Acute Kidney Injury After Transcatheter Aortic Valve Replacement Mediates the Effect of Chronic Kidney Disease

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BACKGROUND: Acute kidney injury (AKI) after transcatheter aortic valve replacement (TAVR) is associated with increased mortality. However, it is controversial whether AKI affects prognosis per se, being linked to baseline chronic kidney disease (CKD) and bleeding complications. The aim of this study was to disentangle, applying mediation analysis, the association between AKI and clinical outcome, considering CKD and bleedings.

METHODS AND RESULTS: Consecutive patients undergoing TAVR were prospectively enrolled at 5 high-volume centers in Italy. AKI was defined according to Valve Academic Research Consortium-3 consensus, whereas bleeding with Bleeding Academic Research Consortium. Primary outcome was all-cause mortality after 1-year follow-up. Among 2621 patients undergoing TAVR, AKI occurrence was associated with 1-year mortality. This association of AKI with the primary end points remained significant after adjusting for baseline risk estimators, either Society of Thoracic Surgeons score (hazard ratio [HR], 2.78 [95% CI, 1.95–3.80], P<0.001) or EuroSCORE-II (HR, 1.85 [95% CI, 1.35–2.56], P<0.001). Both AKI and CKD significantly and independently affected primary outcome (HR, 3.06 [95% CI, 2.01–4.64], P<0.001 and HR, 1.82 [95% CI 1.27–2.65], P<0.01, respectively). The estimated proportion of the total effect of CKD mediated via AKI was, on average, 15%, 95% CI, 4%–29%, P<0.001. The significant effect of Bleeding Academic Research Consortium 2–5 bleedings on the primary outcome was not mediated by AKI.

CONCLUSIONS: AKI occurs in 1 out of 6 patients and significantly mediates one fifth of the effect of baseline CKD on all-cause mortality after TAVR. Our analysis supports a systematic effort to prevent AKI during TAVR, which may potentially translate into improved patients’ 1-year survival.

Key Words: acute kidney injury ■ complications ■ transcatheter aortic valve replacement

Transcatheter aortic valve replacement (TAVR) has become the standard of care for patients with severe symptomatic aortic stenosis who are at intermediate and high risk for surgery.1,2 As TAVR is also becoming an attractive therapeutic option for patients at lower surgical risk, prompt recognition and management of intra- and periprocedural complications become pivotal. Acute kidney injury (AKI) is frequently found in patients following TAVR and it is associated with increased morbidity and mortality.3–5

The most important risk factor for AKI, in patients receiving iodinated contrast,6 is reduced renal function because of chronic kidney disease (CKD),7,8 a strong predictor of long-term mortality after TAVR.9–11 Therefore, it is controversial whether AKI, a potentially preventable complication of TAVR, causally mediates
the virtually unmodifiable impact of CKD on clinical outcome. Likewise, bleeding complications increase the risk of AKI and impact on mortality after TAVR. A recent analysis of competing risks in patients undergoing percutaneous coronary intervention for acute coronary syndrome, showed that AKI is individually responsible for one fifth of the clinical impact of stage 4 to 5 chronic kidney disease considering also bleeding complications.

**What Are the Clinical Implications?**
- This implies that preventive measures aimed to reduce AKI incidence might eventually improve outcome with a sizable number of patients needed to save 1 life.

**Nonstandard Abbreviations and Acronyms**

| Acronym | Definition |
|---------|------------|
| AKI     | acute kidney injury |
| BARC    | Bleeding Academic Research Consortium |
| TAVR    | transcatheter aortic valve replacement |

**CLINICAL PERSPECTIVE**

**What Is New?**
- Transcatheter aortic valve replacement is increasingly becoming a mainstay in the treatment of patients with aortic stenosis.
- Acute kidney injury (AKI) is a relative common complication of patients undergoing transcatheter aortic valve replacement and associated with poor outcome; however, the incidence of AKI is more frequent in patients with baseline chronic kidney disease and may also be mutually associated with transcatheter aortic valve replacement related bleeding complications; therefore, it is not clear which and how much is the individual contribution on outcome of AKI over the baseline patient risk.
- With multivariable mediation analysis we aimed to disentangle this complex clinical puzzle, we showed that AKI is individually responsible for one fifth of the clinical impact of stage 4 to 5 chronic kidney disease considering also bleeding complications.

**METHODS**

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

**Study Population**

Consecutive patients undergoing successful TAVR were prospectively enrolled in local clinical registries of 5 high-volume centers in Italy: IRCCS Ospedale Policlinico San Martino (Genoa), IRCCS Policlinico San Donato (Milan), Città Della Salute e della Scienza, (Turin), Ospedale Niguarda Ca’ Granda (Milan), and Magna Graecia University (Catanzaro), between January 2014 to December 2019.

Individual patient-level data were merged in an ad hoc database; we excluded patients who died within 24 hours from TAVR and patients who did not have a serum creatinine (SCr) assessment at ≥48 hours; we also excluded patients on permanent hemodialysis at baseline.

All patients signed an informed consent allowing the use of their anonymized clinical information for medical research purposes, as approved by the local (Genova, Italy) institutional review board. The study complies with the Declaration of Helsinki.

**Study Protocol and Definitions**

Patients underwent TAVR according to standard of care. Both balloon expandable and the self-expandable valves were used. The femoral artery was mainly approached percutaneously using a preclosure technique. Prosthesis size was determined with computed tomographic scan. Rapid right ventricular pacing (range 160–200 beats/min) was generally performed during balloon dilation for native aortic valves or implanted bioprosthetic valves. Iodixanol (Visipaque, GE Healthcare, Buc, France), iohexol (Omnipaque, GE Healthcare), or iomeprol (Iomeron, Bracco, Milano, Italy) were used during TAVR procedure. Cardiac catheterization or any other significant examination requiring dye administration use were avoided for 72 hours before TAVR.

SCr was measured at baseline and until discharge daily. Clinical assessment was scheduled at 1 and 6 months after the procedure and at 1 year of follow-up. Glomerular filtration rate (GFR) was estimated (e) with Modification of Diet in Renal Disease study equation. AKI was defined according to the Kidney Disease Improving Global Outcome classification as recommended by Valve Academic Research Consortium 3 consensus.

Briefly, stage 1 AKI was defined as increase in SCr >0.3mg/dL or >1.5 to 2x above baseline. An increase in SCr >2 to 3x above baseline defined stage 2 AKI,
whereas an increase in SCr >3x above baseline or baseline SCr of 4 mg/dL with an increase of 0.5 mg/dL, defined stage 3 AKI.

Primary outcome measure was all-cause death after 1 year of follow-up. In-hospital stroke, vascular complications, myocardial infarction were defined according to the Valve Academic Research Consortium 3 consensus; bleeding events were defined according to the Bleeding Academic Research Consortium (BARC).

Statistical Analysis
Categorical variables were expressed as count (percentage) and compared with the $\chi^2$ test; continuous variables were expressed as mean (SD) or median (interquartile range) and compared with the Student $t$ test, analysis of variance (ANOVA) or the respective nonparametric test according to distribution.

The hazard ratios (HRs) and 95% CI of AKI, bleeding complications, and baseline CKD on 1-year all-cause mortality were estimated by fitting Cox proportional hazard regression models. We used the Society of Thoracic Surgeons (STS) and logistic EuroSCORE II, both universally accepted baseline risk stratifiers for HR esteem adjustment.

Next, we performed mediation analysis to elucidate the association between baseline estimated GFR (eGFR) as independent variable and 1-year mortality. We fitted a restricted cubic splines model with 4 knots; the same approach was used between baseline eGFR and 1-year mortality; contrast dose was included in the latter model for risk adjustment.

Figure 1. Patient's flow.
AKI indicates acute kidney injury; BARC, Bleeding Academic Research Consortium; and TAVR, transcatheter aortic valve replacement.
and indirect effect. The occurrence of BARC 2, 3, or 5 bleeding complication and contrast dose (by quartiles) were included as covariates for risk adjustment into the models for mediation analysis. We performed several sensitivity analyses of this approach to verify the consistency of our results: first, we included only patients who received fully percutaneous TAVR, therefore excluding surgical accesses; second, we included only stage 2 and 3 (more severe) AKI events; third, we used a softer baseline eGFR cutoff of 45 mL/min per 1.73 m²; finally, we explored the variable of BARC 2, 3, or 5 bleeding events as mediator, while keeping into the model the same covariates.

A P value lower than 0.05 was considered statistically significant; data were managed and analyzed in R environment 3.6.2 “dark and stormy night” (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patients

A total of 2696 consecutive patients undergoing TAVR were included (Figure 1). We excluded 34 patients who died within 24 hours of TAVR (of whom 7 experienced bleeding complications), 15 patients on chronic hemodialysis, and 26 patients with missing SCr values, leading to a final population of 2621 patients. Our sample included 1209 (46.1%) men, and mean age was 82±6.4 years. Median eGFR was 61.1 [45.7, 77.1] mL/min per 1.73 m² in patients without AKI and 50.6 [35.0, 68.9] mL/min per 1.73 m² in patients with AKI, P<0.001. STS score and EuroSCORE II values were 6.6 [4.0, 11.9] and 4.9 [3.1, 8.1], respectively, with higher values in AKI compared with no AKI. All baseline characteristics are depicted in Table 1, whereas procedural variables are shown in Table 2.

AKI and All-Cause Mortality

AKI occurred in 452 patients (17.3%), of whom 381 (84.2%) had stage 1, 41 (9.1%) stage 2, and 63 (13.9%) stage 3 AKI (Table 2).

Patients with AKI had significantly higher all-cause mortality at 30 days and after 1-year follow-up (Figure 2 and Table 3), with a crude HR of 2.18 (95% CI, 1.65–2.86, P<0.001), which was still significant after adjusting for STS 2.78 (95% CI, 1.95–3.80, P<0.001) or EuroSCORE II 1.85 (95% CI, 1.35–2.56, P<0.001). We also found a statistically significant gradient of effect

Table 1. Baseline Population Characteristics

|                          | No AKI       | AKI          | P value |
|--------------------------|--------------|--------------|---------|
| No. (%)                  | 2169 (82.7)  | 452 (17.3)   |         |
| Age, y                   | 82.1 (6.5)   | 81.8 (6.3)   | 0.319   |
| Male sex                 | 986 (45.5)   | 223 (49.3)   | 0.146   |
| Body mass index, kg/m²   | 25.4 (22.9–28.4) | 25.4 (23.1–28.1) | 0.816   |
| History of coronary artery disease | 750 (34.9) | 169 (37.6) | 0.291 |
| New York Heart Association class | | | 0.008 |
| 1                        | 44 (2.0)     | 9 (2.0)      |         |
| 2                        | 456 (21.1)   | 121 (26.8)   |         |
| 3                        | 1550 (71.7)  | 289 (63.9)   |         |
| 4                        | 111 (5.1)    | 33 (7.3)     |         |
| Chronic obstructive pulmonary disease | 419 (19.4) | 90 (19.9) | 0.856 |
| Diabetes                 | 608 (28.1)   | 146 (32.3)   | 0.083   |
| Prior myocardial infarction | 419 (19.4) | 85 (18.8) | 0.838 |
| Any prior valve procedures | 140 (6.5) | 26 (5.8) | 0.639 |
| Baseline hemoglobin, g/dL | 12.0 (10.8–13.2) | 11.5 (10.4–12.6) | <0.001 |
| N-terminal pro-B-type natriuretic peptide, ng/mL | 2917.0 (1279.0–6218.0) | 4433.5 (1568.2–9660.5) | 0.002 |
| Serum creatinine (mg/dL) baseline | 1.1 (0.8–1.3) | 1.2 (0.9–1.8) | <0.001 |
| eGFR, mL/min per 1.73 m² | 61.1 (45.7–77.1) | 50.6 (35.0–68.9) | <0.001 |
| eGFR <30, mL/min per 1.73 m² | 137 (6.3) | 93 (20.6) | <0.001 |
| eGFR <45, mL/min per 1.73 m² | 511 (23.6) | 180 (39.8) | <0.001 |
| Atrial fibrillation      | 713 (33.3)   | 157 (35.2)   | 0.481   |
| Left ventricular ejection fraction (%) | 53.9 (11.4) | 52.6 (11.7) | 0.039 |
| Logistic EuroSCORE II   | 6.3 (3.9–11.4) | 7.2 (4.4–13.0) | 0.017 |
| Society of Thoracic Surgeons score | 4.8 (3.0–7.8) | 5.5 (3.5–9.4) | 0.005 |

AKI indicates acute kidney injury; and eGFR, estimated glomerular filtration rate.
Crimi et al. Post TAVR AKI Mediates CKD Prognostic Effect

between stage 2 to 3 AKI and primary outcome as compared with stage 1 AKI and no AKI (Figure S1 through S4).

**Bleedings, CKD, and All-Cause Mortality**

There were 609 (23%) bleeding complications (BARC 2, 3, or 5), after excluding 7 events occurring in patients within 24 hours of TAVR and were significantly associated with poor 30-day and 1-year all-cause mortality (Table 3 and Figure S2); STS and EuroSCORE II-adjusted HR for the association of BARC 2, 3, and 5 bleedings on primary outcome were respectively 1.76 (95% CI, 1.27–2.44, \(P<0.001\)) and 1.65 (95% CI, 1.18–2.29, \(P<0.001\)).

CKD stage 3b-5 (eGFR <45 mL/min per 1.73 m\(^2\)) was found in 691 (26.4%) of patients, whereas CKD stage 4 to 5 (eGFR <30 mL/min per 1.73 m\(^2\)) was found in 230 (8.8%) of patients. After 1-year follow-up, 44 (19.1%) patients with CKD died compared with 202 (8.4%) patients without CKD (Figure S3). Higher CKD stages were associated with statistically significant unadjusted (Figures S3 and S4) and STS/EuroSCORE II-adjusted increased risk of 1-year mortality, with HRs, respectively, of 1.71 (95% CI, 1.25–2.35, \(P<0.001\)) and 1.54 (95% CI, 1.12–2.13, \(P<0.001\)) for stage 3 and 1.95 (95% CI, 1.32–2.87, \(P<0.001\)) and 2.06 (95% CI, 1.37–3.12, \(P<0.001\)) for stage 4 to 5 CKD.

**Effect of Baseline eGFR on AKI and 1-Year Outcome**

We explored the interplay between baseline eGFR and AKI with restricted cubic splines, showing that there was a j-curve relationship with a flat, low risk (OR \(≈1\)) of AKI for eGFR >60 mL/min per 1.73 m\(^2\). The risk of AKI increased exponentially (Figure 3A) for lower eGFR values. Likewise, we found a similar, though softer, exponential relationship between baseline eGFR and 1-year outcome (Figure 3B). Therefore, we included baseline eGFR as binary variable in the mediation analysis, using cutoffs at 30 (main analysis) and 45 mL/min per 1.73 m\(^2\) (sensitivity analysis), corresponding to CKD stage 4 to 5 and CKD stage 3b-5, respectively.

**Mediation Analysis**

As expected, baseline eGFR <30 mL/min per 1.73 m\(^2\) (CKD stage 4–5), bleeding complications and contrast dose were all significantly associated with the development of AKI (Table 4). CKD 4–5, AKI, bleedings, but not contrast dose except for the highest quartile (>250 mL), were significantly associated with the primary outcome (Figure 4).

The indirect effect of baseline eGFR on the primary outcome through AKI was characterized by an OR of 1.02 (95% CI, 1.01–1.07, \(P=0.0024\)) at bootstrap analysis. The estimated proportion of the total effect of eGFR <30 mL/min per 1.73 m\(^2\) (CKD stage 4–5) on the primary outcome mediated through AKI was on average 15% (95% CI, 4%–29%, \(P<0.001\)), being 10% (95% CI, 3%–22%, \(P<0.01\)) in patients who were non-CKD 4

### Table 2. TAVR Procedural Characteristics

|                      | No AKI       | AKI          | \(P\) value |
|----------------------|--------------|--------------|-------------|
| No. (%)              | 2169 (82.7)  | 452 (17.3)   |             |
| LV-aortic max gradient, mm Hg | 78.6 (24.7)  | 79.9 (25.4)  | 0.334       |
| LV-aortic mean gradient, mm Hg | 47.8 (14.9)  | 47.5 (15.6)  | 0.699       |
| TAVR valve in valve | 77 (3.6)     | 17 (3.8)     | 0.938       |
| Balloon expandable valve | 582 (26.8)   | 151 (33.4)   | 0.006       |
| Procedural access    | <0.001       |              |             |
| Transfemoral         | 1662 (89.0)  | 311 (83.2)   |             |
| Transsclavian        | 131 (7.0)    | 30 (8.0)     |             |
| Transapical          | 59 (3.2)     | 28 (7.5)     |             |
| Transcarotid         | 16 (0.9)     | 4 (1.1)      |             |
| Transcaval           | 0 (0.0)      | 1 (0.3)      |             |
| Any surgical access  | 306 (17.0)   | 88 (25.1)    | <0.001      |
| Valve type           | <0.001       |              |             |
| Sapien XT            | 91 (4.2)     | 15 (3.3)     |             |
| Sapien 3             | 447 (20.6)   | 117 (25.9)   |             |
| Sapien 3 ultra       | 52 (2.4)     | 21 (4.6)     |             |
| Corevalve–evolute    | 878 (40.5)   | 203 (44.9)   |             |
| Lotus                | 311 (14.3)   | 62 (13.7)    |             |
| Symetis–accurate neo | 144 (6.6)    | 13 (2.9)     |             |
| Allegra              | 6 (0.3)      | 2 (0.4)      |             |
| Portico              | 195 (9.0)    | 18 (4.0)     |             |
| Direct flow          | 45 (2.1)     | 1 (0.2)      |             |
| Predilatation        | 708 (32.7)   | 165 (36.5)   | 0.128       |
| Postdilatation       | 682 (31.4)   | 133 (29.4)   | 0.431       |
| Procedural time      | 84.0 (63.0–120.0) | 103.0 (75.2–143.8) | <0.001 |
| Contrast dose, mL    | 196.5 (95.0) | 227.4 (102.0) | <0.001 |
| Ranked contrast dose, mL | <0.001          |              |             |
| <100                 | 149 (9.0)    | 13 (3.9)     |             |
| 100–149              | 389 (23.6)   | 49 (14.6)    |             |
| 150–199              | 417 (25.3)   | 88 (26.2)    |             |
| >200                 | 693 (42.1)   | 186 (55.4)   |             |
| Paravalvular leak    | 0.001        |              |             |
| Absent-trivial       | 803 (47.6)   | 204 (58.8)   |             |
| 1+                   | 762 (45.1)   | 117 (33.7)   |             |
| 2+                   | 113 (6.7)    | 24 (6.9)     |             |
| 3+                   | 10 (0.6)     | 2 (0.6)      |             |
| Hospitalization length, d | 8.0 (5.0–11.2) | 11.0 (8.0–19.0) | <0.001 |
| Serum creatinine (mg/dL) post TAVR | 1.0 (0.8–1.3) | 1.8 (1.4–2.9) | <0.001 |

AKI indicates acute kidney injury; LV, left ventricular; and TAVR, transcatheter aortic valve replacement.
to 5 and 20% (95% CI, 6%–36%, \( P < 0.01 \)) in patients with CKD 4 to 5 patients, respectively (Tables 4 and 5).

**Sensitivity Analyses**

After excluding the 394 patients with any surgical access, the average mediation effect of AKI was still significant, being 11% (95% CI, 2%–24%, \( P < 0.04 \)) on the primary outcome.

Mediation analysis including only AKI stage 2 and 3 events showed an increased proportion of effect mediated by AKI, being 21% (95% CI, 7%–40%, \( P = 0.0016 \)) (Table 5).

When we used a less strict definition of CKD, setting a cutoff value at 45 mL/min per 1.73 m² (CKD stage 3b–5), the proportion of mediated effect by any AKI events was 11% (95% CI, 3%–20%, \( P = 0.0012 \)). On the contrary, any BARC 2, 3, or 5 events were a nonsignificant mediator of CKD effect on the primary outcome, with an average proportion of mediated effect of 3% (95% CI, –2% to –11%, \( P < 0.18 \)) (Tables 4 and 5).

**DISCUSSION**

In this large contemporary cohort of patients undergoing TAVR in 5 high-volume centers in Italy, we found that (1) AKI occurs in 1 out of 6 patients and doubled the risk of all-cause mortality after 1-year follow-up, even after adjusting for baseline patient risk profile with either STS or logistic EuroSCORE II; and (2) baseline eGFR, bleeding complications, and iodinated contrast are predictors of primary outcome and AKI, with differential effects in a complex network of mutual interplay.

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**Table 3. TAVR-Related Clinical Events**

| Event                                      | No AKI (%) | AKI (%) | \( P \) value |
|--------------------------------------------|------------|---------|---------------|
| No. (%)                                    | 2169 (82.7)| 452 (17.3)|               |
| All-cause mortality at 30-d                | 54 (2.5)   | 23 (5.1) | 0.005         |
| All-cause mortality at 1-y follow-up       | 174 (8.0)  | 72 (15.9)| <0.001        |
| Cardiovascular-cause mortality             | 91 (4.1)   | 37 (8.1) | <0.001        |
| AKI                                        | 452 (100.0)|         | <0.001        |
| Stage AKI                                  |            |         |               |
| 1                                          | 348 (77.0) |         | <0.001        |
| 2                                          | 41 (9.1)   |         |               |
| 3                                          | 63 (13.9)  |         |               |
| Bleeding complications (Bleeding Academic Research Consortium\(^2\) 2, 3, or 5) | 456 (21.6) | 145 (32.9) | <0.001        |

Mortality was assessed at 1-year follow-up, other events were assessed in-hospital. AKI indicates acute kidney injury; and TAVR, transcatheter aortic valve replacement.
AKI, a potentially preventable complication, mediates one fifth of the effect of baseline CKD, one of the strongest predictors of mortality after TAVR, on all-cause mortality after 1-year follow up. AKI, variously defined, is a common complication after TAVR, with a widely variable incidence across studies ranging from 8.3% to 57% 4,10,25–27 and it is linked to increased short- and long-term mortality.28 In our cohort, AKI development was associated with a doubling of mortality risk after 1-year follow-up (15.9% versus 8.0%, \( P < 0.001 \), Figure 2), with a clear stepwise effect: the worse the AKI stage, the worse the impact on mortality (Figures S1 through S4). This is in line with current literature10,26 and, importantly, it was maintained after adjusting for universally accepted baseline risk stratifiers, supporting a strong link between AKI and unfavorable outcome after TAVR.

Nonetheless, baseline CKD and BARC bleeds resulted as both strong AKI and primary outcome predictors. Thus, whether AKI prevention may eventually translate into an improved clinical outcome is debatable.6,14,22 To clarify this important point, we explored the interplay between baseline CKD; TAVR-associated events such as AKI; BARC 2, 3, or 5 bleeds; and their association with 1-year mortality. The disentanglement of these complex relationships is highlighted in Figure 4.

Patients with CKD stage 4 to 5 showed a significantly increased risk of AKI after TAVR. Both AKI and CKD independently affected 1-year mortality, although the magnitude of effect of the latter was higher than that of the former. AKI mediated on average, one sixth to one fifth of the 1-year mortality risk conferred by baseline CKD stage 4 to 5. This finding is of clear clinical relevance: indeed, 1 year after TAVR, the absolute risk difference between patients without and with CKD in our cohort is 8.7%, which leads to a theoretical number needed to treat of 11.5, if we could virtually improve eGFR and abate CKD. Nonetheless, our analysis shows that one fifth to one sixth of this effect can be tackled via AKI prevention, with a sizable number needed to treat ranging around 50. We believe that this finding is truly hypothesis generating and might deserve to be tested in properly sized clinical trials.

Importantly, the results of mediation analysis were consistent among the explored subgroups; the effect of AKI was still significant in patients receiving fully percutaneous TAVR, which is relevant as surgical access has been reported as a strong predictor of AKI itself.26 Furthermore, we found a gradient of effect with higher proportion of significant AKI-mediated effect when we considered only severe (eg, stage 2–3) AKI. We found a lower proportion of AKI-mediated effect when we included stage 3b in our CKD definition, giving further strength to the overall picture.

Being, to the best of our knowledge, the first mediation analysis on the role of AKI after TAVR, our result can be put into a perspective only with similar analyses in different scenarios.22 Weisbord et al. looked at AKI in patients undergoing elective coronary procedures; even though they could ascertain an association between AKI and an increased incidence of clinical events (death, need for dialysis, or persistent impairment in kidney function at 90 days), the authors failed to show a significant proportion of effect mediated by AKI over the baseline risk conferred by CKD. The diverging results may be explained by different patients’ characteristics (median age was 69 years, 93% men versus 82 years and 43% men in our cohort), different contrast dose (median 85 mL compared with >200 mL in our cohort), and, more likely, the different procedure. In fact, TAVR, as compared with percutaneous coronary intervention, is associated with a remarkable shift of the prerenal component responsible for SCr change, being characterized by a transient hypotension during valve implantation, rapidly followed by an increase in
cardiac and urine output owing to the acutely reduced afterload.29–31

Our results, instead, are consistent with those shown by Rothenbühler et al. in a mediation post hoc analysis of the MATRIX (Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox) trial,14 in which bleeding events were taken into account. The authors showed that AKI and bleedings were mutually linked and that the mortality benefit of the radial as compared with the femoral approach was mainly driven by AKI and not by the well-known reduction in bleeding rates afforded by radial access. This is in line with the disentanglement of the risks of TAVR-associated complications, with the highlighting of AKI as an independent player (see Figure 4), and with the lack of significant mediator effect of bleeding events seen in our analysis.

Regarding contrast reduction8 largely considered as the mainstay of AKI prevention, any increase in dye dose compared with the lowest quartile significantly raised the risk of AKI (Table 5), whereas only the highest contrast quartile was significantly associated with the primary outcome. In this view, it is likely that contrast dose mainly acts as proxy for complex or complicated TAVR procedures. In addition, even after adjusting for contrast dose the risk of developing AKI was very low for a baseline eGFR above 45 mL/min per 1.73 m², (see Figure 3A), setting a reasonable cutoff for patients deserving heightened attention and stronger AKI prevention efforts.

Limitations

The first limitation to acknowledge is the retrospective nature of analysis; nonetheless, data derive from prospectively collected local registries of 5 high-volume TAVR centers. This could partially explain the relatively high use of contrast medium in comparison to other large randomized prospective studies.

Second, SCr assessment and need for hemodialysis after discharge were not routinely recorded, and therefore we could not include them as outcome measures. Third, the timing of in-hospital bleeding events was not consistently collected, negating multistate and competing risk models.14 However, multiple sensitivity analysis showed consistent results with a clear gradient in associated risk between CKD stages; moreover,

### Table 4. Building Mediation Analysis

|                         | 8     | Exp (8) | Lower 95% CI | Upper 95% CI | Pr (>|z|) |
|-------------------------|-------|---------|--------------|--------------|----------|
| Estimating direct effect on all-cause at 1-y follow up |       |         |              |              |          |
| (Intercept)             | −2.9846 | 0.05   | 0.03         | 0.07         | <0.001   |
| CKD 4–5—eGFR <30 (mL/min per 1.73m²) | 1.2841 | 3.61   | 2.42         | 5.40         | <0.001   |
| Bleedings (BARC 2, 3, or 5) | 0.7427 | 2.10   | 1.51         | 2.93         | <0.001   |
| Contrast dose Q1 <137 mL [reference category] |       |         |              |              |          |
| Q2 137–180mL           | −0.0271 | 0.97   | 0.59         | 1.59         | 0.9141   |
| Q3 181–250mL           | 0.2585  | 1.29   | 0.81         | 2.08         | 0.2851   |
| Q4 >250mL              | 0.7041  | 2.02   | 1.29         | 3.18         | 0.0023   |
| Estimating effect on mediator (AKI) |       |         |              |              |          |
| (Intercept)             | −2.622 | 0.07   | 0.05         | 0.10         | <0.001   |
| CKD 4–5—eGFR <30 (mL/min per 1.73m²) | 1.537  | 4.65   | 3.32         | 6.52         | <0.001   |
| Bleedings (BARC 2, 3, or 5) | 0.441  | 1.55   | 1.19         | 2.03         | 0.0013   |
| Contrast dose Q1 <137 mL [reference category] |       |         |              |              |          |
| Q2 137–180mL           | 0.578  | 1.78   | 1.20         | 2.65         | 0.0042   |
| Q3 181–250mL           | 0.918  | 2.50   | 1.70         | 3.68         | <0.001   |
| Q4 >250mL              | 1.144  | 3.14   | 2.13         | 4.62         | <0.001   |
| Estimating overall effect on all-cause at 1-y follow up |       |         |              |              |          |
| (Intercept)             | −3.0324 | 0.05  | 0.03         | 0.07         | <0.001   |
| CKD 4–5—eGFR <30 (mL/min per 1.73m²) | 1.1176 | 3.06   | 2.01         | 4.64         | <0.001   |
| AKI                    | 0.6065  | 1.83   | 1.27         | 2.65         | 0.0012   |
| Bleedings (BARC 2, 3, or 5) | 0.7013 | 2.02   | 1.44         | 2.81         | <0.001   |
| Contrast dose Q1 <137 mL [reference category] |       |         |              |              |          |
| Q2 137–180mL           | −0.0663 | 0.94  | 0.57         | 1.54         | 0.7931   |
| Q3 181–250mL           | 0.1907  | 1.21   | 0.75         | 1.95         | 0.4338   |
| Q4 >250mL              | 0.6099  | 1.84   | 1.16         | 2.91         | 0.0092   |

AKI indicates acute kidney injury; BARC, Bleeding Academic Research Consortium20; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; and Q, quartile.
the severity of AKI was proportional to the percentage of mediated effect. Finally, we could not find a significant association between CKD and in-hospital BARC 2, 3, and 5 bleedings. Whereas this was not a focal point of our analysis, this finding may derive by the exclusion of earlier events after TAVR by study protocol and is in line with the result of a recent meta-analysis.10 AKI occurred in 1 out of 6 patients after TAVR and doubled the risk of all-cause mortality after 1-year follow-up, even after adjusting for baseline risk profile. AKI mediates one fifth of the effect of baseline CKD on all-cause mortality. Our analysis supports a systematic effort to prevent AKI after TAVR by reducing contrast dose and minimizing bleeding complications.

**Table 5. Mediation Analysis of CKD Through AKI**

|                          | B  | Exp (B) | 95% CI lower | 95% CI upper | P value |
|--------------------------|----|---------|---------------|---------------|---------|
| Any AKI                  |    |         |               |               |         |
| CKD 4–5—eGFR <30 (mL/min per 1.73 m²) |    |         |               |               |         |
| ACME (average)           | 0.02276 | 1.02    | 0.00688       | 0.04          | 0.0024  |
| ADE (average)            | 0.12788 | 1.14    | 0.06839       | 0.19          | <0.001  |
| Proportion of mediated (average) | 0.15107 | 0.04595 | 0.29          | 0.0024       |
| AKI stage 2 and 3        |    |         |               |               |         |
| CKD 4–5—eGFR <30 (mL/min per 1.73 m²) |    |         |               |               |         |
| ACME (average)           | 0.03148 | 1.03    | 0.01086       | 0.06          | 0.0016  |
| ADE (average)            | 0.12022 | 1.13    | 0.05968       | 0.18          | <0.001  |
| Proportion of mediated (average) | 0.20753 | 0.07058 | 0.4           | 0.0016       |
| Any AKI                  |    |         |               |               |         |
| CKD 3–5—eGFR <30 (mL/min per 1.73 m²) |    |         |               |               |         |
| ACME (average)           | 0.01042 | 1.01    | 0.000317      | 0.02          | 0.0012  |
| ADE (average)            | 0.08354 | 1.09    | 0.05065       | 0.12          | <0.001  |
| Proportion of mediated (average) | 0.11088 | 0.0334  | 0.2           | 0.0012       |

ACME indicates average causal mediator effect; ADE, average direct effect; AKI, acute kidney injury; CKD, chronic kidney disease; and eGFR, estimated glomerular filtration rate.

**CONCLUSIONS**

Among a large cohort of patients undergoing TAVR, we demonstrated that AKI occurs in one sixth and significantly mediates one fifth of the effect of baseline CKD on all-cause mortality.
CKD on all-cause mortality after the procedure. Further studies are urgently needed to disentangle this complex scenario and to encourage a systematic effort to prevent AKI during TAVR, finally potentially leading to an improvement of patients’ 1-year survival.

**ARTICLE INFORMATION**

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**Supplemental Material**

Figures S1–S4

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Supplemental Material
Figure S1. Cumulative all-cause mortality in patients stratified for stage of AKI occurring after TAVR.
Figure S2. Cumulative all-cause mortality in patients stratified for BARC 2-5 bleeding occurring after TAVR.
Figure S3. Cumulative all-cause mortality in patients stratified for eGFR below or above 30 ml/min/1.73 m² occurring after TAVR.
Figure S4. Cumulative all-cause mortality in patients stratified for eGFR below or above 45 ml/min/1.73 m² occurring after TAVR.