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# Transcatheter Aortic Valve Replacement-Associated Acute Kidney Injury: An Update

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**Keywords**
Transcatheter aortic valve replacemen · Transcatheter aortic valve implantation · Acute kidney injury · Chronic kidney disease

**Abstract**
***Background:*** Transcatheter aortic valve replacement (TAVR) is a relatively novel minimally invasive procedure for the treatment of symptomatic patients with severe aortic stenosis. Although it has been proven effective in improving mortality and quality of life, TAVR is associated with serious complications, such as acute kidney injury (AKI). ***Summary:*** TAVR-associated AKI is likely due to several factors such as sustained hypotension, transapical approach, volume of contrast use, and baseline low GFR. This narrative review aims to present an overview of the latest literature and evidence regarding the definition of TAVR-associated AKI, its risk factors, and its impact on morbidity and mortality. The review used a systematic search strategy with multiple health-focused databases (Medline, EMBASE) and identified 8 clinical trials and 27 observational studies concerning TAVR-associated AKI. Results showed that TAVR-associated AKI is linked to several modifiable and nonmodifiable risk factors and is associated with higher mortality. A variety of diagnostic imaging modalities have the potential to identify patients at high risk for development of TAVR-AKI; however, there are no existing consensus recommendations regarding their use as of this time. The implications of these findings highlight the importance of identifying high-risk patients for which preventive measures may play a crucial role, and should be maximized. ***Key Message:*** This study reviews the current understanding of TAVR-associated AKI including its pathophysiology, risk factors, diagnostic modalities, and preventative management for patients.



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## Introduction

Transcatheter aortic valve replacement (TAVR) is among the newer, well-studied interventions for treating symptomatic patients with severe aortic stenosis (AS) [1]. Numerous studies have proven its efficacy and benefit in terms of mortality and improvement in quality of life [2–5]. However, TAVR is a procedure associated with significant risks. Peri- and postprocedural complications remain high in TAVR even with improving experience and techniques [6]. Patients undergoing TAVR are older and sicker than the typical patient undergoing other types of common angiographic procedures [1]. A significant portion of patients who undergo TAVR have a significant baseline comorbidity burden. Transcatheter valve replacement remains a major issue affecting outcome and survival [6]. Acute kidney injury (AKI) is a well-known potential TAVR complication with serious clinical implications [7]. AKI is defined as an increase in serum creatinine by at least ≥0.3 mg/dL or 1.5- to 2-fold increase from baseline, with a urine output reduction of <0.5 mg/kg/h for at least 6 h starting from 72 h to 7 days postprocedure [8]. This is based on the Valve Academic Research Consortium-2 (VARC-2) that closely follows the three-tiered classification system of acute kidney injury network [8] (see Table 1).

In the first few years following the introduction of TAVR, incidence of AKI was comparable to patients who underwent surgical aortic valve replacement (SAVR) [9]. At that time, the 30-day mortality rate was 7.8–29%, 2.5 times higher than patients who did not develop AKI, with hospital length of stay prolonged by 2.5 times [7]. Owing to significant technological advancements and increased operator experience, rates of TAVR-associated AKI have slowly declined over time [10, 11].

Most cases of AKI in TAVR are mild. However, the impact of AKI is worse, especially among older and sicker patients with actual or potential baseline kidney impairment [1]. The risk is further compounded if the patient needs to undergo other common angiographic procedures [1]. Higher acute kidney injury network classification is significantly linked to increased mortality [1]. TAVR patients represent a particular patient group concerning the presence of comorbidities and often even concerning their age [6]. After 70 years of age, the kidneys have lost between 30% and 50% of their functioning nephron due to chronic ischemic changes. A significant number of the remaining glomeruli manifest some degree of sclerosis, next to concomitant tubular and vascular changes leading to functional alterations, including a reduction in renal blood flow of up to 50% from age 20 to age 80 years [6].

This narrative review aims to present an overview of the latest literature and evidence regarding the definition of TAVR-associated AKI, and its impact on morbidity and mortality. An extensive review of risk factors potentially linked to higher incidence of AKI post-TAVR has been done and compared across the available literature to help in the risk stratification of patients who undergo TAVR.

## Incidence of TAVR-Associated AKI

AKI is a frequent complication after TAVR and affects outcome and survival [6]. Previous studies showed that patients have an increased risk of postprocedural AKI after TAVR, but whether differences in patient risk profiles confounded the results is unclear [12] (see Table 2).

In the recent work by Julien et al. [13], out of 107,814 patients who had TAVR in the USA, 11,566 (10.7%) experienced postprocedural AKI. Among patients who developed AKI, 10,220 (9.5%) experienced stage 1 AKI, 134 (0.1%) stage 2 AKI, and 1,212 (1.1%) stage 3 AKI [13]. However, the incidence of AKI after TAVR seems to be improving in the latest registries, perhaps owing to significant improvement in technology and surgeon experience [13]. A similar study by Abbas et al. [10], utilizing the US National Inpatient registry, reported a similar percentage at 11.5% (20,045/173,760). In Asia, Tay et al. [14], using the Asian Pacific Society of Interventional Cardiology (APSIC)-supported transcatheter aortic valve implantation (TAVI) registry, noted that AKI was the most common TAVI complication, occurring in 6.8% (77 of 1,125) of Asian patients who underwent TAVI, followed by major vascular complications (5.8%, 65 of 1,125). On the other hand, analyzing the Asian TAVI registry, Yoon et al. [15], reported that AKI occurred less frequently (28 of 848 or 3.3%) than bleeding (92 of 848 or 10.8%) and vascular complications (82 of 848 or 9.7%).

## Pathophysiology

TAVR is generally performed in elderly and high-risk patients with a high prevalence of CKD and heart failure [16]. Furthermore, TAVR requires a contrast agent and manipulation of large catheters in the aorta that enhance the risk of contrast-induced nephropathy and distal embolization of atherosclerotic debris to the renal vascular bed [16]. The occurrence of short periods of hypotension (aortic balloon valvuloplasty,

**Table 1.** VARC-2 definition of AKI (AKIN classification)

| Stage | Serum creatinine | Urine output |
|---|---|---|
| Stage 1 | Increase in serum creatinine to 150–199% (1.5–1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L) OR | Urine output <0.5 mL/kg/h for >6 but <12 h |
| Stage 2 | Increase in serum creatinine to 200–299% (2.0–2.99% × increase compared with baseline) OR | Urine output <0.5 mL/kg/h for >12 but <24 h |
| Stage 3 | Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of at least 0.5 mg/dL (44 mmol/L) OR | Urine output <0.3 mL/kg/h for ≥24 h OR anuria for ≥12 h |

VARC-2, Valve Academic Research Consortium-2; AKIN, acute kidney injury network. The increase in creatinine must occur within 48 h. Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.

rapid pacing, and valve delivery) may also help precipitate renal damage [16]. AKI in TAVR patients is most likely a combination of prerenal azotemia and direct nephrotoxic influences, leading to renal ischemia and acute tubular necrosis [6]. Causes of prerenal azotemia include (among others) hypovolemia, hemorrhage, impaired cardiac output, or renal vasoconstriction caused by vasoconstrictive medication [6].Thus, AKI after TAVR can be considered the common final path resulting from prerenal azotemia due to pre-, intra-, and postoperative factors and additional nephrotoxic influences resulting in acute tubular necrosis [6]. Predictors of AKI, in descending order of AKI risk, include CKD (odds ratio [OR] 3.52 [3.4–3.64]), weight loss (OR 3.01 [2.82–3.2]), liver disease (OR 2.29 [2.13–2.46]), and congestive heart failure (OR 2.01 [1.92–2.1]) [6]. Cerebrovascular accidents, COPD, metastatic cancer, and peripheral vascular disease were also mentioned to increase AKI risk in TAVR [10]. Moriyama et al. [17] using the Finn registry reported that among TAVR-related variables, the European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG) bleeding grades 2 and 3 (OR 9.94 [3.82–27]) and at least moderate paravalvular leakage (OR 4.12 [1.39–10.7]) are significantly associated with AKI occurrence post-TAVR.

## Risk Factors

Risk factors are shown in Figure 1.

*Hypotension*

Sustained intraoperative hypotension during TAVR is a well-documented contributor to AKI. AKI may result from several factors, such as pericardial effusion, vascular bleeding complications, drug reactions, and rapid pacing while the balloon-expandable valve is deployed [18]. In the study of Nunes-Filho et al. [19], major intraoperative bleeding leading to hypotension was significantly associated with the development of AKI in the postoperative period. Similar findings have been seen as well in other studies [17, 20, 21]. Renal injury arising from prolonged hypotension during TAVR may be prevented through early recognition [18].

*Contrast Dye*

AKI resulting from contrast use/administration is an important complication of several procedures. In the setting of TAVR, there is conflicting evidence regarding the association between contrast volume (CV) and the development of AKI postprocedurally [22–24]. The group of Elhmidi et al. [22] reported that the amount of contrast use was not associated AKI. On the other hand, both Miura et al. [23] and Andò et al. [24] reported that CVs remain a key factor in contrast-induced AKI. Miura et al. [23] reported that in their cohort, AKI was found in 8.6% and the CV was significantly higher among those who developed AKI. There was no observed difference in the occurrence of AKI seen among patients where iso-osmolar contrast versus low osmolar contrast medium was used [25].

*Blood Transfusion*

The clinical decision to transfuse packed red blood cells (pRBCs) during cardiac surgery, including TAVR, depends on various factors, including preoperative anemia, perioperative fluid administration, and institution-specific transfusion thresholds. However, there was conflicting evidence coming from observational cohort studies examining the association between pRBC transfusion and the development of post-TAVR AKI [22, 26, 27]. To help

**Table 2.** Studies examined (clinical trials and observational cohort studies)

| Author | Study participants | Area/ population | AKI | Non-AKI | Author | Study participants | Area/population | AKI | Non-AKI |
|---|---|---|---|---|---|---|---|---|---|
| *Clinical trials* | | | | | | | | | |
| Chandrasekhar et al. [71] 2021 | 802 | Europe North America | 139 | 663 | Beve et al. [75] 2019 | 191 | France | 8 | 183 |
| Feistritzer et al. [72] 2021 | 447 | Germany | 55 | 392 | Goel et al. [76] 2019 | 802 | Europe North America | 132 | 670 |
| Razuk et al. [73] 2021 | 798 | Europe North America | 66 | 732 | Yamawaki et al. [77] 2017 | 1,458 | Japan | 134 | 1,324 |
| Thiele et al. [74] 2020 | 438 | Germany | 39 | 399 | | | | | |
| *Observational studies* | | | | | | | | | |
| Sudarsky et al. [66] 2022 | 210 | Israel | 38 | 172 | Moriyama et al. [17] 2021 | 4,555 | Finland | 57 | 4,498 |
| Zahid et al. [34] 2021 | 216,023 | USA | 27,871 | 188,152 | Kaur et al. [67] 2020 | 33,325 | USA | 9,740 | 23,585 |
| Tay et al. [14] 2021 | 1,125 | Hong Kong, Japan, Philippines, Singapore, Taiwan | 77 | 1,048 | Peillex et al. [63] 2020 | 100 | France | 10 | 90 |
| Abbas et al. [10] 2021 | 173,760 | USA | 20,045 | 153,715 | Venturi et al. [68] 2020 | 489 | Italy | 33 | 456 |
| Julien et al. [13] 2021 | 156,421 | USA | 11,566 | 144,855 | Elbadawi et al. [32] 2020 | 530 | USA | 145 | 385 |
| Witberg et al. [20] 2021 | 1,038 | Israel | 115 | 923 | Patel et al. [43] 2020 | 893 | UK | 67 | 826 |
| *Observational studies* | | | | | | | | | |
| Merchant et al. [28] 2019 | 116 | USA | 20 | 96 | Mohanney et al. 2019 | 51,685 | USA | 8,394 | 43,291 |
| Miura et al. [23] 2019 | 81 | Japan | 7 | 74 | Kumar and Garg [9] 2018 | 8,004 | USA | 1,496 | 6,508 |
| Andò et al. [24] 2019 | 596 | USA | 73 | 523 | Cocchieri et al. [70] 2018 | 253 | France, Italy, Netherlands, UK, Poland, Finland, Denmark, Norway, Germany, Austria | 31 | 222 |
| Elbadawi et al. [32] 2019 | 975 | USA | 141 | 834 | Nunes-Filho et al. [19] 2018 | 794 | Brazil | 143 | 651 |

**Table 2** (continued)

| Author | Study participants | Area/ population | AKI | Non-AKI | Author | Study participants | Area/population | AKI | Non-AKI |
|---|---|---|---|---|---|---|---|---|---|
| Elbadawi et al. [32] 2019 | 6,672 | USA | 1,410 | 5,262 | Gupta et al. [38] 2018 | 8,885 | USA | 1,484 | 7,401 |
| *Observational studies* | | | | | | | | | |
| Kandathil et al. [49] 2018 | 106 | USA | 20 | 86 | | | | | |
| Shishikura et al. [30] 2018 | 278 | Australia | 92 | 186 | | | | | |
| Thongprayoon et al. [31] 2017 | 386 | USA | 50 | 336 | | | | | |
| Meneguz-Moreno et al. [69] 2017 | 221 | Brazil | 52 | 169 | | | | | |

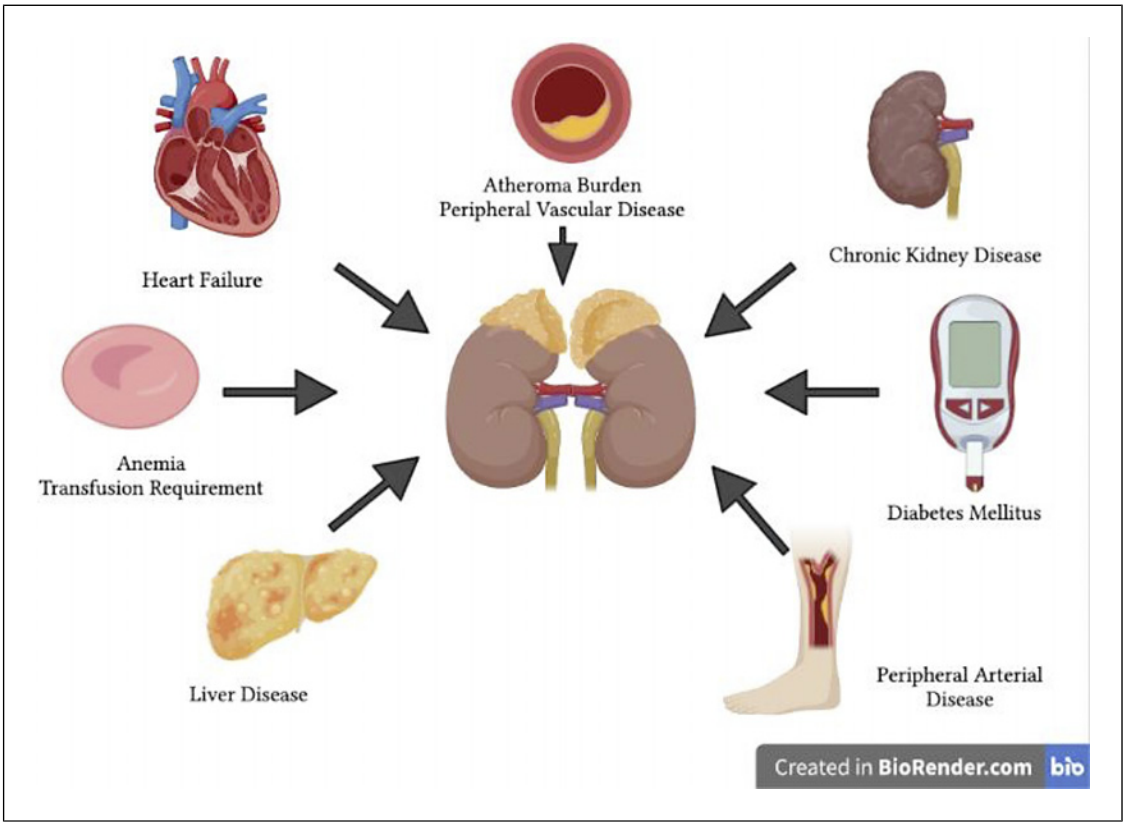


**Fig. 1.** Common factors associated with AKI following TAVR.

**Table 3.** Novel tests/screening tests

| Imaging | Author (year published) | Findings | Comments |
|---|---|---|---|
| MSCT imaging of the aorta | Shishikura et al. [30] (2018) | AKI occurred in 92 patients (33.1%) after TAVR. AKI was associated with a greater PAV above (30.4±8.2 vs. 21.3 ± 5.8%; $p$ = 0.02) but not below (28.9±7.7 vs. 25.8 ± 6.1%; $p$ = 0.41) the renal arteries | Suprarenal aortic atheroma burden is associated with AKI's occurrence, severity, and recovery after TAVR |
| Multidetector CT | van Rosendael et al. [50] (2015) | In patients with AKI, the burden of overall (87.5% [75–90%] vs. 71.4% [50–87.5%]; $p < 0.001$) and noncalcified atherosclerosis (42.9% [22.2–62.5%] vs. 12.5% [0–28.6%]; $p < 0.001$) and the maximum plaque thickness (5.7±1.8 mm vs. 4.5±1.4 mm; $p < 0.001$) were larger compared with patients without AKI | In patients undergoing TAVI, postprocedural AKI was associated with the extent of the noncalcified atherosclerotic plaque burden of the thoracic aorta |
| CT angiogram | Kandathil et al. [49] (2018) | Subjects with bilateral main renal artery stenosis greater than or equal to 50% had significantly greater odds (OR: 4.84; 95% CI: 1.41–16.54; $p$ = 0.01) of developing post-TAVR AKI than did subjects with unilateral or no stenosis greater than or equal to 50% in the main renal arteries. Subjects who developed post-TAVR AKI had significantly higher aortic and iliac arterial calcification scores than subjects who did not develop post-TAVR AKI (mean±SD, 21.4±5.6 vs. 17.9±6.7; $p$ = 0.04) | AKI, as a complication of TAVR, is more likely to develop in patients with bilateral renal artery stenosis greater than or equal to 50% or severe atherosclerotic calcification of the aorta and iliac arteries. |
| Elevated renal resistive index (RRI) through renal Doppler ultrasound (RDU) evaluation | Peillex et al. [51] (2020) | It was found that 10% of patients presented with AKIsCr and AKIsCyC. The cohort showed higher baseline RRI values (0.76±0.7) than normal known and accepted values. AKIsCyC had significant higher postprocedural RRI 1 day (day 1) after TAVR (0.83±0.1 vs. 0.77±0.6, 95% CI, $p$ = 0.005) | 24-h post-TAVR evaluation by Doppler-based resistive index is associated with AKI occurrence up to day 3<br>A Doppler-based renal resistive index is an easy, objective, reliable, and low-cost tool that succeeded to identify an at-risk population for AKI and able to improve the post-TAVR management |
| Doppler-based renal arterial resistive index | Sinning et al. [52] (2010) | At baseline, renal RI showed no difference between patients who developed AKI and those who did not (0.78±0.09 vs. 0.80±0.11, $p$ = 0.47). Already 4 h after TAVI, the RI significantly increased in patients developing AKI (0.94±0.08 vs. 0.79±0.06, $p$ = 0.001) and was related to the grade of postprocedural, paraprosthetic regurgitation ($p$ = 0.003). A cutoff value for the RI of ≥0.83 (AUC 0.88, 95% CI: 0.73–0.96, $p$ = 0.0001) predicted AKI after TAVI with a sensitivity of 91% and a specificity of 92% and was superior to serum creatinine and cystatin C | Measurement of the Doppler-based renal RI helps to early identify patients at risk for AKI after TAVI. Findings suggest that the RI might mirror hemodynamic alterations after TAVI rather than local renal damage |

**Table 3** (continued)

| Imaging | Author (year published) | Findings | Comments |
|---|---|---|---|
| CTA of the renal arteries to determine RAC | Mirzai et al. [64] (2022) | A lower chance of eGFR improvement was seen in the group with severe RAC The results were consistent in the subgroup analysis of patients with bilateral severe RAC ($n$ = 40; OR: 0.19; 95% CI: 0.05–0.69; $p < 0.05$) and remained associated with lower odds of improvement in renal function after propensity score matching (OR: 0.46; 95% CI: 0.29–0.72; $p <$ 005) | Severe RAC was associated with poor renal recovery post-TAVR. Severe RAC was defined as calcification involving >50% of the cross section on either side where RAS becomes hemodynamically significant<br>The change in eGFR was assessed as either improvement increased by 10% or more or no improvement (remained within 10% of baseline or decreased by 10% or more) |

MSCT, multislice computed tomography; PAV, percent atheroma volume; CTA, CT angiography.



clarify this, Merchant et al. [28] conducted a multivariate analysis to assess the independent association of pRBC transfusion with post-TAVR AKI. The study showed that the total number of pRBC transfusions is significantly associated with post-TAVR AKI, even after adjusting for other clinical parameters (e.g., pre-TAVR estimated glomerular filtration rate [eGFR], nadir measured periprocedure hemoglobin, and post-procedure inotrope/vasopressor use) [28]. Platelet activation, inflammation, and free radical generation resulting from a blood transfusion and cardiopulmonary bypass are presumed to cause AKI [28]. The number of blood transfusions, but not the indication for transfusion, predicted AKI [29]. Hence, blood transfusion should be administered restrictively in TAVR.

*Aortic Atheroma Burden*

Intraprocedural atheroembolization of debris during catheter manipulation is considered a potential risk factor for TAVR-associated AKI [30, 31]. Atheroembolic renal disease is premised to cause AKI due to dislodgement of cholesterol crystals during maneuvering of a large catheter across the aorta and deployment of the transcatheter prosthesis within a calcified aortic valve [1]. The percent atheroma volume (PAV), particularly above the renal artery, has been shown to predict AKI occurrence and delayed recovery. In the study of Shishikura et al. [30], greater aorta atheroma volume above the renal arteries was observed in patients with AKI ($PAV_{\text{above renal arteries}}$, 30.4 ± 8.2% vs. 21.3 ± 5.8%, $p$ = 0.02; $TAV_{\text{above renal arteries}}$, 62.8 ± 18.2 vs. 41.1 ± 12.8 $cm^3$, $p$ = 0.02). In contrast, the degree of aorta atheroma burden below renal arteries was not significantly different in patients with and without AKI [28]. Moreover, the presence of either renal artery stenosis or aortic calcification was also noted to be significantly associated with post-TAVR AKI [30]. However, it is not clear whether early identification of elevated PAV or if deployment of embolic protection device can reduce AKI risk in TAVR [1].

*Access*

Various access methods for TAVR have been used and studied. Among them, transfemoral (TF) access appears to have the least risk for TAVR-associated AKI [32]. On the other hand, alternative non-TF approaches, particularly the transapical (TA) approach, have been identified to be an independent predictor of post-TAVR AKI [9, 13, 16, 31]. In the study of Kumar and Garg [9], using the National Inpatient Sample (NIS) from 2011 to 2014, they found out that the TA approach is associated with AKI after TAVR (1.62 [1.39–1.88]) [32]. This finding was supported by the study of Julien et al. [13], which revealed that AKI was higher in nonfemoral access site compared with percutaneous femoral access (OR: 2.33; 95% CI: 1.69–3.22; $p < 0.001$). Furthermore, the group of Saia et al. [16] analyzed 102 patients who underwent TAVR and found out that the incidence of AKI was 66.7% in TA route versus 30.3% in TF route. They concluded that the only independent predictor of AKI was TA access with an HR between 4.57 and 5.18 based on their model. Moreover, the study by Thongprayoon et al. [33] showed that AKI was more common in TA approach versus TF approach (58 vs. 36%). Finally, the group of Thongprayoon et al. [27] evaluated 366 patients who underwent TAVR and analyzed outcomes based on the approach used [33]. In their cohort, AKI occurred significantly

**Table 4.** Novel serum biomarkers

| Novel serum biomarkers | Author (year published) | Findings | Comments |
|---|---|---|---|
| 5-Adenosylhomocysteine | **Elmariah et al. [46] (2016)** Authors performed liquid chromatography–mass spectrometry–based metabolite profiling on plasma from patients undergoing TAVR and subjects from the community-based Framingham Heart Study ($N$ = 2,164) | Only 5-adenosylhomocysteine was differentially detected in patients that went on to developed AKI 5-Adenosylhomocysteine was predictive of AKI after adjustment for eGFR | The probability of developing AKI after TAVR significantly increased with increasing tertile of baseline plasma 5-adenosylhomocysteine, such that none of those in the lowest tertile developed AKI compared to 50% of patients in the highest tertile |
| Serum beta 2 (β2) microglobulin | **Zaleska-Kociecka et al. [78] (2017)** Eighty consecutive patients who were 70 years of age or older and who were having surgical ($n$ = 40) or transcatheter ($n$ = 40) aortic valve replacement were recruited in a prospective study. The biomarkers were tested before the procedure, 6 times afterwards, at discharge and at a 6-month follow-up visit | The baseline β2-microglobulin level was the strongest predictor of AKI as a complication of transcatheter aortic valve replacement (OR 5.277, $p$ = 0.009). Its level 24 h after the procedure reached the largest AUC of 0.880 ($p$ < 0.001) for detecting acute kidney injury | Serum β2-microglobulin had the potential to predict acute kidney injury complicating transcatheter valve replacement and to diagnose it as early as 24 h after both the transcatheter and the surgical procedures |

higher in TA compared to TF (38 vs. 18%, $p$ < 0.01) [33]. Possible mechanisms includes the fact that patients undergoing TA approach have more severe peripheral vascular disease and instrumentation of the aorta may lead to AKI from cholesterol embolization and dislodgment of calcium plaques [33].

*Heart Failure*

Preexisting heart failure is a well-known risk factor for developing AKI in numerous clinical settings. In the population of post-TAVR patients, those with preexisting heart failure were found to have a significantly higher risk for TAVR-associated AKI [9, 10, 34]. In the study by Abbas et al. [10], they analyzed the data from NIS (2015–2018); at baseline, congestive heart failure was associated with increased risk of AKI (OR: 2.01; 95% CI: 1.92–2.10). This was corroborated with the study of Zahid et al. [34] who also used the data from NIS (2011–2018). They analyzed a total of 216,023 hospitalizations for TAVR. Out of that cohort, 12.9% had AKI and congestive heart failure at baseline was associated with increased risk (OR: 2.03; CI: 1.96–2.10) [34].

*Diabetes Mellitus*

Various studies have discussed how diabetes mellitus (DM) affects morbidity and mortality in patients with cardiovascular disease as well as percutaneous and surgical procedures and how DM facilitates the genesis of renal failure leading to possible dialysis. Hence, it is included in the surgical scores Society of Thoracic Surgeons (STS) score and European System for Cardiac Operative Risk Evaluation (EuroSCORE) II for prognosis of short-term outcomes after cardiac surgery [35]. Even so, a retrospective cohort by Schewel et al. [35] demonstrated a trivial influence of DM on short- and mid-term outcomes after TAVR, especially for the occurrence of AKI and mortality.

*Peripheral Artery Disease*

Peripheral artery disease (PAD) is a frequent comorbidity seen among patients undergoing TAVR, mainly owing to its shared risk factors with AS (e.g., hypertension, dyslipidemia, DM, smoking, AKI) [36]. In clinical trials, the prevalence of PAD in patients undergoing TAVR ranged from 27.8% to 41.3% [3, 37]. In the Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) Transcatheter Valve Therapy (TVT) database, Fanaroff et al. noted that 25% of patients undergoing TF TAVR and 50% of patients undergoing non-TF TAVR had PAD [36]. Further observational studies have linked the presence of PAD to the development of post-TAVR AKI [10, 30, 38]. These findings were also

**Table 5.** Novel urine biomarkers

| Novel urinary biomarker | Author (year published) | Findings | Comments |
|---|---|---|---|
| Cystatin C and neutrophil gelatinase-associated lipocalin (NGAL) | **Arsalan et al. [79] (2018)** Prospective study of 483 patients with severe AS undergoing elective TAVR. Peri-interventional AKI was defined by VARC-2 (Valve Academic Research Consortium) criteria. Blood assessment for biomarker measurement (creatinine, cystatin C, NGAL) was performed before and 4, 24, 48, 72 h after TAVR. Patients were followed up for 12 months | When comparing maximum biomarker differences of NGAL and cystatin C within 72 h post-TAVR, both biomarkers were highly associated with AKI Cystatin C is better at distinguishing between AKI stages as it predicts stage 3, while NGAL does not | Cystatin C distinguishes AKI better than NGAL, making it a valuable parameter for preoperative risk assessment and early detection |
| TIMP-2 and IGFBP7 (Urinary G1 cell cycle arrest proteins) | **Dusse et al. [80] (2016)** Prospective observational trial, 40 patients undergoing TAVI (either transaortic or TA) were enrolled. Serial measurements of TIMP-2 and IGFBP7 were performed in the early postinterventional course. The primary clinical endpoint was the occurrence of AKI stage 2/3 according to the KDIGO classification | ROC analyses of TIMP-2 and IGFBP7 on day 1 after TAVI revealed a sensitivity of 100% and a specificity of 90% for predicting AKI | Early elevation of urinary cell cycle arrest biomarkers after TAVR is associated with developing postoperative AKI [TIMP-2]*[IGFBP7] provides excellent diagnostic accuracy in predicting AKI that is superior to serum creatinine |
| TIMP-2 and IGFBP7 | **Zaouter et al. [81] (2018)** In a prospective observational study, 62 consecutive patients were scheduled for a TAVR. AKI was assessed based on the KDIGO criteria. Biomarkers and RRI were measured concomitantly before TAVR, at the first micturition postimplantation, and the first micturition the morning after the procedure | Twenty-two patients (35%) developed AKI. On the first day after TAVR, urinary TIMP-2 and IGFBP7 concentrations increased significantly in patients who developed AKI (0.1, [interquartile] [0.1–0.35] to 0.40 [0.10–1.00] vs. 0.2 [0.1–0.5] to 0.10 [0.10–0.20], $p = 0.012$) with an area under the receiver-operating characteristic curve of 0.71 [0.55–0.83]. Sensitivity was 0.57, and specificity was 0.83 for a cutoff value of 0.35. No significant increases in RRI were found in patients who developed AKI | TIMP-2 and IGFBP7 do not detect AKI at an early stage accurately in patients undergoing TAVR |

TAVR, transcatheter aortic valve replacement; TAVI, transcatheter aortic valve implantation; AKI, Acute kidney injury; KDIGO, Kidney Disease Improving Global Outcomes; RRI, renal resistive index; TIMP-2, tissue inhibitor of metalloproteinase-2; IGFBP7, insulin-like growth factor-binding protein 7; ROC, receiver-operating characteristics.

supported in a meta-regression analysis done by Wang et al. which identified PAD as an independent predictor of post-TAVR AKI [39].

*Chronic Kidney Disease*

Chronic kidney disease (CKD) has long been problematic in AS and vice versa. Their simultaneous presence predicts worse clinical outcomes and frequently worsens the other [40]. Patients with CKD are at increased risk of AKI after SAVR and TAVR [41]. CKD, even in moderate to severe stages, is associated with an increased risk of AS [42]. Preoperative renal dysfunction is common among the AVR population and is associated with diminished long-term survival [42]. Among patients with CKD not on dialysis, the presence of AS is associated with a significantly higher cardiac

**Table 6.** AKI reduction strategies (Elmariah et al. [46], 2016; Kornowski and Tang [61], 2021; Shroff et al. [56], 2021)

| Pre-TAVR | During TAVR | Post-TAVR |
|---|---|---|
| Nephrology consult | Use of contrast-sparing techniques | Appropriate cessation of concomitant nephrotoxins (e.g., aminoglycosides, nonsteroidal anti-inflammatory agents, vancomycin) |
| Always ensure euvolemia at the time of staged or ad hoc PCI | Use of low-osmolar or iso-osmolar contrast media or diluted contrast media (50:50) | Optimization of calcineurin inhibitor drug levels (if applicable) |
| Prehydration such as the standard nephroprotective volume infusion protocols should be used with extreme caution in patients with AS | Adopt transradial approach for PCI prior to TAVR and TF approach during TAVR if patient's vessel anatomy permits | Nephrology consult |
| Given the association between elevated right atrial pressures and AKI after PCI, appropriate diuresis must be done before PCI and TAVR | Shortening of rapid pacing runs and periods of hypotension/hypoperfusion | |
| Reduce IV contrast exposure, such as by spacing out the interval between CT angiography/cardiac catheterization and TAVR | Conservative blood transfusion thresholds | Conservative blood transfusion thresholds |

AKI, acute kidney injury; TAVR, transcatheter aortic valve replacement; PCI, percutaneous coronary intervention; CT, computed tomography.

and all-cause mortality; lower eGFR is associated with increased mortality in these patients [43]. The group of Thongprayoon et al. [31] noted a dose-response relationship between the incidence of AKI and progressive stages of CKD. CKD is an established risk factor for structural valve deterioration, an acquired intrinsic deterioration of bioprosthetic leaflets or supporting structures manifesting as thickening, calcification, tearing, or disruption of the prosthetic material and leading to hemodynamic dysfunction and eventual bioprosthetic valve failure [44]. In addition, the presence of CKD can predispose to a more calcified and hostile landing zone for transcatheter heart valves and thus potentially increase the risk of nonstructural valve deterioration (e.g., paravalvular leak), infective endocarditis, and valve thrombosis, which are also important causes of bioprosthetic valve failure [44]. The exclusion of patients with advanced CKD or on hemodialysis from the seminal SAVR versus TAVR trials hampers our ability to make informed treatment decisions in this patient cohort [44]. Cubeddu et al. [2] investigated the changes in the CKD stage following TAVR and identified variables associated with pre- and-post-TAVR eGFR. They assessed the association of post-TAVR eGFR with mortality [2]. They concluded that in patients with severe AS undergoing TAVR, even with baseline impaired eGFR, the CKD stage is more likely to stay the same or improve than worsen. AS may contribute to a cardiorenal syndrome that improves with TAVR [2].

*5-Adenosylhomocysteine*

5-Adenosylhomocysteine is the metabolic precursor of homocysteine and adenosine and is a potent inhibitor of methylation reactions in the body [45]. Elevated plasma levels of this metabolite have been observed in patients with renal impairment and may have utility as a subclinical biomarker for kidney injury. Elmariah et al. [46] performed metabolomic profiling in a cohort of high-risk individuals undergoing TAVR to identify biomarkers predictive of postprocedural AKI. In their study, 5-adenosylhomocysteine was found to be predictive of AKI after TAVR, independent of the patients' baseline eGFR. It provided a more robust AKI prediction than baseline eGFR and was also significantly predictive of post-TAVR survival. Hence, 5-adenosylhomocysteine

**Table 7.** Summary of findings of this review

| *Key findings* |
|---|
| AKI is one of the most common complications of TAVR |
| AKI post-TAVR is almost never benign |
| AKI after TAVR can be considered the common final path resulting from pre-, intra-, and postoperative factors and additional nephrotoxic influences |
| Baseline GFR, diabetes, and TA approach are the most common risk factors for post-TAVR AKI |
| There are promising urine and serum biomarkers for detecting early AKI post-TAVR, but current evidence is still controversial |
| Use of imaging studies like aorta atheroma burden and calcification of renal arteries hold promise in detecting patients at high risk for AKI |
| Prevention of AKI post-TAVR cannot be overemphasized, and operator must know the pre-, intra-, and postprocedural steps to mitigate post-TAVR AKI |
| There is a lack of data on gender and ethnic difference in post-TAVR AKI |

may be a sensitive indicator of subclinical renal dysfunction before and after TAVR.

*Race*

Several studies were done to assess possible racial disparities in patients who will undergo TAVR [47, 48]. Hernandez-Suarez et al. [48] used data from the NIS from 2012 to 2014 to investigate on the racial disparities among Hispanics, African Americans, and Non-Hispanic White who underwent TAVR. The study showed that there is an increased incidence of AKI among the Hispanics (OR: 1.65; 95% CI: 1.23–2.21; $p < 0.01$). However, a study by Alqahtani et al. [47], who utilized data from the NIS (from 2011 to2014), showed that the risk of having AKI was similar among Caucasians and African Americans.

## Screening Modalities

The development of AKI is associated with increased morbidity and mortality, and efforts should be made before TAVR Table 3 to identify factors that can be used to predict who will develop post-TAVR AKI [49]. Several screening modalities were identified but currently no recommendation to use any of these novel imaging tests (see Tables 4, 5). Shishikura et al. [30] introduced the role of preoperative CT imaging of aortic sclerosis as a tool in evaluating patients at risk for AKI after TAVR. They also suggested that atheroma burden proximal to the renal arteries predicts stages of AKI and its recovery post-TAVR [30]. Preoperative CT imaging of aortic atherosclerosis could be used to evaluate the risk of atherothromboembolism triggering AKI after TAVR [30]. The group of van Rosendael et al. [50] used a multidetector CT scan to determine the correlation between aortic valve calcification, atherosclerosis burden, and plaque characteristics of the thoracic aorta (including aortic root, ascending aorta, aortic arch, and descending aorta) in the occurrence of AKI. They concluded that in patients undergoing TAVR, postprocedural AKI was associated with the extent of noncalcified atherosclerotic plaque burden of the thoracic aorta [50]. Kandathil et al. [49] explored the utility of CT scans. They found that AKI as a complication of TAVR is more likely to develop in patients with bilateral renal artery stenosis greater than or equal to 50% or severe atherosclerotic calcification of the aorta and iliac arteries [49]. Elevated renal resistive index, determined by renal Doppler ultrasound evaluation, has been associated with AKI development and increased systemic arterial stiffness [51]. The study of Peillex et al. [51] showed that Doppler-based renal resistive index is an easy, objective, reliable, and low-cost tool to identify an at-risk population for AKI. This was corroborated by the study of Sinning et al. [52].

## Preventive Strategies

Strategies and pathways in reducing AKI risk following TAVR are not new as AKI is a well-established complication in other cardiovascular procedures such as percutaneous coronary intervention and cardiac surgery [53]. It is of paramount importance to identify patients at high risk for developing AKI and plan preoperative interventions to reduce AKI post-TAVR. Preprocedural interventions can be approached according to type of risk factor, i.e., modifiable such as volume of contrast to be used, prevention of hypotension, use of TF approach, and the nonmodifiable such as severity of peripheral arterial disease and baseline GFR [53].

Standard TAVR uses contrast agents during aortic angiography for valve implantation and for evaluating the function of the implanted valve. Fluids are usually carefully given to prevent contrast-induced AKI. Several guidelines, such as that from the American Heart Association,

European Society of Urogenital Radiology, and the Canadian Association of Radiologists, recommend the administration of fluids before and after giving the contrast medium to reduce the risk of developing contrast-induced AKI [54–56]. Fluids include sodium chloride (0.9%) or sodium bicarbonate (1.4%) [54]. The typically recommended regimen for prophylaxis is isotonic volume expansion with normal saline. The usual volume expansion regimen begins 1 h before, to continue 2–12 h after administration of contrast, with doses from fixed to weight-based volumes. Ultimately, studies show that longer regimens (around 12 h) decrease the risk of AKI versus shorter regimens [55]. Dorval et al. assessed the efficacy and safety of the RenalGuard system, which is designed to reduce contrast-induced AKI occurrence by attaining precise, real-time automated hydration balance using a closed-loop isotonic volume hydration monitoring and infusion system [57]. The authors report that this novel system could dynamically balance volume hydration without major device-related complications. Furthermore, Putzu et al. ascertained that RenalGuard therapy was associated with significantly lower AKI incidence (OR 0.32 [0.19–0.50], $p < 0.00001$) and the need for renal replacement therapy (OR 0.19 [0.05–0.76], $p = 0.02$) compared with control, with no associated life-threatening adverse events reported among the patients who underwent the therapy [58].

*Management*

Renal replacement therapy, including hemodialysis, is commonly indicated in patients with AKI to help maintain homeostasis of body fluids, osmolality, electrolytes, and pH. In a recent meta-analysis by Gargiulo et al. [59], the new need for dialysis due to the TAVR-associated AKI was reported to occur in 5.8% (89 of 1,528) of patients. Although dialysis is a known strategy in AKI management, Ferro et al., utilizing the UK TAVI registry, reported that mortality estimates were significantly higher in patients necessitating postprocedural dialysis than in those who did not undergo dialysis after the procedure (log-rank $p < 0.001$) and even in those who were already undergoing dialysis before the procedure (log-rank $p < 0.001$) [60].

*Prognosis*

The effect of TAVR on renal function can be described as a double-edge sword. On one hand, multiple modifiable and nonmodifiable risk factors can result in AKI, and on the other hand, the benefits of TAVR on the patient's hemodynamics will improve renal perfusion and will reduce the systemic venous pressure [61]. The occurrence of AKI after TAVR was strongly associated with 30-day, 1-year and long-term mortality [62]. The concept of recovery from AKI (AKR) is not new and is still unclear in term of prognosis [62–64]. AKR is defined as 25% improvement in eGFR at 48 h after TAVR [65]. The group of Kliuk-Ben Bassat et al. [62] analyzed 1,086 consecutive TAVR patients, AKI occurred in 201 patients (18.5%). In a 7-year follow-up, patients with recovery from AKI had significantly better long-term mortality compared to those who had no improvement in kidney function (38.2 vs. 56.6% in the nonrecovery group; $p = 0.022$) [62]. This was in contrast to the short-term results of Azarbal et al. [65] where there were higher hospital and 30-day mortality in patients who had recovery from AKI versus unchanged renal function patients albeit not significant as compared to AKI (hospital mortality 1% AKR, 0.59% unchanged vs. 18.75% AKI; $p < 0.001$; and 30-day mortality 3.98% AKR, 2.77% unchanged vs. 22.92% AKI; $p < 0.001$). It is important to note that Azarbal et al. [65] excluded patients without baseline CKD (eGFR >60 mL/min) for multivariable analysis as opposed to the former. The association of AKR with mortality is further evidenced by the group of Peillex et al. [63], which analyzed 584 patients who underwent TAVR and looked at kidney function recovery. In their cohort, AKI and AKR patients experienced an increased cardiovascular mortality compared to unchanged renal function patients (14.6% and 17.8%, respectively, vs. 8.1%, CI 95%, $p < 0.022$) [63]. Recent data from the group of Mirzai et al. [64] revealed that severe renal artery calcification was associated with poor renal recovery post-TAVR. They retrospectively analyzed patients with severe AS who underwent TAVR from 2014 to 2017 using CTA images. They found out that the group with severe renal artery calcification (calcification involving >50% of the cross section on either side) had a lower chance of eGFR improvement (OR: 0.45; 95% CI: 0.25–0.79; $p < 0.05$) [64].

## Conclusion

TAVR-associated AKI is one of the most common acute complications of TAVR. It is a well-described complication with a prevalence of 10% and predicts poor short- and long-term outcomes. Risk factors can be classified as modifiable and nonmodifiable (sustained intraoperative hypotension, contrast use vs. heart failure, and CKD). There are several novel diagnostic modalities

that could potentially serve as risk markers, although current evidence of these modalities is in its infancy. This highlights the importance of identifying those high-risk patients in whom preventive measures should be focused and always keeping in mind that the treatment of post-TAVR AKI is almost always prevention (See Tables 6, 7). This current study has potential limitations inherent to review articles and is, therefore, subject to biases and clinical and/or statistical heterogeneity.

## Conflict of Interest Statement

The authors have no conflicts of interest to declare.


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