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ORIGINAL STUDIES

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Volume of contrast to creatinine clearance ratio predicts early mortality and AKI after TAVI

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Abstract

The volume of contrast to creatinine clearance ratio (CV/CrCl) is a useful indicator of the risk of acute kidney injury (AKI) in patients undergoing percutaneous interventional procedures. Association between CV/CrCl and adverse outcome after transcatheter aortic valve implantation (TAVI) was suggested but it is not well established. A large retrospective multicenter cohort of 1381 patients treated with TAVI was analyzed to assess the association between CV/CrCl and the risk of AKI and mortality at 90 days and 1 year after TAVI. Patients receiving renal replacement therapy at the time of TAVI were excluded. CV/CrCl ≥ 2.2 was associated with the risk of AKI and 90 days mortality after TAVI after adjustment for age, sex, diabetes, baseline left ventricular function, baseline chronic kidney disease (CKD), previous myocardial infarction and peripheral vascular disease (hazard ratio [HR]: 1.16, 95% confidence interval [CI]: 1.09–1.22, $p < 0.0001$). Importantly, CV/CrCl was associated with the adverse outcome independently from the presence of baseline CKD (p for interaction = 0.22). CV/CrCl was independently associated with the individual components of the composite primary outcome including AKI (odds ratio: 1.18, 95% CI: 1.08–1.28, $p < 0.0001$) and 90 days mortality (HR: 1.90, 95% CI: 1.01–3.60, $p = 0.047$) after TAVI. AKI (HR: 1.94, 95% CI: 1.21–3.11, $p = 0.006$) but not CV/CrCl was associated with the risk of 1-year mortality after TAVI. CV/CrCl is associated with excess renal damage and early mortality after TAVI. Procedural strategies to minimize the CV/CrCl during TAVI may improve early clinical outcomes in patients undergoing TAVI.

KEYWORDS

acute kidney injury, outcomes, renal damage, TAVI

Gabriele Venturi and Roberto Scarsini contributed equally to this study.

1 | INTRODUCTION

The volume of contrast to creatinine clearance ratio (CV/CrCl) is an index recommended to quantify the contrast volume administered during interventional procedures to minimize the risk of acute kidney injury (AKI), especially in patients with baseline impaired renal function and other risk factors for AKI.[1]

AKI is a significant predictor of suboptimal clinical outcome after transcatheter aortic valve implantation (TAVI).[2–4] Patients with severe aortic stenosis (AS) who are candidates for TAVI are usually elderly, with multiple comorbidities and impaired renal function. However, CV/CrCl has been less extensively studied in patients undergoing TAVI.

Previously, an association between larger CV/CrCl and the risk of AKI in patients treated with TAVI was observed.[5,6] Moreover, an impact of larger CV/CrCl on mortality was suggested.[7] However, these evidence derive from relatively small retrospective experiences, based mainly on first-generation TAVI procedures. Therefore, confirmation of the prognostic value of CV/CrCl in large contemporary TAVI registry is lacking.

The purpose of this study is (1) to assess the association of CV/CrCl with AKI and early mortality after TAVI in a large unselected multicenter cohort registry (2) to define the safe dose of contrast media on the basis of estimated renal function in patients undergoing TAVI.

2 | METHODS

2.1 | Study population

The study cohort included patients undergoing TAVI in a large multicentre registry of patients with severe AS treated in two European institutions (University Hospital of Verona [Italy] and John Radcliffe Hospital Oxford [United Kingdom]).

For patients treated at John Radcliffe Hospital Oxford, prospectively collected anonymized data were extracted from a centrally administered and managed database under audit authorization no. 5172 from the Oxford University Hospitals NHS Trust. Data about patients treated at the University of Verona Health Centre were prospectively collected in the Verona Valvular Registry, approved by the local IRB (CESC, $n = 1918$).

The baseline clinical data and procedural data were collected by a dedicated staff member and forwarded to the coordinating center.

Patients were excluded from the analysis if they required renal replacement therapy at baseline, if baseline CrCl was not available, if contrast medium amount was not available or if SCr measurements for AKI assessment after procedure were not available. Moreover, patients were excluded if lost at follow-up at 90 days after TAVI. Medical records of all patients who died within 90 days after TAVI were reviewed to ensure data accuracy.

All the patients provided written informed consent for data collection and anonymous elaboration, according to the local Ethics Committee.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

2.2 | Procedures

The bio-prosthesis choice was performed according to the computed tomography scans analysis and operators' preferences.

The prostheses reported in the present registry were the following: Edwards SAPIEN valve, SAPIEN-XT, SAPIEN-3 and 3-Ultra System (Edwards Lifesciences), Medtronic CoreValve, Evolut R or PRO (Medtronic), Portico TAVI system (Abbott Vascular), Accurate Neo Aortic Valve system (Boston Scientific).

When coronary angiography was performed during the same TAVI procedure, the reported contrast volume and CV/CrCl include the total amount of contrast dye administered during the interventional procedure.

2.3 | Contrast medium and preventive measures

In all cases, patients were administered intra-arterial iso-osmolar contrast medium (Iodixanol) or low-osmolar contrast medium (Iohexol, Iopromide).

Standard measures to prevent AKI were adopted based on the risk profile of each patient, according to the available guidelines at the moment of the procedure.[1,8–10]

The standard practice was to start isotonic saline hydration 12 h before the procedure in patients with abnormal baseline renal function. The infusion rate was standardized at 1 ml/kg/h of 0.9% saline, except in cases of severe left ventricular (LV) dysfunction (LV ejection fraction [LVEF] < 35%) when the infusion rate was reduced to 0.5 ml/kg/h.

Intravenous hydration was given for at least 24 h after the procedure and was further continued if any increment of SCr compared with baseline was detected.

Diabetic patients suspended metformin at least 24 h before the procedure and restarted it 48 h after the procedure, except in case of the development of CI-AKI.

2.4 | Definitions

CV/CrCL was calculated as the ratio between the contrast medium amount and estimated creatinine clearance (CrCl) calculated for each patient using the Cockcroft–Gault formula, as previously reported.[11,12]

AKI was defined and classified according to KDIGO criteria.[13]

Chronic kidney disease (CKD) was defined as an CrCl <60 ml/min/1.73 m^2 at baseline.

Severe AS was defined according to the current European Guidelines criteria.[14]

2.5 | Endpoints

The primary endpoint was the association of CV/CrCl with AKI and/or mortality at 90 days after TAVI.

The secondary endpoints were the association of CV/CrCl with the individual components of the primary endpoint, including AKI and mortality at 90 days after TAVI. The association of CV/CrCl and AKI with mortality at 12 months after TAVI was also assessed.

2.6 | Statistical analysis

The normal distribution of the variables was tested using the Shapiro–Wilk test and histograms.

Continuous variables are presented as mean and standard deviation if normally distributed and compared with unpaired *t* test. Categorical data are reported as a percentage and compared with the χ^2 test or Fisher exact test as appropriate.

Predictors of AKI were investigated using logistic regression. Variables associated with AKI at univariate with a $p < 0.1$ were included in the multivariate regression model. Multicollinearity of variables included in the final model used was assessed using variance inflation factor analysis.

The validity of the model was tested using the Hosmer–Lemeshow goodness-of-fit test.

Receiver-operator characteristics (ROC) curve analysis was used to determine the optimal cut off for CV/CrCl in predicting the primary endpoint.

Survival analysis and endpoint comparison between groups were performed with the Cox regression analysis to calculate hazard ratio (HR) with 95% confidence interval (CI) and the log-rank test. Kaplan–Meier curves were constructed. HR were adjusted for possible confounders including age, sex, and variables with a $p < 0.1$ at univariate analysis. The test for proportional-hazards assumption was applied to confirm the validity of the model.

The possible effect modification of baseline CKD, vascular complications, intraprocedural bleeding, concomitant PCI, and the interventional team who performed the TAVI procedure was assessed using interaction analysis and sensitivity analysis.

Different logistic regression models were constructed to evaluate the incremental predictive value of the combined assessment of CV/CrCl compared with contrast medium volume and CrCl, considered separately. The accuracy of the models was assessed using ROC curve analysis. The areas under the curves were compared using the DeLong method.

Statistical analysis was performed with Stata version 15.1 (StataCorp LLC). A $p < 0.05$ was considered significant.

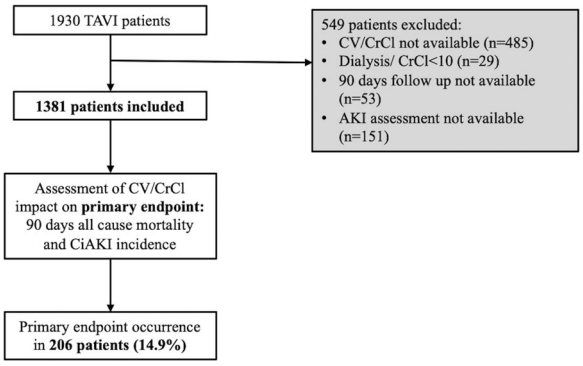


FIGURE 1 Study flowchart. AKI, acute kidney injury; CV/CrCl, volume of contrast to creatinine clearance ratio; TAVI, transcatheter aortic valve implantation

3 | RESULTS

3.1 | Study population

A total of 1381 patients with severe AS, who underwent TAVI at John Radcliffe Oxford University Hospital and at Verona University Hospital between March 15th, 2010 and October 21st, 2020, were included in this study. Details of patient selection are shown in Figure 1.

Mean age at the time of TAVI was 81.9 ± 6.4 years, and 52.1% were female. Baseline CrCl was 55.5 ± 24.4 ml/min and 64.8% had baseline CKD. Other baseline clinical data and procedural data are shown in Table 1.

3.2 | CV/CrCl

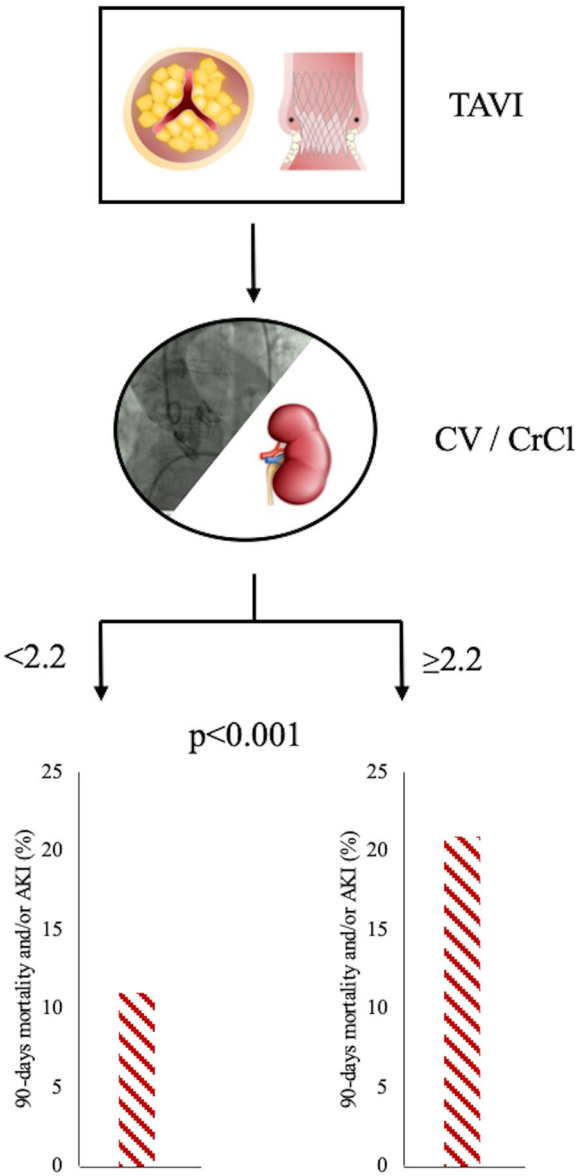
The mean dose of contrast medium was 108.67 ± 59.90 ml, whereas the mean CrCl was 55.47 ± 24.41 ml/min. The mean CV/CrCl was 2.31 ± 1.67. CV/CrCl was significantly higher in patients who developed the primary endpoint (AKI and/or mortality at 90 days after TAVI) (2.99 ± 2.10 vs. 2.20 ± 1.56, $p < 0.0001$).

At ROC curve analysis CV/CrCl ≥2.2 was identified as the optimal cut-off in predicting the composite outcome (Figure S2).

3.3 | Primary endpoint

The primary endpoint (AKI and/or mortality at 90 days after TAVI) occurred in 206 (14.9%) patients. Baseline characteristics of patients undergoing primary endpoint are reported in Table 1.

At Cox regression analysis, CV/CrCl was associated with an excess risk of AKI and early mortality after TAVI (hazard ratio [HR]: 1.16, 95% confidence interval [CI]: 1.09–1.22, $p < 0.0001$) after adjustment for age, sex, baseline left ventricular function, baseline CKD, previous myocardial infarction and peripheral vascular disease (Central illustration; Table 2).



Central illustration. CV/CrCl was associated with an excess risk of AKI and early mortality after TAVI (HR: 1.16, 95% CI: 1.09–1.22, $p < 0.0001$) after adjustment multiple confounders.

The association between CV/CrCl and the primary endpoint was not significantly influenced by the presence of baseline CKD (p for interaction = 0.22; Figure 2).

Notably, CV/CrCl remained significantly associated with the primary endpoint when only transfemoral TAVI were considered (HR: 1.08, 95% CI: 1.04–1.13, $p < 0.0001$; Table S1) when cases with procedural complications were excluded (HR: 1.14, 95% CI: 1.06–1.22, $p < 0.0001$; Table S2) and when cases with concomitant PCI were excluded (HR: 1.18, 95% CI: 1.11–1.24, $p < 0.0001$; Table S3).

3.4 | AKI

Post-TAVI AKI occurred in 169 (12.2%) cases: 147 (10.6%) were Stage 1 according to KDIGO classification, 19 (1.4%) Stage 2 and 3 Stage 3 (0.2%).[13]

At the logistic regression analysis CV/CrCl was independently associated with AKI after adjustment for age, sex, diabetes, basal CKD, and PVD (odds ratio: 1.18, 95% CI: 1.08–1.28, $p < 0.001$; Table 3).

CV/CrCl ≥ 2.2 predicted AKI with an AUC of 0.62 (95% CI: 0.57–0.67). When the analysis was limited to the severe AKI (Stages 2 and 3) the AUC was 0.65 (95% CI: 0.548–0.762).

3.5 | Ninety days all-cause mortality

Fifty-two (3.7%) patients died at 90 days after TAVI. Previous MI, diabetes, baseline CKD, PVD, impaired left ventricular function at baseline, and a higher CV/CrCl were associated with early mortality after TAVI (Table 4).

Notably, patients with CV/CrCl ≥ 2.2 demonstrated a higher mortality rate at 90 days than those with CV/CrCl ≤ 2.2 (log-rank: 9.2, $p = 0.002$; Figure 3).

After adjustment for clinical confounders including previous MI, diabetes, baseline CKD, PVD, and impaired LVEF, CV/CrCl ≥ 2.2 was significantly associated with early mortality after TAVI (HR: 1.90, 95% CI: 1.01–3.59, $p = 0.047$). Similarly, AKI was significantly associated with an excess early mortality (HR: 2.45, 95% CI: 1.28–4.71, $p = 0.007$; Figure S1).

3.6 | One-year mortality

Data on the clinical outcome at 1 year after TAVI were available for 1054 (76.3%) patients. One hundred (9.5%) patients died at 1 year after TAVI. Cox regression analysis of the 1-year mortality is presented in Table S4.

CV/ClCr was not significantly associated with the risk of 1-year mortality after TAVI (log-rank 0.0, $p = 0.959$; Figure S2). Conversely, AKI remained associated with the excess mortality at 1 year after TAVI after adjustment for confounders (HR: 1.94, 95% CI: 1.21–3.11, $p = 0.006$; Figure 4; Table S4).

3.7 | Renal function at long term after TAVI

Data on renal function at long-term after TAVI (685 [322–1094] days) was available for 582 patients (42.1%). CrCl was significantly worse at long-term follow-up in patients who experienced AKI than those without postprocedural AKI (Figure 5).

TABLE 1 Clinical and procedural characteristics of the study cohort

Variable	Overall (1381, 100%)	Endpoint + (206, 14.9%)	Endpoint− (1175, 85.1%)	*p* Value
Sex (male, %)	52.1%	49.5%	52.5%	0.450
Hypertension	86.6%	89.9%	86.0%	0.398
Diabetes	26.6%	35.6%	25.1%	**0.002**
Previous MI	11.4%	16.3%	10.5%	**0.022**
PVD	41.7%	52.0%	39.9%	**0.002**
Previous PCI	34.8%	22.9%	20.7%	0.751
Basal CKD	64.8%	75.2%	63.0%	**<0.001**
Age (years)	81.90 ± 6.43	82.43 ± 5.43	81.81 ± 6.60	0.205
Weight (kg)	73.60 ± 15.26	73.92 ± 16.74	73.54 ± 15.00	0.740
BMI	26.58 ± 5.06	26.94 ± 6.03	26.51 ± 4.87	0.270
Basal creatinine (mg/dl)	1.13 ± 0.47	1.30 ± 0.62	1.10 ± 0.43	**<0.001**
Basal CrCl	55.47 ± 24.4	48.51 ± 21.90	56.70 ± 24.64	**<0.001**
Poor LVEF (<30%)	9.1%	14.3%	8.2%	**0.013**
Fair LVEF (30%–50%)	20.4%	15.9%	21.2%	0.096
Good LVEF (>50%)	70.5%	69.8%	70.6%	0.862
Contrast medium amount (ml)	108.67 ± 50.90	124.10 ± 72.69	105.96 ± 56.98	**<0.001**
CV/CrCl	2.31 ± 1.67	2.99 ± 2.10	2.20 ± 1.56	**<0.001**
CV/CrCl high (≥2.2)	39.8%	55.8%	37.0%	**<0.001**
Procedural time (min)	84.55 ± 36.86	103.82 ± 47.21	81.22 ± 3.68	**<0.001**
PCI concomitant (*n*, %)	2.3%	1.5%	2.5%	0.613
Approach (Trans Femoral *n*, %)	87.5%	83.0%	88.2%	**0.022**
Edwards Sapien	42.4%	45.6%	41.9%	0.321
Medtronic CoreValve	37.8%	37.9%	37.8%	1.000
Boston accurate	19.8%	16.5%	20.3%	0.218

Abbreviations: BMI, body mass index; CrCl, creatinine clearance; CKD, chronic kidney disease; Endpoint+, AKI and/or mortality at 90 days after TAVI; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

4 | DISCUSSION

In this study, we assessed the impact of contrast dose to CrCl ratio on the risk of AKI and mortality after TAVI.

The main findings of our study are: (1) a contrast dose on the basis of CrCl predicted AKI and 90 days mortality after TAVI, irrespectively of the baseline CKD; (2) A contrast volume restricted to less than twice the CrCl significantly reduced the risk of acute adverse outcome after TAVI; (3) AKI but not CV/CrCl was associated with 1-year survival after TAVI.

AKI is a common complication among patients undergoing TAVI.[15] The incidence of CI-AKI following TAVI changes dramatically among different registries, ranging from nearly 4% to more than 57%.[16,17] AKI is associated with adverse clinical outcomes in the short and long term after TAVI.[2-4] Moreover, AKI is also associated with a higher rate of hospital readmission,[18] a longer length of stay,[19] cerebrovascular accidents,[20] and the need for renal replacement therapy.[20] Our data further corroborate previous findings on the impact of AKI on the clinical outcome of patients treated with TAVI. Notably, patients who experienced AKI demonstrated a significantly higher risk of mortality at 90 days (HR: 3.59, 95% CI: 1.94–6.65, $p < 0.001$) and 1 year (HR: 2.42; 95% CI: 1.74–4.35, $p < 0.001$) after TAVI.

The toxic effect of contrast media is an important component of the AKI pathogenesis.[21] Other patient-related AKI predictors including baseline CKD,[22] DM,[23] peripheral arterial disease,[23] impaired left

TABLE 2 Univariate and multivariate Cox regression analysis for primary endpoint.

	Univariate regression analysis			Multivariate regression analysis		
Variable	**HR**	**95% CI**	***p* Value**	**HR**	**95% CI**	***p* Value**
Sex (male, %)	0.90	0.68; 1.18	0.451	0.89	0.66–1.19	0.431
Age (years)	1.01	0.99; 1.03	0.232	1.0	0.98–1.04	0.420
Hypertension	1.38	0.69; 2.75	0.361	-		
Diabetes	1.55	1.16; 2.06	0.003	1.55	1.14–2.10	0.004
Previous MI	1.54	1.06; 2.23	0.024	0.99	0.92–1.06	0.89
PVD	1.53	1.16; 2.01	0.002	1.0	0.95–1.05	0.872
Previous PCI	1.12	0.64; 1.95	0.696	-		
Basal CKD	1.67	1.22; 2.30	0.001	1.28	0.87–1.86	0.247
Weight (kg)	1.00	0.99; 1.01	0.749	-		
BMI	1.01	0.99; 1.04	0.290	-		
Poor LVEF (<30%)	1.69	1.12; 2.53	0.012	1.97	1.28–3.04	0.002
CV/CrCl	1.17	1.12; 1.24	<0.001	1.16	1.09–1.22	<0.0001
CV/CrCl > 2.2	1.95	1.48; 2.57	<0.001	-		
PCI concomitant (*n*, %)	0.62	0.20; 1.93	0.406	-		

Note: Bold-face values were used to indicate signifcant values (<0.005).

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

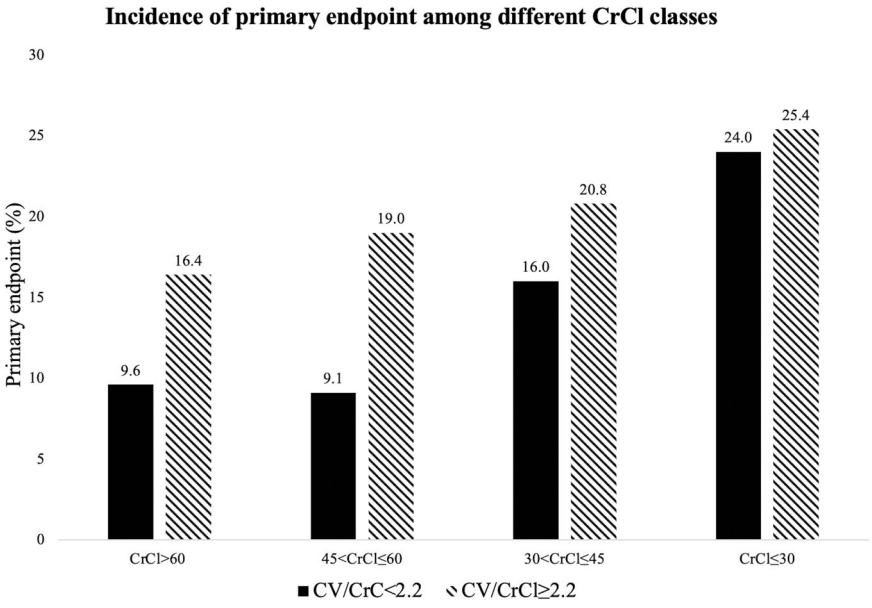


FIGURE 2 Incidence of the primary endpoint stratified according to different CrCl values at baseline. In striped columns, incidence of primary endpoint for patients with CV/CrCl ≥ 2.2. In black columns, incidence of primary endpoint for patients with CV/CrCl < 2.2. CV/CrCl, volume of contrast to creatinine clearance ratio [Color figure can be viewed at wileyonlinelibrary.com]

ventricular function,[2,24] and extra-valvular cardiac damage may stratify the baseline risk of patients undergoing TAVI.[25] Moreover, periprocedural variables may contribute to the risk of AKI, including embolization to the renal vasculature[26] and renal hypoperfusion related to vascular complications, bleeding or rapid pacing. Therefore, especially in high-risk TAVI candidates, it is paramount to minimize the contrast volume, which is the only modifiable procedural factor related to AKI.

Also, CV/CrCl has been proposed and validated as an index to predict the risk of AKI among patients undergoing angiographic procedures.[11,27] Last guidelines on myocardial revascularization by the European society of cardiology[12] recommended to minimizing the volume of contrast media, ideally to a CV/CrCl cut point <3.7, in patients with moderate or severe CKD (National Kidney Foundation stages 3b and 4).

Previously, a ROC-derived threshold of CV/CrCl > 3.7 was associated with increased risk of AKI in a smaller cohort of TAVI

TABLE 3 Univariate and multivariate regression analysis for AKI

Variable	Univariate regression analysis			Multivariate regression analysis		
	OR	95% CI	*p* Value	OR	95% CI	*p* Value
Sex (male, %)	0.90	0.65; 1.24	0.512	1.01	0.71-1.42	0.979
Hypertension	1.19	0.57; 2.50	0.642	-		
Diabetes	1.49	1.06; 2.10	0.023	1.45	1.01-2.09	**0.049**
Previous MI	1.30	0.81; 2.09	0.280	-		
PVD	1.37	0.99; 1.89	0.058	1.34	0.96-1.89	0.088
Previous PCI	1.05	0.54; 2.02	0.892	-		
Basal CKD	1.63	1.13; 2.34	0.008	1.24	0.81-1.91	0.319
Age (years)	1.02	0.99; 1.04	0.271	1.00	0.97-1.03	0.883
Weight (kg)	1.00	0.99; 1.01	0.594	-		
BMI	1.02	0.99; 1.05	0.156	-		
LVEF	0.98	0.75 1.29	0.90			
CV/CrCl	1.25	1.15; 1.35	<0.001	1.18	1.08-1.28	**<0.0001**

Note: Bold-face values were used to indicate signifcant values (<0.005).

Abbreviations: AKI, acute kidney injury; BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CV/CrCl, volume of contrast to creatinine clearance ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OR, odds ratio; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

TABLE 4 Univariate and multivariate Cox regression analysis for 90 days mortality

Variable	Univariate regression analysis			Multivariate regression analysis		
	HR	95% CI	*p* Value	OR	95% CI	*p* Value
Sex (male, %)	0.85	0.49; 1.46	0.559	-		
Diabetes	1.65	0.94; 2.91	0.084	1.53	0.83-2.82	0.177
Previous MI	2.47	1.29; 4.71	**0.006**	0.99	0.88-1.12	0.937
PVD	3.12	1.72; 5.63	**<0.001**	1.01	0.94-1.08	0.838
Previous PCI	1.26	0.34; 4.66	0.728	-		
Basal CKD	3.04	1.43; 6.46	**0.004**	2.40	1.02-5.65	**0.046**
Age (years)	1.02	0.97; 1.06	0.423	-		
Weight (kg)	0.99	0.98; 1.02	0.728	-		
BMI	0.10	0.94; 1.05	0.886	-		
LVEF	0.57	0.40; 0.83	**0.003**	0.57	0.39-0.84	**0.004**
CV/CrCl > 2.2	2.09	1.21; 3.62	**0.009**	1.90	1.01-3.60	**0.047**

Abbreviations: BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; CV/CrCl, volume of contrast to creatinine clearance ratio; HR, hazard ratio; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease.

patients.[5] Notably, in the present study, a lower safety threshold of contrast dose to estimated renal function (CV/CrCl ≥ 2.2) was observed in a larger multicenter cohort of patients. Importantly, CV/CrCl was significantly associated with the adverse clinical outcome irrespectively of baseline CKD and the occurrence of procedural complications during TAVI. These findings highlight the paramount importance of limiting the contrast volume in the fragile setting of patients undergoing TAVI. Ultra-low contrast dose protocols have been developed and may help to keep the CV/CrCl below the safety threshold, especially in high-risk patients.[28,29]

The hemodynamic improvement induced by TAVI may counterbalance the detrimental effects of contrast dye and other possible procedural renal insults related to the procedure. In fact, Venturi et al. observed that patients undergoing TAVI had a significantly lower risk of AKI compared with patients undergoing coronary procedures after matching for clinical characteristics and baseline renal function.[30] Moreover, in patients with AS and bystander coronary artery disease,

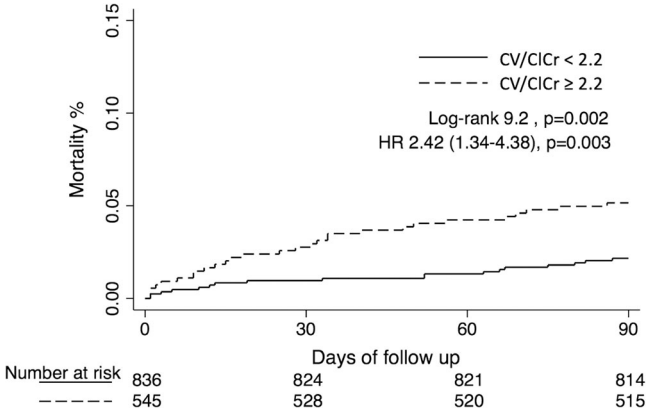


FIGURE 3 Survival analysis at 90 days. Kaplan–Meier curves were constructed for patients with high CV/CrCl (dashed line) versus Low CV/CrCl (continuous line). CV/CrCl, volume of contrast to creatinine clearance ratio; HR, hazard ratio [Color figure can be viewed at wileyonlinelibrary.com]

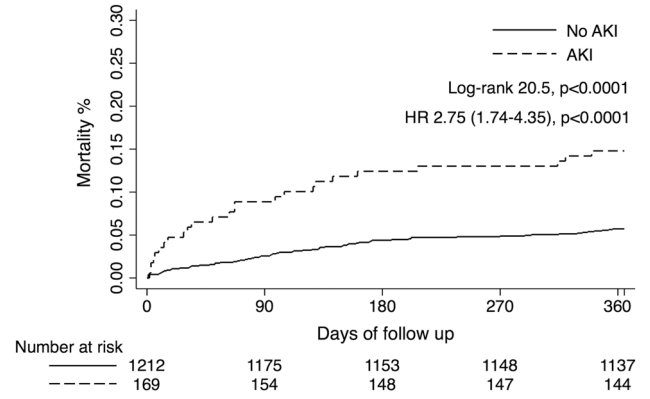


FIGURE 4 Survival analysis at 90 days. Kaplan–Meier curves were constructed for patients who developed AKI (dashed line) versus those without AKI (continuous line). AKI, acute kidney injury; HR, hazard ratio

the incidence of AKI appears to be higher when coronary procedures are performed before TAVI in a staged fashion compared with concomitant TAVI and coronary procedures.[31] These recent data may suggest an interaction between the prompt hemodynamic improvement after TAVI and the increased renal perfusion in preventing AKI.

Also, patient-tailored AKI prevention protocols focused on Left ventricular end-diastolic pressure have been investigated and validated so far, further corroborating the hypothesis of an interaction between hemodynamic condition and AKI risk.[32]

The long-term impact of contrast medium and AKI on the renal function has not been extensively studied in patients treated with TAVI. In our cohort, the estimated renal function was significantly worse at long-term follow-up (685 [322–1094] days) in patients who experienced AKI than those without post-procedural AKI. Notably, AKI was associated with increased risk of mortality at 1 year after TAVI confirming what observed by other investigators.[2]

On the other hand, in this study CV/CrCl was not associated with excess mortality at 1 year of follow-up. This is in contrast with what observed by others.[7] Giannini et al. found that patients with CV/CrCl > 3.2 had a significantly higher risk of mortality at a median time of 643 days after TAVI.

The discordance between our results may be related to the significantly larger sample size of our cohort, and different CV/CrCl threshold used for the analysis. Interestingly, the results did not change when different CV/CrCl cut-offs were used to stratify the risk of long-term mortality (Figure S3). Nevertheless, a CV/CrCl ≥ 2.2 was significantly associated with early mortality after TAVI. Moreover, AKI was a strong predictor of adverse outcome at 1 year after TAVI and was associated with larger CV/CrCl.

In our multi-center analysis, we noticed a decrease of average contrast dye over the years. Also, mortality rate, as well as AKI incidence, decreased from the first TAVI experience to the last years (Figure S4). Although likely multifactorial, as better patient baseline conditions (as suggested by the lowering trend of the STS score over the years—Figure S4) and increased operators' expertise, we believe

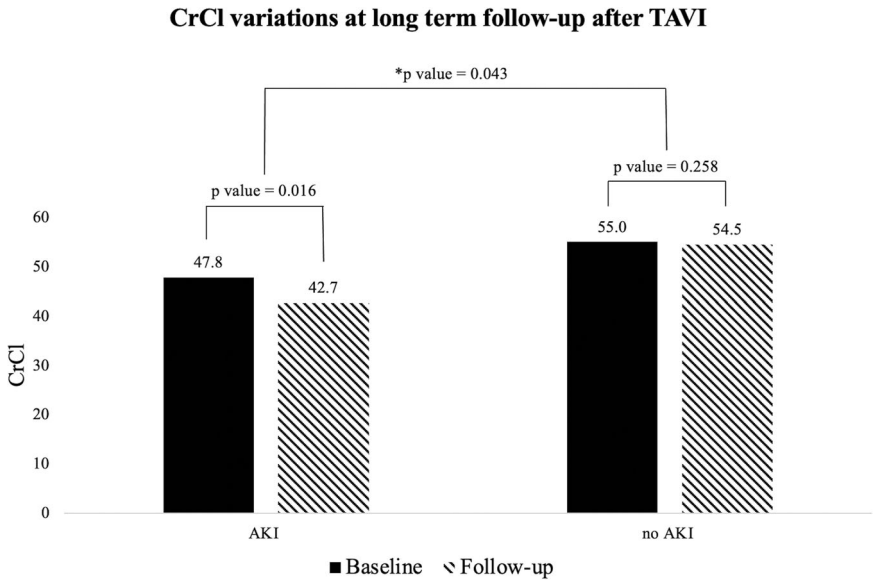


FIGURE 5 Renal function at long-term follow-up: AKI versus no AKI. In black columns, CrCl values at baseline; in striped columns CrCl at last available follow-up. AKI, acute kidney injury; TAVI, transcatheter aortic valve implantation

that minimizing contrast medium could play a key role in further improving TAVI outcomes in the next year.

4.1 | Limitations

Our study has limitations. First of all, this is a retrospective analysis of a multicenter prospectively enrolled cohort of patients. Therefore, although the survival analysis was adjusted for clinical and procedural confounders, it is not possible to exclude the residual influence of confounding factors.

Second, serum creatinine measurements were not standardized between the enrolling centres and were not available at long-term follow-up for all the patients.

Third, preventive measures, including preprocedural and post-procedural hydration protocols were not standardized and left to the physician's decision.

Long-term data on renal function after TAVI was available for the minority of patients (42.1%). Therefore, we cannot exclude a selection bias for patients with worse outcomes.

Lastly, specific cause of death was not available for many patients.

5 | CONCLUSION

Contrast volume to estimated renal function ratio is associated with excess renal damage and early mortality after TAVI. In particular, a contrast dose larger than twice the CrCl increases the risk of AKI and 90 days mortality after TAVI. Procedural strategies to minimize the CV/CrCl may improve early clinical outcomes in patients undergoing TAVI.

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AUTHOR CONTRIBUTIONS

All authors contributed significantly to the completion of the study and the article, including reading and approval of the article in its final form.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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