STS-PROM score, renal function, and glucose-metabolic control were also not different between the 2 study groups (Table 1). No difference in AS severity was observed, even though the rate of low gradient (LG) AS was higher among SGLT2i users ($p = 0.008$) (Table 2). Thus, SGLT2i users had a significantly lower baseline LVEF compared to no-SGLT2i ones ($p = 0.009$) (Table 2). No significant difference was observed in baseline EVCD, with a similar percentage of patients presenting advanced EVCD with right chamber involvement in both groups (Table 2). Medical therapy at hospital admission was similar in both groups, except for a higher rate of mineral-corticoid receptor antagonist use among SGLT2i users (Supplementary Table 1). Procedural data are reported in Supplementary Table 2. Vascular access, procedural time, and contrast dose did not

Table 1 Study population baseline characteristics, clinical presentation and laboratory tests of SGLT2i users and no-SGLT2i users, according to the presence of CKD

	No CKD N = 226			CKD N = 288		
	SGLT2i users N = 43	No-SGLT2i users N = 183	*p* -value	SGLT2i users N = 71	No-SGLT2i users N = 217	*p* -value
Baseline characteristics						
Age, years	79 [75–82]	81 [77–84]	0.024	78 [74–82]	82 [78–85]	< 0.001
Male Sex, n (%)	31 (72.1)	124 (67.8)	0.582	48 (67.6)	120 (55.3)	0.068
BMI, kg/m^2	27.7 [24–31.5]	26.4 [23.5–29.3]	0.162	26.3 [23.3–29]	25.6 [23.7–28.8]	0.701
BSA, m^2	1.9 [1.8–2]	1.8 [1.7–1.9]	0.004	1.9 [1.8–2]	1.8 [1.7–1.9]	0.071
Hypertension, n (%)	34 (79.1)	152 (83.1)	0.537	55 (77.5)	185 (85.3)	0.126
Dyslipidemia, n (%)	40 (93)	152 (83.1)	0.101	56 (78.9)	183 (84.3)	0.288
COPD, n (%)	5 (11.6)	35 (19.1)	0.246	14 (19.7)	43 (19.8)	0.986
Cancer, n (%)	4 (9.3)	28 (15.3)	0.310	11 (15.5)	26 (12)	0.443
AF, n (%)	18 (41.9)	61 (33.3)	0.291	43 (60.6)	91 (41.9)	0.006
PAD, n (%)	8 (18.6)	37 (20.2)	0.812	16 (22.5)	54 (24.9)	0.689
Previous HF hospitalization, n (%)	11 (25.6)	31 (16.9)	0.190	28 (39.4)	77 (35.5)	0.548
CAD, n (%)	24 (55.8)	82 (44.8)	0.193	46 (64.8)	135 (62.2)	0.697
Prior PCI, n (%)	15 (34.9)	51 (27.9)	0.363	27 (38)	94 (43.3)	0.433
Prior CABG, n (%)	5 (11.6)	17 (9.3)	0.642	13 (18.3)	43 (19.8)	0.781
Prior MV surgery, n (%)	0 (0)	6 (3.3)	0.229	1 (1.4)	2 (0.9)	0.726
STS PROM score	4.5 [3–6.9]	4.2 [3–7]	0.768	7.2 [4.2–11.5]	7.1 [4–12.1]	0.751
Clinical presentation						
Angina, n (%)	8 (18.6)	19 (10.4)	0.135	11 (15.5)	44 (20.3)	0.373
Syncope, n (%)	3 (7)	22 (12)	0.343	7 (9.9)	12 (5.5)	0.202
Dyspnea, n (%)	42 (97.7)	172 (94)	0.099	68 (95.8)	207 (95.4)	0.893
NYHA ≥ 2, n (%)	38 (88.4)	168 (91.8)	0.476	65 (91.5)	207 (95.4)	0.220
Admission lab test						
Hemoglobin, g/dl	12.7 ± 1.9	12.1 ± 1.7	0.108	11.8 ± 1.7	11.6 ± 1.6	0.223
Creatinine, mg/dL	0.90 ± 0.15	0.89 ± 0.18	0.696	1.70 ± 0.40	1.56 ± 0.40	0.017
eGFR, mL/min/m^2	76 ± 11	74 ± 12.4	0.364	37 ± 10	38 ± 10	0.604
HbA1c, mmol/mol	44 [41–52]	47 [38–55]	0.759	53 [40–58]	47 [41–56]	0.354
NT pro-BNP, ng/L	1864 [436–10172]	1951 [450–4580]	0.633	3248 [1207–9388]	4343 [2071–9175]	0.505

Continuous variables are presented as mean ± SD or as median [IQR]; while categorical variables as number (%).CKD, chronic kidney disease; SGLT2i, sodium-glucose co-transporter 2 inhibitors; BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; PAD, peripheral artery disease; HF, heart failure; CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MV, mitral valve; 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

Table 2 Baseline echocardiographic characteristics and cardiac damage staging of SGLT2i users and no-SGLT2i users, according to the presence of CKD

	No CKD N = 226			CKD N = 288		
	SGLT2i users N = 43	No-SGLT2i users N = 183	*p* -value	SGLT2i users N = 71	No-SGLT2i users N = 217	*p* -value
LVEDDi, mm/m^2	27 ± 5	28 ± 4	0.704	29 ± 4	28 ± 4	0.075
LVEDVi, mm/ m^2	70 ± 33	64 ± 27	0.362	74 ± 26	70 ± 24	0.321
IVS, mm	13 [12–14]	12 [11–14]	0.182	12 [11–13]	12 [11–13]	0.327
LV Mass index, g/m^2	127 ± 27	119 ± 31	0.113	131 ± 31	127 ± 30	0.336
2D BP LVEF, %	44 [35–55]	50 [40–60]	0.009	38 [28–47]	45 [36–55]	0.001
LAVi, ml/m^2	44 ± 15	46 ± 20	0.106	46 ± 18	49 ± 14	0.055
E/e' mean	15 ± 5	16 ± 6	0.156	19 ± 7	18 ± 7	0.557
Significant MR, n (%)·	14 (32.6)	50 (27.3)	0.493	22 (31)	80 (36.9)	0.368
Significant TR, n (%)·	10 (23.3)	23 (12.6)	0.074	17 (23.9)	52 (24)	0.997
Significant AR, n (%)·	6 (13.9)	23 (12.6)	0.807	13 (18.3)	36 (16.6)	0.738
TAPSE, mm	19 [17–24]	19 [17–24]	0.474	18 [15–20]	19 [17–22]	0.017
PASP, mmHg	35 [33–47]	36 [30–46]	0.887	40 [33–50]	41 [34–55]	0.490
Peak aortic jet velocity, m/s	4.1 ± 0.8	4 ± 0.7	0.586	3.5 ± 0.5	4 ± 0.7	< 0.001
Max AV gradient, mmHg	60 ± 25	65 ± 22	0.178	50 ± 15	60 ± 20	< 0.001
Mean AV gradient, mmHg	46 ± 28	42 ± 14	0.895	34 ± 14	40 ± 15	0.023
AVA, cm^2	0.73 ± 0.19	0.73 ± 0.17	0.913	0.80 ± 0.17	0.72 ± 0.18	0.001
AVAi, cm^2/m^2	0.39 ± 0.09	0.41 ± 0.10	0.166	0.43 ± 0.09	0.40 ± 0.10	0.001
LF AS, n (%)	19 (44.2)	44 (24)	0.008	38 (53.5)	85 (39.2)	0.034
Extra-valvular Cardiac Damage Staging, n (%)						
Stage 0	2 (4.7)	14 (7.7)	0.436	2 (2.8)	6 (2.8)	0.657
Stage 1	5 (11.6)	41 (22.4)		6 (8.5)	25 (11.5)	
Stage 2	21 (48.8)	82 (44.8)		29 (40.8)	98 (45.2)	
Stage 3	6 (13.9)	18 (9.8)		14 (19.7)	45 (20.7)	
Stage 4	9 (20.9)	28 (15.3)		20 (28.2)	43 (19.8)	

Continuous variables are presented as mean ± SD or as median [IQR]; while categorical variables as number (%).CKD, chronic kidney disease; SGLT2i, sodium/glucose cotransporter 2 inhibitors; LVEDDi, left ventricular end-diastolic diameter indexed; LVEDVi, left ventricular end-diastolic volume indexed; IVS, interventricular septum; LV, left ventricle; 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

differ between the 2 cohorts. A similar rate of significant paravalvular leak, permanent pacemaker implantation, vascular and neurological complications, and bleeding events was observed between the 2 study groups (Supplementary Table 2).

Patients with CKD: SGLT2i versus no-SGLT2i users

Among CKD patients, SGLT2i users were significantly younger compared to patients not treated with SGLT2i ($p < 0.001$), with no sex differences. Cardiovascular risk factors, comorbidities, and clinical presentation were similar between the two groups, except for a higher rate of atrial fibrillation among SGLT2i users (Table 1). The STS-PROM score and glucose-metabolic control were not different between the 2 study groups (Table 1). Similar to patients without CKD, CKD patients treated with SGLT2i had more frequently LG AS ($p = 0.034$), thus showing a lower LVEF ($p = 0.001$), a lower peak aortic velocity ($p < 0.001$), and a lower mean aortic valve gradient ($p = 0.023$) (Table 2). No differences in EVCD were observed between the two groups, with around 45% of patients presenting advanced EVCD with right chamber involvement in both groups (Table 2). Medical therapy at hospital admission was similar in both groups (Supplementary Table 1). Procedural characteristics and success did not differ between the 2 study groups (Supplementary Table 2).

Impact of SGLT2i on AKI occurrence

The distribution of SCr and changes in individual SCr values at baseline, within 48 h after TAVI, and at hospital discharge stratified by the presence of CKD are shown in Fig. 1.

Among patients without CKD, the mean SCr at hospital admission was 0.90 ± 0.17 mg/dl (eGFR 74 ± 12 ml/min/m^2), with no significant differences between SGLT2i and no-SGLT2i users. AKI occurred in 7.1% of the cases, regardless of SGLT2i use. Thus, no significant changes in SCr levels were observed across the 3 timepoints in both SGLT2i and no-SGLT2i users, with the mean post-TAVI and discharge SCr being similar in the 2 study groups ($p = 0.328$ and $p = 0.896$, respectively) (Fig. 2). At

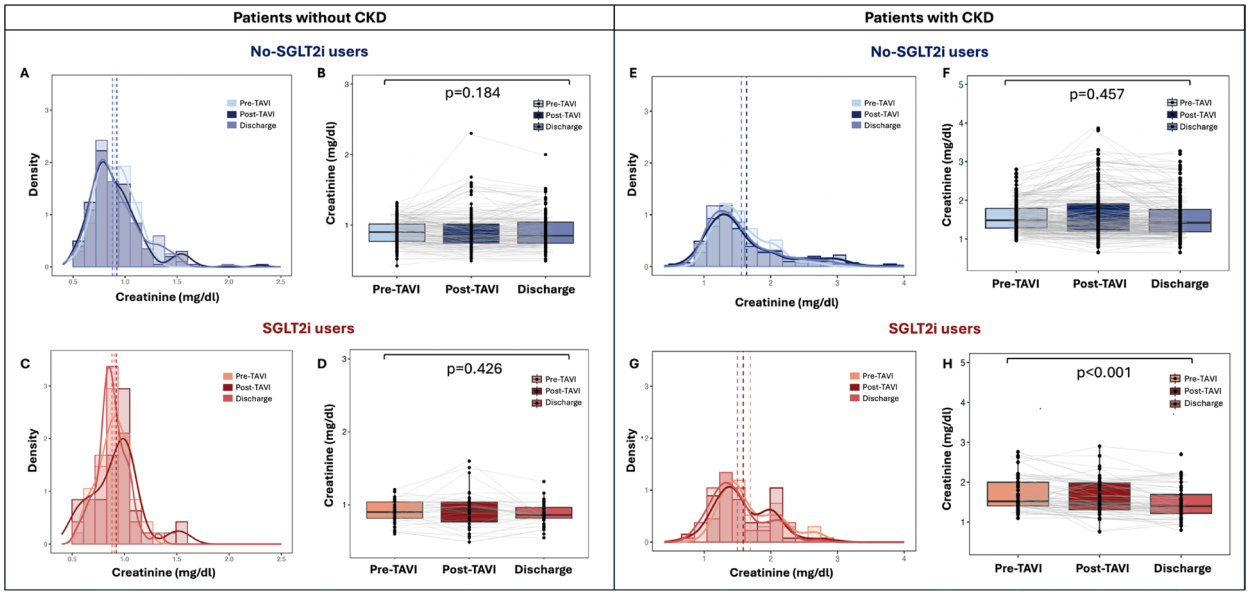
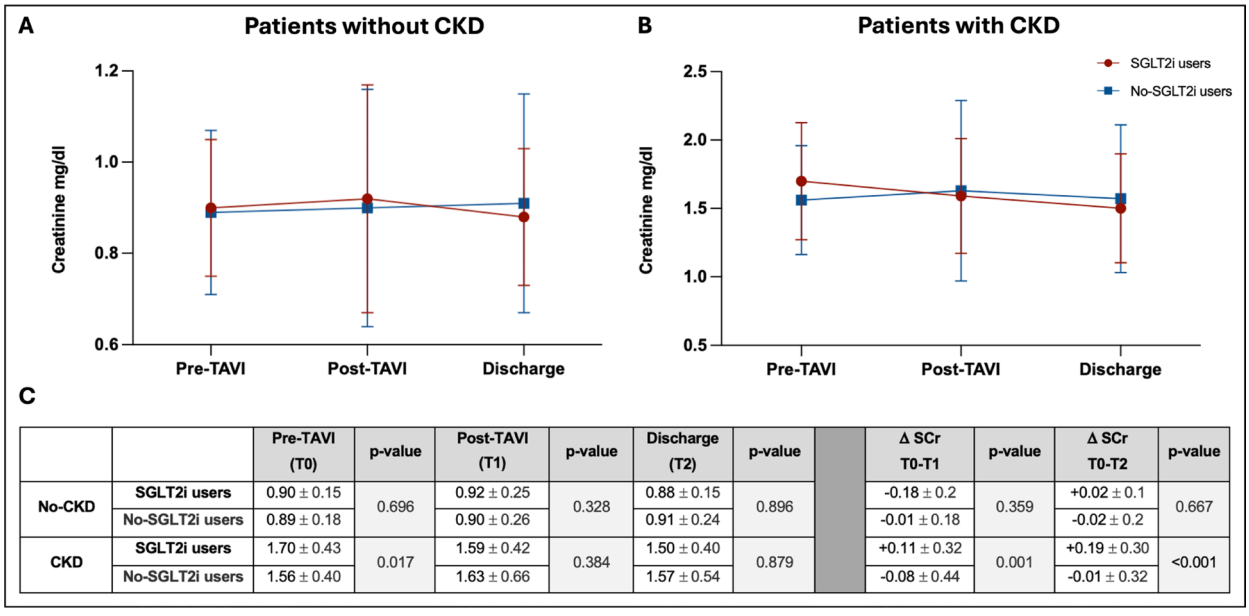


Fig. 1 Distribution (panels A, C, E, G) and boxplot with strip chart (panels B, D, F, H) showing individual serum creatinine values at hospital admission, post-TAVI, and hospital discharge, stratified by the presence of CKD. Paired data of admission, post-TAVI, and discharge were compared for each group using the Friedman test. SGLT2i, sodium-glucose co-transporter 2 inhibitors; CKD, chronic kidney disease; TAVI, transcatheter aortic valve implantation



		Pre-TAVI (T0)	p-value	Post-TAVI (T1)	p-value	Discharge (T2)	p-value		Δ SCr T0-T1	p-value	Δ SCr T0-T2	p-value
No-CKD	SGLT2i users	0.90 ± 0.15	0.696	0.92 ± 0.25	0.328	0.88 ± 0.15	0.896		-0.18 ± 0.2	0.359	+0.02 ± 0.1	0.667
	No-SGLT2i users	0.89 ± 0.18		0.90 ± 0.26		0.91 ± 0.24			-0.01 ± 0.18		-0.02 ± 0.2	
CKD	SGLT2i users	1.70 ± 0.43	0.017	1.59 ± 0.42	0.384	1.50 ± 0.40	0.879		+0.11 ± 0.32	0.001	+0.19 ± 0.30	<0.001
	No-SGLT2i users	1.56 ± 0.40		1.63 ± 0.66		1.57 ± 0.54			-0.08 ± 0.44		-0.01 ± 0.32	

Fig. 2 At the top, a line plot with error bars showing the changes of the creatinine values across the 3-time points of the study (pre-TAVI, post-TAVI, and hospital discharge), in patients with and without CKD, comparing those treated with SGLT2i vs. no-SGLT2i users. Red lines represent the SGLT2i users; blue lines represent the no-SGLT2i users. At the bottom, the table summarizing creatinine values and statistical comparisons at each time point, including *p* -values and changes in serum creatinine (ΔSCr). SGLT2i, sodium-glucose co-transporter 2 inhibitors; CKD, chronic kidney disease; TAVI, transcatheter aortic valve implantation; ΔSCr, changes in serum creatinine values

multivariable analysis, after adjusting for confounding factors, LVEF (OR 0.94; 95% CI 0.89–0.98, $p = 0.019$), advanced EVCD stages (OR 3.89; 95% CI 1.25–12.14, $p = 0.018$) and bleeding events (OR 5.73; 95% CI 1.56–11.14, $p = 0.003$), were found as independent predictors of AKI (Table 3).

Among CKD patients, the mean SCr at hospital admission was higher in SGLT2i users compared to no-SGLT2i ones (1.70 ± 0.40 mg/dl versus 1.56 ± 0.40 mg/dl, $p = 0.017$) (Table 1 and Fig. 2). Notably, AKI occurred more frequently in no-SGLT2i users compared to those treated with SGLT2i (19.8% versus 8.5%, $p = 0.027$) (Fig. 3). Indeed, despite the similar SCr values after TAVI

Table 3 Univariable and multivariable analysis testing predictors of AKI, stratified by the presence of CKD

AKI	No-CKD						CKD					
	Univariable analysis			Multivariable analysis			Univariable analysis			Multivariable analysis		
Variables	OR	95%CI	*p* -value	OR	95%CI	*p* -value	OR	95%CI	*p* -value	OR	95% CI	*p* -value
Age	0.95	0.87–1.03	0.228	–	–	–	0.98	0.92–1.03	0.465	–	–	–
Gender, male	0.52	0.15–1.87	0.313	–	–	–	0.59	0.31–1.04	0.091	–	–	–
Hypertension	0.62	0.21–2.03	0.431	–	–	–	3.55	1.06–4.91	0.040	3.04	0.85–9.87	0.087
Dyslipidemia	1.05	0.29–3.86	0.940	–	–	–	1.06	0.46–2.43	0.888	–	–	–
COPD	2.27	0.74–6.95	0.150	–	–	–	1.22	0.58–2.56	0.609	–	–	–
AF	2.57	0.92–7.19	0.122	–	–	–	1.13	0.61–2.08	0.706	–	–	–
PAD	3.52	0.93–6.23	0.109	–	–	–	2.09	1.08–4.03	0.028	1.92	0.93–3.95	0.078
CAD	3.61	0.74–5.12	0.223	–	–	–	1.27	0.66–2.43	0.475	–	–	–
Hemoglobin, g/dl	0.94	0.69–1.29	0.716	–	–	–	0.63	0.35–1.09	0.113	–	–	–
HbA1c	1.03	0.95–1.13	0.461	–	–	–	1.04	0.98–1.08	0.106	–	–	–
LVEF	0.93	0.89–0.98	0.004	0.94	0.89–0.98	0.019	0.96	0.93–0.99	0.003	0.95	0.92–0.98	0.001
EVCD Staging 3–4	4.93	1.71–4.23	0.003	3.89	1.25–12.14	0.018	1.25	0.67–2.32	0.477	–	–	–
Contrast dose, ml	0.99	0.99–1.01	0.459	–	–	–	1.01	0.99–1.01	0.241	–	–	–
Bleeding events*	5.66	1.41–10.23	< 0.001	5.73	1.56–11.14	0.003	3.69	1.42–9.59	0.007	2.81	1.01–7.93	0.045
MRA	1.41	0.51–3.91	0.521	–	–	–	0.56	0.28–1.11	0.094	–	–	–
RAASi	0.98	0.35–2.82	0.977	–	–	–	0.72	0.39–1.33	0.294	–	–	–
ARNI	–	–	–	–	–	–	0.36	0.46–2.84	0.362	–	–	–
Diuretics	2.18	0.93–5.07	0.559	–	–	–	1.45	0.87–2.52	0.681	–	–	–
Statins	1.35	0.37–4.94	0.646	–	–	–	0.86	0.42–1.76	0.675	–	–	–
SGLT2i	0.98	0.28–3.61	0.977	–	–	–	0.77	0.45–0.93	0.032	0.70	0.42–0.91	0.014

AKI, acute kidney injury; CKD, chronic kidney disease; OR, Odds Ratio; CI, Confidence Interval; COPD, chronic obstructive pulmonary disease; AF, atrial fibrillation; PAD, peripheral artery disease; CAD, coronary artery disease; HbA1c, glycated hemoglobin; LVEF, left ventricle ejection fraction; EVCD, extra-valvular cardiac damage; MRA, mineralocorticoid receptor antagonists; RAASi, renin–angiotensin–aldosterone system inhibitors; ARNI, angiotensin receptor/neprilysin inhibitor; SGLT2i, sodium/glucose cotransporter 2 inhibitors

* Bleeding events were defined according to the Valve Academic Research Consortium 3 (VARC-3) criteria, by *Généreux P, Piazza N, Alu MC* et al., *J Am Coll Cardiol 2021*

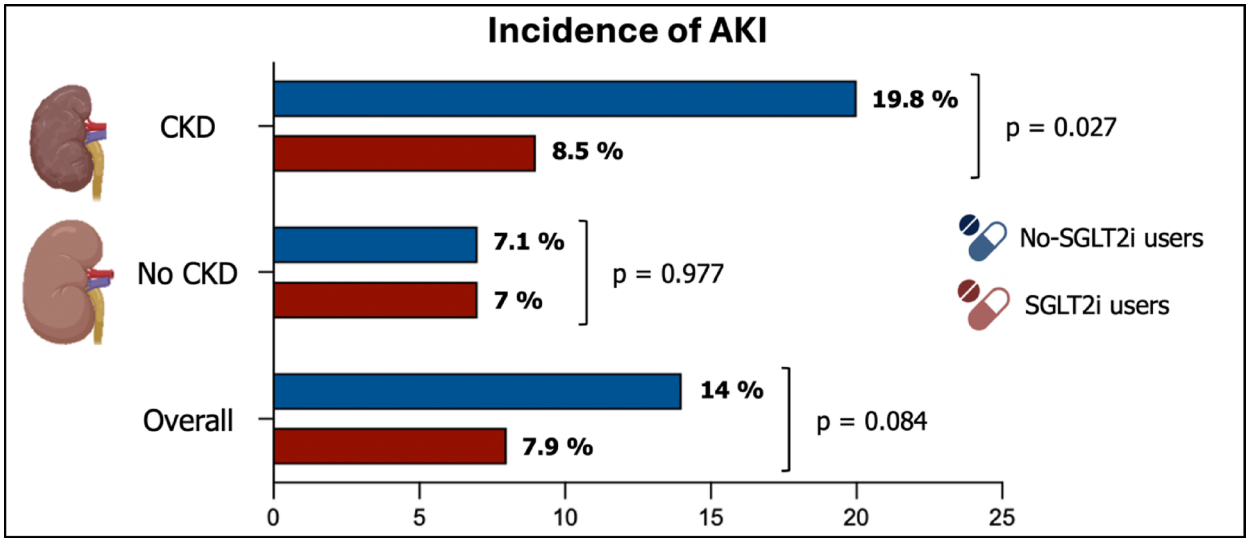


Fig. 3 Rate of AKI stratified according to the presence of CKD. SGLT2i, sodium-glucose co-transporter 2 inhibitors; AKI, acute kidney injury; CKD, chronic kidney disease

and at hospital discharge between the two groups, the increase in SCr values compared to baseline (ΔSCr) was significantly higher among no-SGLT2i users ($p = 0.001$ after TAVI and $p < 0.001$ at hospital discharge) (Fig. 2). Remarkably, in patients treated with SGLT2i, SCr levels significantly decreased after TAVI and at hospital discharge compared to baseline values ($p < 0.001$, Fig. 1—Panel H). Accordingly, eGFR values at hospital discharge were significantly higher among SGLT2i users versus those treated with other antidiabetic drugs

(Supplementary Fig. 2). Among CKD patients, at multivariable analysis, after adjusting for confounding factors, the use of SGLT2i was identified as an independent predictor of a lower rate of AKI (OR 0.70; 95% CI 0.42–0.91, $p = 0.014$), together with LVEF (OR 0.95; 95%CI 0.92–0.98, $p = 0.001$). Conversely, bleeding events were found to be independent predictors of a higher AKI risk (OR 2.81; 95%CI 1.01–7.93, $p = 0.045$) (Table 3).

Impact of AKI on long-term outcomes

Overall, during a median follow-up of 24 ± 15 months, 146 (28.4%) patients experienced MACEs, with 112 (21.7%) deaths, among which 58% were related to cardiovascular causes. Eighty (15.6%) patients had HF hospitalization (Supplementary Table 3). Kaplan–Meier estimates at 2-year follow-up are shown in Supplementary Fig. 3. Patients experiencing AKI, compared to those who did not, had a higher incidence of MACE both in the no-CKD (log-rank p -value = 0.025; HR 2.45; 95%CI 1.28–7.69) and CKD cohort (log-rank p -value < 0.001; HR 2.55; 95% CI 1.51–4.31).

Discussion

This study investigated the occurrence of AKI in diabetic patients with severe AS undergoing TAVI, comparing those treated with SGLT2i versus no-SGLT2i users, stratified by the presence of CKD. The main findings include: i) SGLT2i use had no impact on renal function in patients without CKD, with AKI occurring in 7.1% of the cases, regardless of SGLT2i use; ii) among CKD patients, AKI occurred more frequently in no-SGLT2i users compared to those receiving SGLT2i (19.8% versus 8.5%, $p = 0.027$), with a significant rise in post-TAVI and discharge SCr values for no-SGLT2i users ($p = 0.001$ after TAVI and $p < 0.001$ at hospital discharge); iii) only in the CKD group, SGLT2i use was identified as an independent predictor of lower rate of AKI occurrence; iv) patients who developed AKI had a higher incidence of MACE at follow-up, regardless of CKD.

The interplay between diabetes mellitus, CKD, and the risk of AKI after TAVI

AKI is an increasingly recognized complication following TAVI, contributing to increased short- and long-term mortality as well as greater healthcare costs [9, 12]. Its etiology is multifactorial and patient-specific, encompassing heterogeneous mechanisms such as contrast-induced nephropathy, plaque embolization, hemodynamic instability during rapid ventricular pacing, and paravalvular regurgitation impairing renal perfusion. Despite advancements in TAVI techniques and valve technologies, recent large registries reported a 5% incidence of AKI in TAVI patients in contemporary practice [19]. The AKI risk might further increase in some populations, i.e., patients with T2DM and CKD. In the present study, which specifically focused on T2DM patients, we observed a slightly higher overall AKI incidence in patients without CKD (7%), with rates up to 17% among those with concomitant CKD. Diabetic patients are at increased risk of AKI due to underlying endothelial dysfunction, heightened systemic inflammation, and altered renal hemodynamics associated with both diabetes and CKD [13, 20, 21]. In patients with severe AS, the reduced cardiac output may exacerbate these mechanisms, especially when combined with the presence of diabetes-related microvascular disease. This issue is highly relevant in clinical practice, as approximately 30% of patients undergoing TAVI are diabetic [22].

Therefore, we performed a multicenter study involving a contemporary cohort of diabetic patients undergoing TAVI, who underwent a comprehensive assessment of SCr at least at three timepoints (i.e. baseline, within 48 h post-TAVI, and at hospital discharge) [11, 21]. This enabled a thorough evaluation of AKI occurrence and characterization of SCr trend. In contrast to previous studies, which were conducted before the widespread adoption of SGLT2i, this study is the first to offer valuable insights into the potential protective effect of SGLT2i against AKI in diabetic patients undergoing TAVI.

Predictors of AKI

Among patients without CKD, the risk of AKI appeared to be mainly driven by underlying cardiac comorbidities and bleeding events without any influence of SGLT2i use. Indeed, reduced LVEF and advanced EVCD can be considered as markers of a more compromised cardiac status, where even subtle drops in blood pressure or renal perfusion during TAVI or due to bleeding events might increase the risk of AKI [16, 23–25].

Conversely, patients with CKD who were not treated with SGLT2i exhibited an almost threefold higher incidence of AKI compared to those without CKD. Interestingly, CKD patients treated with SGLT2i demonstrated a similar risk of AKI compared to those without CKD, suggesting that SGLT2i use alone was effective in mitigating the excess risk of AKI associated with CKD. Despite having higher baseline SCr values, these patients demonstrated a reduced risk of AKI compared to CKD patients receiving other antidiabetic medications. After adjusting for potential confounders, SGLT2i use emerged as an independent predictor of a lower AKI rate, suggesting the potential nephroprotective effect of SGLT2i in diabetic patients undergoing TAVI.

Bleeding events were independent predictors of AKI regardless of the presence of CKD. Possible mechanisms include hypotension and hemodynamic instability due to bleeding episodes, which may result in renal hypoperfusion and further kidney injury. Additionally, the need

for blood transfusions with their associated inflammatory response could contribute to the deterioration of renal function [26, 27]. Interestingly, in patients with and without CKD, the amount of contrast media did not significantly impact the occurrence of AKI in patients undergoing TAVI. This finding aligns with prior studies and is likely attributable to the relatively low contrast volume typically used during TAVI procedures over the last years [9].

The nephroprotective effects of SGLT2i

The potential mechanisms underlying the renal protection conferred by SGLT2i are multifaceted. Due to natriuresis and glucose-induced osmotic diuresis, SGLT2 inhibition improves tubuloglomerular feedback by enhancing sodium delivery to the macula densa, inducing afferent arteriolar vasoconstriction, and consequently reducing glomerular hyperfiltration, a process particularly vulnerable to disruption during the hemodynamic fluctuations of TAVI [28, 29]. Furthermore, SGLT2i attenuate oxidative stress, inflammation, renin–angiotensin–aldosterone and sympathetic nervous system overactivity, which collectively contribute to renal injury [7, 30]. They also mitigate peritubular fibrosis and enhance tubular resistance to ischemic stress, thereby preserving renal architecture. Additionally, stabilization of renal perfusion through SGLT2 inhibition may reduce susceptibility to AKI triggered by procedural hypotension and contrast exposure during TAVI [29]. This nephroprotective effect is particularly important in patients with pre-existing CKD, who typically exhibit compromised renal homeostasis and altered hemodynamics even before undergoing TAVI. This finding aligns with prior reports showing the beneficial effect of SGLT2i in reducing contrast-induced AKI among patients with coronary artery disease [20, 31–33].

Clinical implications

The occurrence of AKI was confirmed to significantly affect the prognosis of patients undergoing TAVI, regardless of the presence of CKD [9, 26]. Our findings indicate that diabetic patients with CKD, as well as those without CKD but with significant comorbidities (i.e., reduced LVEF or advanced EVCD), are particularly susceptible to AKI during TAVI. In clinical practice, these risk factors should trigger a more comprehensive pre-procedural assessment and proactive management, implementing preventive measures. Limited data are available about pharmacological strategies to prevent AKI in TAVI patients [19, 34]. Integrating SGLT2i into treatment protocols for these high-risk patients may help mitigate AKI risk, potentially improving clinical outcomes. This approach, combined with enhanced pre- and peri-procedural assessment, multidisciplinary collaboration, and development of tailored institutional protocols, may lead to improved renal and cardiovascular outcomes and a more efficient use of healthcare resources. Although current data are promising, they should be considered hypothesis-generating, as large-scale, randomized controlled trials are necessary to definitively establish the role of SGLT2i in preventing AKI in this setting. Such trials may clarify optimal timing, dosing, and patient selection criteria.

Limitations

Our results should be interpreted considering some limitations. The present analysis was an observational multicenter study with inherent limitations. It cannot be excluded that baseline characteristics might have influenced the results, although most key confounders were similar between SGLT2i and no-SGLT2i users. Moreover, our results cannot be extended to patients with eGFR < 20 ml/min/m^2. In addition, we investigated only the "class effect" of SGLT2i, but not the "drug effect". However, a nationwide real-world analysis suggested that the risk of cardiovascular events was comparable between different SGLT2i, supporting our hypothesis of a "class effect" [35]. Finally, no definitive conclusions can be drawn regarding the nephroprotective effects of the "acute" use of SGLT2i in patients undergoing TAVI, specifically when initiated at hospital admission in treatment-naive patients.

Conclusion

In diabetic patients with CKD undergoing TAVI, SGLT2i therapy was associated with a lower occurrence of AKI compared to those not treated with SGLT2i, suggesting a potential nephroprotective effect in this high-risk population.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02773-x.

Supplementary Material 1

Acknowledgments

None.

Author contributions

PP and MB contributed conception and design of the study; PP, MB, EG, RS, LB, LP, MA, GE, EM, CM, EKDO, FA, MO, MF, VG, NB, FDL, PP, CT, DA, GV and MC organized the database and collected data; PP, MB and EG performed the statistical analysis; PP and MB wrote the first draft of the manuscript; EG and LB wrote sections of the manuscript. EG, LB, RS, MA, LS, RM, FG, EC, DP, AI, DA, JAO, PC, AB, TP, FS, FR, MB, MVDH, CP, and EB revised the article and approved the final version of the manuscript. All authors contributed to manuscript revision and read and approved the submitted version.

Funding

Drs. Belmonte and Drs. De Oliveira report receiving a research grant from the CardioPaTh PhD Program. Rafforzamento e potenziamento dellaricerca

biomedica del SSN", finanziato dall'Unione europea NextGeneration EU Cod. Ricerca PNRR-MAD-2022-12376543 ("Integration of Human Carotid Atherosclerotic Plaques Transcriptomics and Metabolomics-based signature to identify new therapeutic targets and biomarkers for Cardiovascular Diseases"), CUP 167G22000380007, CUP MASTER E57G22000320001

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
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
Not applicable.

Competing interests
The authors declare no competing interests.

Statement of guarantor
E.B. is the guarantor of the research and, as such, had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Permissions Information
The authors do hereby declare that all illustrations and figures in the manuscript are entirely original and do not require reprint permission.

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

Received: 10 March 2025 / Accepted: 5 May 2025
Published online: 21 May 2025

References

1. Wanner C, Inzucchi SE, Lachin JM, et al. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med. 2016;375:323–34.
2. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377:644–57.
3. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347–57.
4. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380:2295–306.
5. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383:1436–46.
6. Scisciola L, Paolisso P, Belmonte M, et al. Myocardial sodium-glucose cotransporter 2 expression and cardiac remodelling in patients with severe aortic stenosis: the BIO-AS study. Eur J Heart Fail. 2024;26:471–82.
7. Paolisso P, Belmonte M, Gallinoro E, et al. SGLT2-inhibitors in diabetic patients with severe aortic stenosis and cardiac damage undergoing transcatheter aortic valve implantation (TAVI). Cardiovasc Diabetol. 2024;23:420.
8. Shah T, Zhang Z, Shah H et al. Effect of sodium-glucose cotransporter-2 inhibitors on the progression of aortic stenosis. JACC Cardiovasc Interv 2025.
9. Bagur R, Webb JG, Nietlispach F, et al. Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. Eur Heart J. 2009;31:865–74.
10. Gargiulo G, Sannino A, Capodanno D, et al. Impact of postoperative acute kidney injury on clinical outcomes after transcatheter aortic valve implantation: a meta-analysis of 5,971 patients. Catheter Cardiovasc Interv. 2015;86:518–27.
11. Généreux P, Piazza N, Alu MC, et al. Valve academic research consortium 3: updated endpoint definitions for aortic valve clinical research. J Am Coll Cardiol. 2021;77:2717–46.
12. Barbanti M, Latib A, Sgroi C, et al. Acute kidney injury after transcatheter aortic valve implantation with self-expanding CoreValve prosthesis: results from a large multicentre Italian research project. EuroIntervention. 2014;10:133–40.
13. Nusca A, Piccirillo F, Viscusi MM, et al. Contrast-induced acute kidney injury in diabetic patients and SGLT-2 inhibitors: a preventive opportunity or promoting element? J Cardiovasc Pharmacol. 2022;80:661–71.
14. Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2022;43:561–632.
15. Dweck MR, Loganath K, Bing R, et al. Multi-modality imaging in aortic stenosis: an EACVI clinical consensus document. Eur Heart J Cardiovasc Imaging. 2023;24:1430–43.
16. Généreux P, Pibarot P, Redfors B, et al. Staging classification of aortic stenosis based on the extent of cardiac damage. Eur Heart J. 2017;38:3351–8.
17. Rossing P, Caramori ML, Chan JCN, et al. Executive summary of the KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease: an update based on rapidly emerging new evidence. Kidney Int. 2022;102:990–9.
18. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and stroke endpoint definitions for clinical trials. Circulation. 2018;137:961–72.
19. Petersen JK, Østergaard L, Carlson N, et al. Impact of acute kidney injury after transcatheter aortic valve replacement: a nationwide study. J Am Heart Assoc. 2024;13: e031019.
20. Paolisso P, Bergamaschi L, Cesaro A, et al. Impact of SGLT2-inhibitors on contrast-induced acute kidney injury in diabetic patients with acute myocardial infarction with and without chronic kidney disease: insight from SGLT2-I AMI PROTECT registry. Diabetes Res Clin Pract. 2023;202: 110766.
21. Khawaja MZ, Thomas M, Joshi A, et al. The effects of VARC-defined acute kidney injury after transcatheter aortic valve implantation (TAVI) using the Edwards bioprosthesis. EuroIntervention. 2012;8:563–70.
22. van Nieuwkerk AC, Santos RB, Mata RB, et al. Diabetes mellitus in transfemoral transcatheter aortic valve implantation: a propensity matched analysis. Cardiovasc Diabetol. 2022;21:246.
23. Belmonte M, Paolisso P, Bertolone DT, et al. Combined cardiac damage staging by echocardiography and cardiac catheterization in patients with clinically significant aortic stenosis. Can J Cardiol. 2024;40:643–54.
24. Abdelfattah OM, Jacquemyn X, Sá MP, et al. Cardiac damage staging predicts outcomes in aortic valve stenosis after aortic valve replacement: meta-analysis. JACC Adv. 2024;3: 100959.
25. Belmonte M, Paolisso P, de Oliveira EK et al. Association of Cardiac Damage and Computed Tomography-Derived Extracellular Volume in Patients Undergoing Transcatheter Aortic Valve Implantation. Can J Cardiol 2025.
26. Liao YB, Deng XX, Meng Y, et al. Predictors and outcome of acute kidney injury after transcatheter aortic valve implantation: a systematic review and meta-analysis. EuroIntervention. 2017;12:2067–74.

27. Avvedimento M, Nuche J, Farjat-Pasos JI, Rodés-Cabau J. Bleeding events after transcatheter aortic valve replacement: JACC State-of-the-Art Review. J Am Coll Cardiol. 2023;81:684–702.
28. Armillotta M, Angeli F, Paolisso P, et al. Cardiovascular therapeutic targets of sodium-glucose co-transporter 2 (SGLT2) inhibitors beyond heart failure. Pharmacol Ther. 2025;270: 108861.
29. van Bommel EJM, Muskiet MHA, van Baar MJB, et al. The renal hemodynamic effects of the SGLT2 inhibitor dapagliflozin are caused by post-glomerular vasodilatation rather than pre-glomerular vasoconstriction in metformin-treated patients with type 2 diabetes in the randomized, double-blind RED trial. Kidney Int. 2020;97:202–12.
30. Urbanek K, Cappetta D, Bellocchio G, et al. Dapagliflozin protects the kidney in a non-diabetic model of cardiorenal syndrome. Pharmacol Res. 2023;188: 106659.
31. Fan G, Lin L, Zuo H, Yan R, Xu C. Sodium-glucose cotransporter 2 inhibitors and contrast-induced nephropathy risk: a meta-analysis. Eur J Clin Pharmacol. 2025;81:337–45.
32. Nusca A, Di Bitonto MP, Spanò A, et al. Effects of novel antidiabetic agents on contrast-associated acute kidney injury in diabetic patients undergoing percutaneous coronary intervention. Am J Cardiol. 2025;240:50–6.
33. Zhao Z, Zheng N, Zhang T, et al. Cardiorenal protection with dapagliflozin in patients with type 2 diabetes mellitus and chronic coronary syndrome undergoing percutaneous coronary intervention: a registry cross-sectional study. Cardiovasc Diabetol. 2025;24:185.
34. Barbanti M, Gulino S, Capranzano P, et al. Acute kidney injury with the renal-guard system in patients undergoing transcatheter aortic valve replacement: the PROTECT-TAVI Trial (PROphylactic effecT of furosEmide-induCed diuresis with matched isotonic intravenous hydraTion in Transcatheter Aortic Valve Implantation). JACC Cardiovasc Interv. 2015;8:1595–604.
35. Suzuki Y, Kaneko H, Okada A, et al. Comparison of cardiovascular outcomes between SGLT2 inhibitors in diabetes mellitus. Cardiovasc Diabetol. 2022;21:67.

Publisher's Note