Circulation

AHA SCIENTIFIC STATEMENT

Evaluation and Management of Aortic Stenosis in Chronic Kidney Disease

A Scientific Statement From the American Heart Association

ABSTRACT: Aortic stenosis with concomitant chronic kidney disease (CKD) represents a clinical challenge. Aortic stenosis is more prevalent and progresses more rapidly and unpredictably in CKD, and the presence of CKD is associated with worse short-term and long-term outcomes after aortic valve replacement. Because patients with advanced CKD and end-stage kidney disease have been excluded from randomized trials, clinicians need to make complex management decisions in this population that are based on retrospective and observational evidence. This statement summarizes the epidemiological and pathophysiological characteristics of aortic stenosis in the context of CKD, evaluates the nuances and prognostic information provided by noninvasive cardiovascular imaging with echocardiography and advanced imaging techniques, and outlines the special risks in this population. Furthermore, this statement provides a critical review of the existing literature pertaining to clinical outcomes of surgical versus transcatheter aortic valve replacement in this high-risk population to help guide clinical decision making in the choice of aortic valve replacement and specific prosthesis. Finally, this statement provides an approach to the perioperative management of these patients, with special attention to a multidisciplinary heart-kidney collaborative team-based approach.

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Patients with a combination of chronic kidney disease (CKD) and aortic stenosis (AS) exhibit distinctive epidemiological and pathophysiological characteristics, presenting diagnostic and management challenges. Patients with CKD have a higher prevalence of the entire spectrum of aortic valve disease, ranging from calcification to stenosis. In a large echocardiography-based observational study, at least mild AS was prevalent in 9.5% in the CKD group versus 3.5% in the non-CKD group.[1] Although CKD and AS have shared risk factors, CKD is independently associated with the development of AS, with an inverse graded relationship between worsening estimated glomerular filtration rate (eGFR) and incident AS.[2] Individuals with eGFR <44 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ have a 20% higher adjusted hazard of incident AS. Progression of AS is accelerated and more unpredictable in patients with CKD; a decline in aortic valve area (AVA) occurs at nearly twice the pace among those with CKD G5 on hemodialysis as in the non-CKD population (≈0.2 cm^2 versus ≈0.1 cm^2 annually).[3] Moreover, AS is associated with higher cardiac and all-cause mortality with CKD.[4] In 1 registry, 5-year survival of severe AS was 42% in CKD compared with 67% in patients without CKD.[1]

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Although aortic valve replacement (AVR) is associated with improved survival,[4,5] not surprisingly, the presence of CKD is also an independent predictor of adverse clinical outcomes in patients after surgical AVR (SAVR) and transcatheter AVR (TAVR) compared with patients without CKD.[6,7] Moreover, it has been increasingly recognized that AS represents a disease not just of the valve but also of the myocardium,[8] but data specific to CKD in regard to myocardial involvement are lacking. Despite the high-risk nature of concomitant AS in CKD G4 to G5D, there is no evidence from randomized trials to guide decision making pertaining to the choice of mechanical versus bioprosthetic SAVR or between various types of bioprostheses or between TAVR and SAVR because these patients have been excluded from all randomized trials (Supplementary Figure A). Clinicians therefore need to rely on observational/registry data, which are generally limited by selection biases and unmeasured confounders, for complex decisions in a high-risk population.

This scientific statement aims to reconcile the above facts into pragmatic clinical care and to delineate best practices for the diagnostic assessment, risk stratification, and management of AS in CKD in the contemporary era. To ensure consistent communication about the stages of CKD across the multidisciplinary teams involved in the management of this population, this statement has adopted the nomenclature proposed by the Kidney Disease: Improving Global Outcomes group (Supplementary Table A).

METHODOLOGY

The need for a scientific statement outlining the evaluation and management of AS in CKD was identified by the American Heart Association Council on Kidney in Cardiovascular Disease. A writing group with expertise in this subject was commissioned to review the current literature and to develop an expert-based consensus summary. The writing group held teleconferences and web-based communications; a manuscript outline was developed, with individual section reviews assigned to teams of authors. All authors had access to the working document to provide input and offered critical review and revisions. The writing group used MEDLINE (minimum, 2010–present) and the Cochrane Central Register of Controlled Trials as the primary sources for the literature search, limited to human subjects and the English language. Related article searches were conducted in MEDLINE to find additional relevant articles. Key relevant search words, medical subject heading descriptors, and abbreviations used in the manuscript are available in Supplementary Table B. Findings from conference proceedings, medical textbooks, and relevant online data sources were also contributed by authors, as well as articles outside the scope of the formal search, contingent on their specific expertise. Supplementary Figure A outlines the distribution of published evidence from randomized trials and observational data in AS across stages of CKD. Because of the absence of much specific information on bicuspid valves and mixed valvular pathology in this population, this statement focuses predominantly on degenerative trileaflet AS.

PATHOPHYSIOLOGY OF CALCIFIC AORTIC VALVE DISEASE IN CKD/ END-STAGE KIDNEY DISEASE

The hallmark of AS in CKD is progressive calcific degeneration, occurring at an earlier age and progressing rapidly.[9] The mechanisms for progressive AS in CKD fall into 2 broad categories: milieu and mediators (Figure 1).[10,11] The uremic milieu is one of retained toxins such as indoxyl sulfate and inflammatory mediators such as oxidized low-density lipoprotein and lipoprotein(a) that promote calcification of the vasculature and myocardial structures.[12] Additional components that contribute include CKD–metabolic bone disease, chronic hypertension, volume overload, and large pressure gradients/flow generated across the aortic valve as a result of hemodialysis, specifically when conducted through an arteriovenous fistula (AVF) or graft. CKD–metabolic bone disease (ie, high circulating phosphorus, increased fibroblast growth factor-23, hyperparathyroidism) appears to be one of the strongest components of this procalcification milieu. Treatment strategies of CKD–metabolic bone disease have been demonstrated either to promote (calcium-based phosphate binders) or to inhibit (calcimimetics, eg, cinacalcet) calcific AS. It remains to be seen whether novel lipid agents (eg, proprotein convertase subtilisin/kexin type 9 inhibitors) will influence the progression of calcific AS; the effect of other lipid-lowering therapies has been controversial.[13]

More generally, the balance of inhibitors/promoters of vascular/valvular calcification in CKD is altered. Inhibitors of calcification include fetuin-A, matrix-Gla-protein, klotho, and osteoprotegerin. The role of fetuin-A in calcific AS in only weakly supported in clinical studies of patients with CKD.[14–16] On the other hand, the end product of fetuin-A complex with calcium hydroxyapatite crystals, calciprotein particles, appears to correlate with outcomes in CKD, including CKD G5D and after kidney transplantation (CKD G5T).[17–20] Specifically, the transformation of primary (binds hydroxyapatite inhibiting calcification) to secondary (promotes calcification) calciprotein particles is a specific marker of increased mineral stress and propensity to calcification. A novel hydroxyapatite binder (SNF472) was recently demonstrated to significantly slow the progression of coronary/aortic calcification in CKD G5HD[21]; further data on outcomes are eagerly awaited.

Osteoprotegerin is a soluble decoy protein for RANK (receptor activator of nuclear factor κ-B), which is normally activated by its ligand (RANKL); this binding promotes calcification and osteogenic transdifferentiation

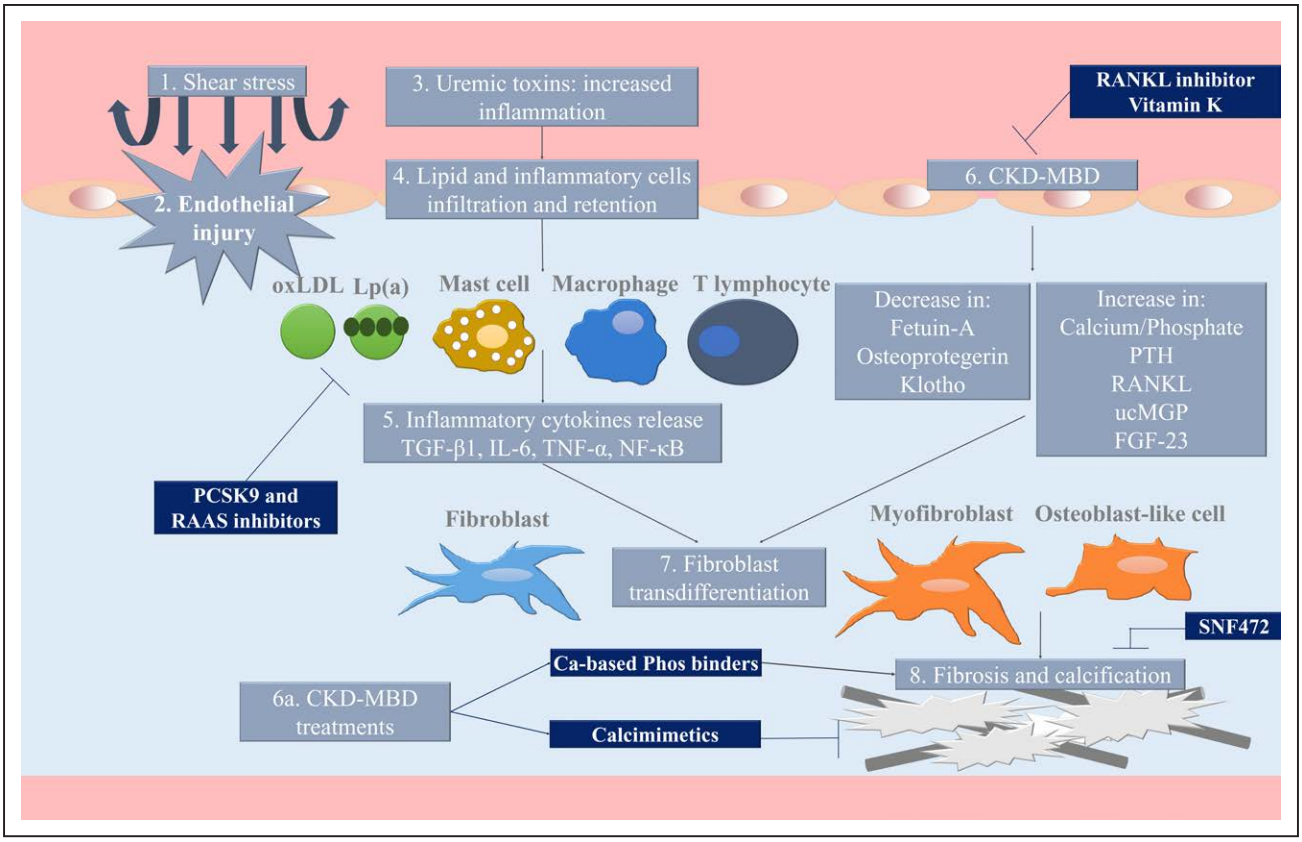

Figure 1. Pathophysiological considerations for the development of calcific aortic stenosis in patients with chronic kidney disease (CKD) and potential targets for intervention.

FGF-23 indicates fibroblast growth factor-23; IL-6, interleukin 6; LP(a), lipoprotein(a); MBD, mineral and bone disorder; NF-κB, nuclear factor κ-B; oxLDL, oxidized low-density lipoprotein; PCSK9, proprotein convertase subtilisin kexin 9; Phos, phosphorus; PTH, parathyroid hormone; RAAS, renin angiotensin aldosterone system; RANKL, receptor activator of nuclear factor κ-B ligand; TGF-β1, transforming growth factor-β1; TNF-α, tumor necrosis factor-α; and ucMGP, uncarboxylated matrix gamma-carboxyglutamic-acid protein. Reproduced from Ternacle et al[10] with permission from Elsevier. Copyright © 2019, Canadian Cardiovascular Society.

of vascular smooth muscle cells in part by stimulation of bone morphogenic protein-2.[22] Currently, it is not clear whether osteoprotegerin is clinically relevant to AS in CKD, but it has been shown to have an association with mitral valve calcification.[23] The RANKL inhibitor denosumab has been demonstrated to inhibit aortic calcification in vitro, but clinical studies are awaited.[24] Patients with CKD G5D often have vitamin K deficiency, which might accelerate calcific AS as a result of a higher proportion of uncarboxylated matrix-Gla-protein. A recent proof-of-concept study suggested that vitamin K supplementation may slow AS progression in patients with normal kidney function.[25] These findings also raise the concern for the use of vitamin K antagonist (VKA) therapy for anticoagulation, which might increase the risk of calcific AS progression.[26,27] Novel anticoagulants may have a preferable risk profile, but specific data in CKD are awaited. Finally, no study has specifically looked at the role of shear stress in the progression of calcific AS in CKD, but experimental models and some indirect human studies suggest that flow-mediated shear stress across the aortic valve mediates the progression of AS in CKD G5HD; the mechanism purportedly involves activation of platelets and release of transforming growth factor-β1 from the activated platelets.[28–30] In CKD G4 to G5D, multiple factors that increase the cardiac output, for example, chronic anemia and AVF, may contribute to shear stress.

Although no specific study has been conducted to compare the risk of AS progression between dialysis modalities, there are theoretical benefits of peritoneal dialysis (PD) over hemodialysis. PD is associated with improved CKD–metabolic bone disease, volume, and inflammatory milieu control, as well as greater preservation of residual kidney function.[31] In patients with CKD G5 approaching the need for dialysis in the context of concomitant AS, a discussion about the potential benefits of PD over hemodialysis in regard to AS progression may be warranted.

CAVEATS WITH ESTABLISHING DIAGNOSIS, GRADING SEVERITY, AND DETERMINING THE PROGNOSIS OF AS

There is insufficient literature pertaining to symptoms associated with hemodynamically significant AS in CKD G5D; clinicians are urged to remain mindful of atypical

Table 1. Imaging Parameters for Assessing AS Severity

Imaging modalities and criteria for severe AS	Specific caveats and recommendations in patients with CKD
Doppler echocardiography	
Primary parameters V_{Peak} ≥4 m/s ΔPm ≥40 mm Hg AVA ≤1.0 cm² Indexed AVA ≤0.6 cm²/m² Secondary parameters DVI <0.25 AVA by planimetry (2D/3D) ≤1.0 cm² Acceleration time >110 ms Acceleration time/ejection time ratio >0.36	Patients with CKD are often in low-flow state, and those with AVF may be in high-flow state. V_{Peak} and ΔPm are highly flow dependent and may underestimate AS severity in low-flow state and overestimate severity in high-flow state. AVA and DVI are less flow dependent but may overestimate AS severity (pseudo-severe) in low-flow state. Patients with CKD often present with discordant grading (ie, nonsevere V_{Peak} and ΔPm with severe AVA and DVI). AVA by planimetry may be difficult to measure in patients with CKD because of extensive calcifications. Acceleration time is dependent not only on AS severity but also on LV systolic function, which is often altered in patients with CKD.
Dobutamine stress echocardiography	
V_{Peak} ≥4 m/s ΔPm ≥40 mm Hg AVA by continuity equation ≤1.0 cm² Projected AVA at normal flow rate ≤1.0 cm²	Dobutamine stress echocardiography is useful to confirm AS severity in patients with CKD with low LVEF, low flow, and discordant grading at resting TTE. Patients with CKD often have limited flow reserve and may not be able to normalize their flow with dobutamine. In such cases, the calculation of the projected AVA at normal flow rate may be helpful to confirm AS severity. Patients with a small LV cavity (low filling pressure and marked concentric LV hypertrophy) may have the potential for hypotension attributable to the initial vasodilatory effects of dobutamine. Patients with CKD have a high prevalence of atrial tachyarrhythmias, which may make administration of dobutamine problematic.
Cardiac CT	
Aortic valve calcium scoring by noncontrast CT Men ≥2000 AU Women ≥1200 AU	Calcium scoring by noncontrast CT is useful to confirm AS severity in: Patients with CKD with preserved LVEF, low flow, and discordant grading at resting TTE Patients with CKD with low LVEF and low-flow state in whom dobutamine stress echocardiography is not feasible or inconclusive. Patients with CKD often have extensive calcifications of the aortic valve/annulus, mitral valve/annulus, aortic root, and LVOT. Calcium score by CT may overestimate hemodynamic severity of AS, especially if calcifications not belonging to the aortic valve are included in the score calculation.
AVA by planimetry on contrast CT ≤1.0 cm²	It is preferable to limit the use of contrast CT in patients with CKD.
Hybrid imaging	
Hybrid AVA ≤1.2 cm²	It is preferable to limit the use of contrast CT in patients with CKD. Hybrid AVA also can be calculated with the flow velocities measured by Doppler and the LVOT area measured by 3D TEE or CMR. Given that hybrid imaging measures larger AVAs, it is recommended to use a larger severity cut point.[32]

AS indicates aortic stenosis; AU, Agatston unit; AVA, aortic valve area; AVF, arteriovenous fistula; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; CT, computed tomography; ΔPm, mean transvalvular pressure gradient; DVI, Doppler velocity index; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOT, left ventricular outflow tract; TEE, transesophageal echocardiography; 3D, 3-dimensional; TTE, transthoracic echocardiography; 2D, 2-dimensional; and V_{Peak}, peak aortic jet velocity.

symptoms and to maintain a high index of suspicion for this high-risk condition. Typical symptoms, for example, dyspnea and presyncope, may overlap with other prevalent conditions in CKD G4 to G5D such as volume overload and anemia and therefore may be masked or not well recognized. More subtle observations such as evidence for intradialytic hypotension, development of atrial dysrhythmias in the peridialysis period, and symptoms of extreme fatigue may be clues to the presence of hemodynamically significant AS in the context of hemodialysis. Transthoracic echocardiography (TTE) is the primary imaging modality to establish diagnosis, to quantify severity, and to follow the progression of AS. Other imaging modalities such as computed tomography (CT) and cardiac magnetic resonance imaging (CMRI) may be used to corroborate diagnosis/severity of AS and to provide prognostic information. This writing group recommends that several pitfalls and caveats be considered with imaging in the context of AS and CKD.

Pitfalls and Caveats With the Echocardiographic Parameters of AS

Severe AS is defined on the basis of 3 primary parameters (Table 1): peak aortic jet velocity (V_{Peak}) ≥4 m/s, mean pressure gradient (ΔPm) ≥40 mm Hg, and AVA using the continuity equation ≤1.0 cm² or ≤0.6 cm²/m² when indexed to body surface area (Figure 2).[33,34] Several secondary

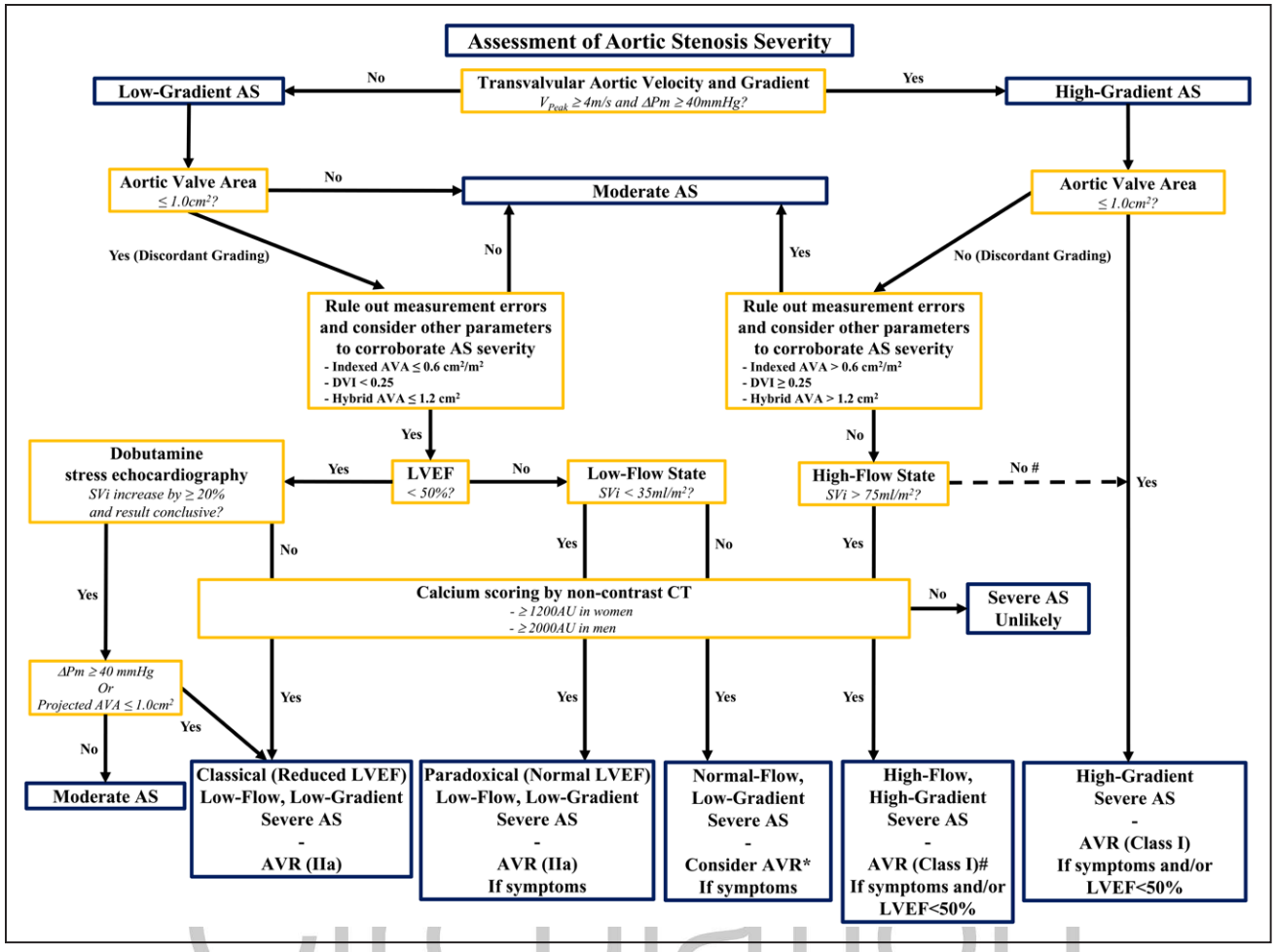

Figure 2. Suggested algorithm to confirm aortic stenosis (AS) severity and to classify the hemodynamic pattern in patients with chronic kidney disease (CKD).

AU indicates Agatston unit; AVA, aortic valve area; AVR, aortic valve replacement; CT, computed tomography; ΔPm, mean pressure gradient; DVI, Doppler velocity index; LVEF, left ventricular ejection fraction; SVi, stroke volume indexed; and V_{Peak}, peak jet velocity. *The guidelines do not provide a recommendation for this subset of patients with normal-flow, low-gradient severe AS. #Guidelines generally recommend AVR in patients with AS or mixed aortic valve disease if V_{Peak} is ≥4 m/s or ΔPm ≥40 mm Hg, regardless of the value of AVA. However, patients with CKD and arteriovenous fistula for hemodialysis may be in a high-flow state, and in such case, the V_{Peak} and ΔPm may overestimate AS severity. In case of discordant grading (severe ΔPm and V_{Peak} with nonsevere AVA and DVI), quantification of aortic valve calcium score by noncontrast CT may be considered to further corroborate AS severity.

parameters may be measured to corroborate AS severity (Table 1), including visual assessment of aortic valve cusp calcification/mobility and Doppler velocity index, which may be useful to identify severe AS (<0.25),[35] especially in cases of extreme variations in the flow states, for example, with AVF. The anatomic AVA (severe if ≤1.0 cm²) is measured by planimetry with the use of TTE, transesophageal echocardiography (TEE), or contrast CT.[36,37] Compared with 2-dimensional echocardiography, 3-dimensional modalities are more accurate because they permit measurement of the smallest and more restrictive valve orifice, therefore avoiding underestimation of AS severity. However, anatomic AVA should be used with caution and integrated into a multiparametric approach because it may underestimate AS severity compared with hemodynamic parameters of AS, and planimetry of the aortic valve orifice is often challenging and inaccurate in patients with CKD because of extensive cusp calcification.[38]

Analysis of ejection dynamics may also provide a semiquantitative assessment of AS severity using acceleration time or the ratio of acceleration time to ejection time (Table 1).[39] The accuracy and interpretation of V_{Peak}, ΔPm, AVA, and Doppler velocity index may be influenced by several factors, including measurement errors, low- or high-flow states, and increased left ventricular afterload caused by hypertension (Table 1).

Measurement Errors in Left Ventricular Outflow Tract Area and Velocity

Given that left ventricular outflow tract (LVOT) diameter ($LVOT_d$) is squared in the calculation of LVOT area, a small error in this measurement may result in a large error in the calculation of stroke volume (SV) and AVA. Meticulous attention to the $LVOT_d$ is imperative, which should be measured in the parasternal long-axis view

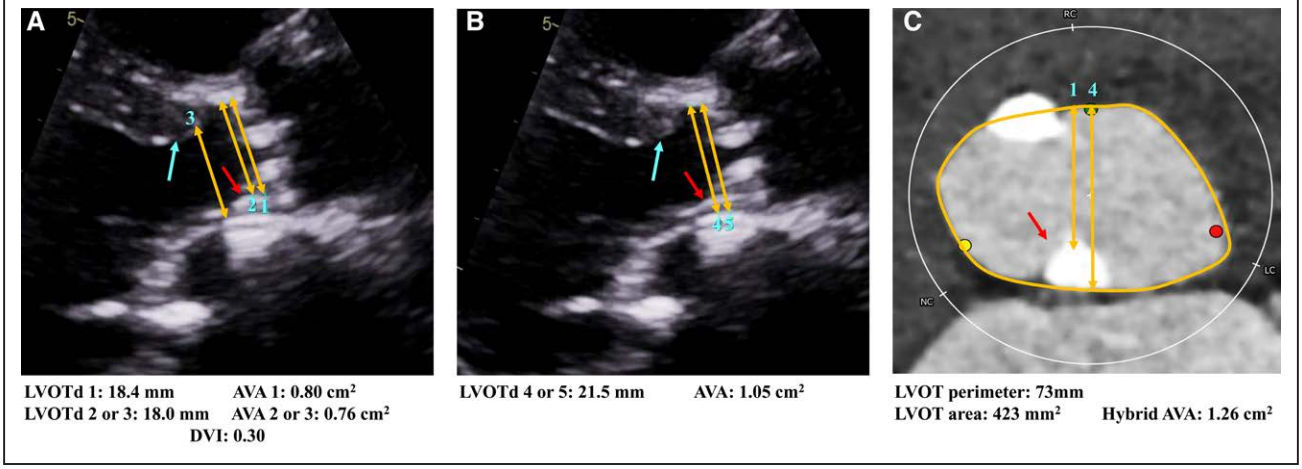

Figure 3. Measurement of left ventricular outflow tract (LVOT) diameter (LVOTd) in patients with aortic stenosis (AS) and chronic kidney disease (CKD). This patient has a prominent septal bulge (green arrow) and severe calcifications of the aortic valve leaflets and annulus extending posteriorly into the LVOT (red arrows). **A**, Measures 1 and 2 of the LVOTd are performed at (1) or close to (2) the aortic annulus, but posteriorly, the cursor is positioned at the inner border of the calcification bar (red arrow), not at the inner edge of the LVOT. Measure 3 is performed ≈5 to 10 mm below the annulus, and anteriorly, the cursor is located at the border of the septal bulge (green arrow). All these measures of LVOTd yield an underestimation of the aortic valve area (AVA) by the continuity equation and would categorize the stenosis as severe. The Doppler velocity index (DVI) is, however, nonsevere, which raises the suspicion for underestimation of LVOTd. **B**, Correct measure of LVOTd performed at (5) or close to (4) the aortic annulus, therefore avoiding the region of the septal bulge (green arrow) anteriorly. In addition, posteriorly, the cursor is positioned at the inner edge of the LVOT and excludes the calcification (red arrow). **C**, Assessment by contrast computed tomography demonstrating the underestimation of the LVOTd by measure 1, while measure 4 is correct. Learning points: Particular attention should be paid to exclude these calcifications from the LVOT measure to avoid underestimation of LVOTd and thus of stroke volume and AVA. Hence, in patients with AS and CKD, it is preferable to measure the LVOTd at the level of aortic annulus, ie, at the base of the aortic valve cusps, or within 2 mm below the annulus.

optimized for and zoomed on the LVOT and aortic valve (Figure 3). The measurement of $LVOT_d$ may be particularly challenging in patients with CKD, especially CKD G5D, because of severe calcification of the aortic annulus extending into the LVOT.[10,40] The combination of severely reduced AVA and nonseverely reduced Doppler velocity index (Table 1) should raise suspicion for $LVOT_d$ underestimation. Patients with severe AS or CKD also often exhibit basal septal hypertrophy (ie, septal bulge), leading to underestimation of $LVOT_d$.[41,42] This abnormality may cause a flow acceleration in the LVOT and thus invalidate AVA calculation by the continuity equation. To overcome the risk of underestimation of $LVOT_d$ by 2-dimensional TTE, other modalities can be used[32,43,44]; for example, hybrid AVA can be calculated from the LVOT area obtained with 3-dimensional TEE/CMR and flow velocities measured by Doppler with TTE. Given that hybrid AVAs (especially those obtained by CT–Doppler imaging) are systematically and substantially larger than the standard AVA measured by TTE, some studies suggest using a larger cutoff value of hybrid AVA to define severe AS (≤1.2 cm^2 rather than ≤1.0 cm^2; Table 1).[32,45]

Implications of CKD-Related Volume and Pressure Overload on Assessment of AS Severity

Patients with CKD typically have chronic volume overload, resulting in left ventricular remodeling (hypertrophy and dilatation), myocardial fibrosis, impaired relaxation, increased filling pressure, systolic dysfunction, and low-flow state.[46,47] In addition, pressure overload related to vascular remodeling and calcification may further contribute to impairment of left ventricular geometry and function in patients with CKD. Both hemodialysis and PD may reverse left ventricular remodeling and hypertrophy by decreasing volume and pressure overload.[48,49] However, the high-flow state induced by AVF may cause right ventricular overload, dilation, and dysfunction in patients undergoing hemodialysis. Hence, we recommend a clinical and TTE evaluation during the first months after the initiation of hemodialysis in AS to reassess severity and associated cardiac remodeling. For CKD G5HD, the TTE examination for the assessment of AS should ideally be timed on the day after hemodialysis when hemodynamics are presumably optimized. Several studies suggest that CKD is associated with faster AS progression.[3,50–54] Hence, in asymptomatic patients with moderate or severe AS and concomitant CKD G4 to G5, we recommend more frequent clinical follow-up (eg, every 6 months) with TTE in those with severe AS or rapid progression, particularly because clinical symptoms may not be reliable.

Implications of Low-Flow State

In patients with concomitant CKD and AS, several factors may lead to a reduction in transvalvular flow, including left ventricular concentric remodeling or hypertrophy, fibrosis, and dysfunction; right ventricular dysfunction; tricuspid or mitral regurgitation; and atrial fibrillation. The SV index, mean flow rate (Q=SV/left ventricular ejection time), and left ventricular ejection

fraction (EF) should be systematically reported in these patients to establish the presence and type of low-flow state. Low flow is defined as an SV index <35 mL/m^2 or mean transvalvular flow rate <200 mL/s.[36,55] There are 2 main types of low-flow states: paradoxical low flow with preserved EF (≥50%) and classic low-flow with reduced EF.[37] Low-flow state may be observed in ≈60% of patients with AS and CKD G5.[56] In CKD G5HD, the AVF artificially increases left ventricular preload and may mask an underlying low-flow state. A low-flow state, especially classic low flow, is associated with worse prognosis in patients with AS.[55,57] In the presence of a low-flow state, V_{Peak} and ΔPm are reduced and may underestimate AS severity, whereas the AVA and Doppler velocity index are decreased and may overestimate severity (Table 1). In patients with low-flow state and discordant grading, that is, nonsevere V_{Peak} (<4 m/s) and ΔPm (<40 mm Hg) combined with severe AVA (≤1.0 cm^2) and Doppler velocity index (<0.25), it is recommended to perform additional imaging such as low-dose dobutamine stress echocardiography or noncontrast CT (Table 1). Low-dose dobutamine stress echocardiography may be helpful in patients with classic low flow (EF <50%); ΔPm increasing to >40 mm Hg confirms the presence of true severe AS.[33,34,37] However, patients with CKD G4 to G5D often have impaired myocardial contractility and thus limited contractile/flow reserve during dobutamine stress echocardiography, sometimes limiting the ability to normalize their flow rate with dobutamine.[32,55,58] Calculation of projected AVA at a normal flow rate (ie, 250 mL/s)[32,57,58] also has been proposed, but specific data in CKD are lacking.

Implications of High-Flow State and Role of Temporary Fistula Compression

An AVF renders the assessment of AS severity more complex by increasing preload, cardiac output, and transvalvular flow. In a high-flow state, V_{Peak} and ΔPm are increased and may overestimate the severity of AS. Conversely, AVA and Doppler velocity index are increased and may underestimate the severity. Acute fistula compression may be used to decrease transvalvular flow rate temporarily and to reassess AS severity during the TTE examination.[59] Hence, AS considered severe on the basis of ΔPm ≥40 mm Hg may be reclassified as nonsevere (ΔPm falling to <40 mm Hg) after fistula occlusion. Although the ΔPm and AVA measured during temporary fistula occlusion theoretically may better reflect the true intrinsic severity of AS, these parameters may nonetheless underestimate the true hemodynamic burden imposed by the AS on the left ventricle. In addition, the method of fistula compression is not standardized and may induce complications such as thrombosis; this risk should be discussed with the patient and the nephrologist. Hence, we do not recommend routine fistula compression during TTE assessment of AS severity, and we recommend that an arteriovenous graft should not be compressed because of the higher thrombotic potential. Theoretically, the concept of the projected AVA at normal flow rate may be applied to the context of patients with hemodialysis and high-flow state; however, this method has been validated only in the context of low-flow AS, not high-flow AS.[60] Thus, for practical purposes, in the presence of AS-related symptoms or left ventricular systolic dysfunction, a high-flow state showing a severe ΔPm (≥40 mm Hg) or V_{Peak} (≥4 m/s) should be considered hemodynamically significant AS and thus an indication for intervention.

Implications of Increased Arterial Load

Patients with CKD often have increased afterload caused by reduced arterial compliance and systemic arterial hypertension, which decrease left ventricular SV, resulting in a decrease in ΔPm for a given degree of AS severity, ultimately contributing to underestimation of AS severity. Furthermore, the faster and earlier arterial pulse wave reflection from the periphery that occurs in patients with reduced compliance may dampen the ΔPm independently of the flow rate.[61] In such patients, the left ventricle faces a double load: valvular (resulting from AS) plus arterial (resulting from hypertension). In this context, it may be useful to calculate the valvuloarterial impedance (Z_{va}), which estimates the global hemodynamic burden imposed by both the stenotic aortic valve and the systemic arterial system[62]: Z_{va}=(SBP+ΔPm)/SV index, where SBP is the systolic blood pressure measured at the time of TTE. Z_{va} >4.5 mm Hg·mL^{-1}·m^{-2} is associated with worse prognosis in AS.[63] Although Z_{va} includes a measure of flow (ie, SV index), it is not flow independent and will tend to overestimate the left ventricular hemodynamic load in patients with low-flow states and underestimate it in those with high-flow states (eg, AVFs).[64] High Z_{va} in the presence of AS that otherwise appears nonsevere should favor the initiation or optimization of antihypertensive medications, whereas high Z_{va} associated with truly severe AS should favor consideration of aortic valve intervention. Among patients with CKD, routine estimation of Z_{va} may be a helpful consideration.

Role of Noncontrast CT to Adjudicate AS Severity

Aortic valve calcific burden strongly correlates with hemodynamic severity, progression rate, and clinical outcomes of AS[65–68] and can be accurately measured by low-radiation-dose (<1 mSv) noncontrast CT with electrocardiographic gating and 3-mm slices using the modified Agatston method.[69] The 2017 European guidelines recommend the use of CT aortic valve calcium scoring to confirm AS severity in patients with a low-flow state and associated discordant grading (Figure 2

and Table 1).[37] Notably, no study has specifically validated the calcium scoring method and AS severity cut points in the CKD population. When aortic valve calcium score is measured in patients with CKD, particular attention should be paid, however, to discriminating between valvular and nonvalvular calcification to avoid overestimation of AS severity. Valvular (aortic and mitral), coronary, and aorta calcium deposits often coexist and are associated with a higher risk of cardiovascular events and death in both the general and CKD populations.[70,71] Quantification of aortic valve calcium score should include the regions of the aortic valve cusps and the aortic annulus but should exclude calcifications belonging to the LVOT, mitral annulus, aortic root, and coronary ostia.[69] It may also be useful to concomitantly measure coronary calcium score because of its incremental prognostic value in patients with CKD.[72]

Role of Invasive Evaluation of AS

If diagnostic uncertainty persists despite noninvasive imaging, invasive cardiac catheterization it is reasonable to confirm severity of AS. AVA calculation using invasive assessment is performed using the Gorlin equation but also has potential for pitfalls, including assumptions in the constant and potential errors in the calculation of the cardiac output.[73] Moreover, like the continuity equation, the Gorlin formula is flow dependent and hence subject to the considerations outlined above, including those of the hemodynamic effects of the AVF. Unfortunately, poor correlation has been reported between noninvasive and invasive techniques of AS assessment in the elderly,[73] thus implying that there is no clear-cut gold standard for AVA estimation. Particularly given the risks involved with invasive assessment (bleeding, stroke, etc), we recommend reliance on noninvasive assessment with TTE for assessment of AS severity in most situations.

Implications of Concomitant Mitral Valve Disease and Annular Calcification

Mitral annular calcification and associated valvular diseases are common in patients with CKD.[56,74] The severity of CKD and duration of dialysis are strongly correlated with the progression of valvular calcific burden, and in turn, the magnitude of valvular calcification is strongly associated with the risk of cardiac events.[71] Extensive mitral annular calcification can lead to a low-flow state as a result of significant mitral stenosis or regurgitation, which may interfere with the assessment of AS severity.[75] In addition, patients with CKD and AS may also require concomitant mitral valve intervention. Hence, TEE and CT should be considered in patients with concomitant AS and mitral annular calcification to confirm AS severity in case of discordant grading, to define the mechanism and severity of mitral valve dysfunction, to assess the extension of calcification into the LVOT and the left ventricular posterior wall, and to help determine the best therapeutic option for the given patient (surgery versus transcatheter versus hybrid).[76]

Role of Imaging for Prognostication in AS

Symptoms are frequently insensitive and nonspecific in older patients with AS with concomitant CKD, in whom subclinical impairment of cardiac function is frequent. Several recent studies suggest that cardiac staging based on a multiparameter integrative approach provides important prognostic value beyond symptoms and left ventricular EF in patients with AS (Supplementary Table C).[77–79] This staging scheme may be useful to optimize the selection of the timing and type of intervention in AS, but a potential limitation is differentiation of the effects of AS from concomitant comorbidities such as CKD. Nonetheless, staging is useful for risk stratification because these high-risk patients may be more vulnerable to the hemodynamic burden imposed by AS.

Assessment of Left Ventricular Fibrosis With CMRI

CMRI is becoming increasingly attractive as a means of risk assessment in AS and is the imaging reference standard for assessment of left ventricular mass and volumes, depicting patterns of left ventricular remodeling more precisely than echocardiography.[80] In the setting of CKD G5D, left ventricular mass index is often elevated as a result of a combination of systemic hypertension and inappropriate suppression of aldosterone production.[81] Therefore, concentric left ventricular remodeling and hypertrophy in this patient population may be disproportionate to the degree of AS. Late gadolinium enhancement imaging is the mainstay of CMRI assessment for myocardial fibrosis and infarct, taking advantage of the fact that gadolinium-based contrast agents are retained in the extracellular space. T1-weighted images are acquired 10 to 15 minutes after contrast administration, and affected areas appear white (high signal), surrounded by black (nulled) myocardium.[82] The presence of focal left ventricular fibrosis in a noninfarct pattern, as evidenced by late gadolinium enhancement imaging on CMRI, is independently associated with mortality in AS.[83,84] CKD G4 to G5D was previously felt to be a contraindication to gadolinium-based contrast administration, given the documented risk of nephrogenic systemic fibrosis with group 1 gadolinium-based contrast agents.[85] Consequently, some studies assessing late gadolinium enhancement and outcomes in AS have explicitly excluded patients with CKD G4 to G5D.[86–88] The ongoing EVOLVED trial (Early

Valve Replacement Guided by Biomarkers of LV Decompensation in Asymptomatic Patients With Severe AS), designed to assess the benefit of intervention for severe asymptomatic AS among patients with midwall late gadolinium enhancement, is also excluding patients with eGFR <30 mL·min^{-1}·1.73 m^{-2}.[89] However, the risk of nephrogenic systemic fibrosis with group 2 gadolinium-based contrast agents (including gadobenate meglumine, gadobutrol, and gadoteridol) in patients with CKD G4 to G5D appears to be extremely low.[85,90] We believe it may be reasonable to perform CMR with a group 2 contrast agent in CKD G4 to G5D after carefully weighing the low risk of nephrogenic systemic fibrosis with potential benefits if imaging findings are likely to substantially affect clinical management and to avoid delayed or missed diagnosis. Overall, the utility of CMR for risk stratification in AS with CKD remains unclear and an opportunity for future research.

T1 mapping is a CMRI technique that may be performed with or without gadolinium-based contrast. As opposed to late gadolinium enhancement imaging (which highlights only focal myocardial fibrosis), noncontrast or native T1 mapping can detect diffuse fibrosis and therefore may be more sensitive for left ventricular damage resulting from AS.[91] Higher native myocardial T1 values in patients with AS have been associated with increased risk of all-cause death and hospitalization for heart failure.[92] However, native T1 values are affected by numerous factors, including sex, age, and imaging scanner attributes. Normative and pathological native T1 values in AS and other disease states have not been well established. In 1 study, patients with CKD G5HD were found to have higher native T1 values than patients with AS.[93] Moreover, native T1 values may decrease slightly after hemodialysis.[94] If native T1 mapping is to be used for risk stratification in patients with CKD with AS, prospective studies with well-standardized protocols will be needed.

Specific Imaging to Guide Periprocedural Management

CT is an important preprocedural diagnostic modality that can be helpful in select patients being evaluated for SAVR (eg, measuring aortic root, evaluating for porcelain aorta, assessing mitral calcification). CT is standard for all anticipated TAVR procedures for precise annular sizing to prevent immediate procedural complications (eg, aortic root injury or risk of coronary occlusion during deployment) and longer-term complications such as patient-prosthesis mismatch. Typically, a comprehensive CT involving an electrocardiographically synchronized (gated) evaluation of the aortic root, followed by nongated acquisition of the aorto/ilio/femoral arterial tree, is obtained before TAVR. Standardized reporting of CT findings recommended by expert consensus ensures comprehensive and consistent transmission of critical information.[95,96] For patients with CKD, it is important to minimize contrast used while simultaneously performing scan optimization techniques to ensure sufficient contrast attenuation for diagnostic image quality. Scan optimization considerations include lower contrast flow rates, multiphasic injection protocols, and prospective high-pitch imaging.[95] Pulerwitz et al[97] compared a very low-contrast volume protocol (20 mL iohexol) for imaging the aortic root, followed by vascular imaging of the femoral arteries, among patients with severe symptomatic AS and CKD G4 to G5 before TAVR. The authors reported excellent interobserver correlation with measurements obtained with very low contrast volume compared with a standard contrast volume protocol for aortic annular/root measurements and vascular imaging, as well as excellent agreement with 3-dimensional TEE measurements. In a systematic review of 1599 patients, Rong et al[98] reported a strong correlation between 3-dimensional TEE and CT in measuring annular area, annular perimeter, annular diameter, and LVOT area. Particularly among those with CKD G4 to G5 and amid concerns for contrast nephropathy, 3-dimensional TEE may offer an attractive option to assist in preoperative planning for all measures other than coronary height determination. Finally, although assessment of coronary stenosis is theoretically feasible with contrast-enhanced CT, an inability to administer β-blocker or nitroglycerin therapy may limit accurate determination of coronary stenosis, particularly with the high burden of coronary calcification in CKD. Smaller case series have described the technique of zero-contrast and no-contrast TAVR performed by eliminating contrast with the help of noninvasive imaging modalities. This technique could offer a promising alternative by reducing the risk of acute kidney injury (AKI).[99,100]

RISK OF AKI WITH AVR

The development of AKI after AVR is associated with a several-fold increase in short- and long-term mortality.[101–103] Preexisting CKD is the most important risk factor for AKI after AVR, with baseline eGFR being a key variable in preprocedural risk calculators. An accurate estimation of incident AKI after AVR is limited by varying definitions of AKI, inclusion criteria, wide sample sizes, single-center experiences, and differing prostheses. The Valve Academic Research Consortium-2 consensus group introduced standardized end points, with incorporation of the Acute Kidney Injury Network classification, in making a standardized diagnosis of AKI after TAVR.[104] Compared with previous criteria, the timing of diagnosis of AKI was extended from 72 hours to 7 days after the procedure, but with the stipulation that the rise in creatinine must occur within 48 hours. Similarly, the 20th International Consensus Conference

of the Acute Disease Quality Initiative Group developed a consensus statement on cardiac or vascular surgery–associated AKI to help streamline reporting and to develop a framework for future research.[105]

AKI After TAVR

The pathogenesis of AKI after TAVR is multifactorial. Preoperative factors associated with AKI include the presence of CKD, hypertension, high preoperative risk score, diabetes, peripheral arterial disease, and chronic obstructive pulmonary disease.[106] There is an inverse correlation between baseline eGFR and risk of AKI.[102,107] Conflicting reports exist with regard to sex-based risk, with some studies showing higher risk in men and others showing higher risk in women.[108] Age is an additional independent risk factor for the development of AKI.[101] In addition to these patient-specific risk factors, contrast-induced AKI risk may be incurred with staged percutaneous coronary intervention (PCI) before TAVR and the use of iodinated contrast media for coronary angiography or cardiac CT angiography as part of the workup for TAVR, in addition to the TAVR itself.[109] These risks are additive, and caution must be exercised before the intervention in patients with multiple risk factors. Several intraoperative factors may also contribute. Incident AKI appears to be higher with the transapical approach compared with the commonly used transfemoral approach.[101] However, it is important to note that the presence of peripheral arterial disease (necessitating a nonfemoral approach) is an independent and important predictor of AKI and can confound this observation. In more recent data, a propensity score–matched analysis of 4949 patients undergoing TAVR reported significantly lower AKI rates with transradial (transfemoral, 9.9%; transradial, 5.7%; $P<0.001$) and vascular access–related complications, as well as 30-day mortality benefit.[110] High-volume centers with increased operator experience also report lower rates of AKI.[111] Intraoperative hypotension, commonly associated with rapid pacing during deployment of the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA), is thought to be associated with AKI, given the high sensitivity of kidney tissue to hemodynamic perturbations.[111] The self-expandable CoreValve system (Medtronic, Minneapolis, MN) does not require rapid pacing. Whether the incidence of AKI is lower with the use of the self-expandable system deserves further analysis. Periprocedural transfusion requirement is another major predictor of AKI with TAVR, reflective of greater hemodynamic instability, with accentuation of the periprocedural inflammatory milieu, resulting in platelet activation and free radical generation. Atheroemboli related to arterial cannulation and vascular instrumentation can contribute to AKI during TAVR. Of note, contrast volume used during the procedure has not consistently been found to be significantly associated with the development of AKI after TAVR,[112] likely related to the widespread use of low-osmolar and iso-osmolar contrast agents and greater clinician awareness.

AKI After SAVR

In addition to preexisting cardiovascular risk factors (eg, hypertension, diabetes, obesity, CKD) that increase risk of postoperative AKI after SAVR, intraoperative considerations influence AKI risk. Perturbations in kidney blood flow during cardiopulmonary bypass, aortic cross-clamping, atheroembolic kidney disease, need for blood transfusions, exogenous vasopressors, and the systemic inflammatory response after cardiac surgery all contribute to the development of AKI.[105] The impact of off-pump versus on-pump coronary artery bypass on AKI has been studied extensively and remains controversial. A meta-analysis of trials (N=17 322 patients) suggested a lower risk for AKI with off-pump coronary artery bypass but no difference in the need for dialysis.[113] A recently published randomized controlled trial (RCT; N=2932 patients) demonstrated that off-pump coronary artery bypass reduced the risk of postoperative AKI compared with on-pump surgery, with no discernable difference in kidney function at 1 year.

Although there is considerable overlap in the risk factors and disease burden of AKI after TAVR and SAVR, a recent meta-analysis (N=19 954 patients) showed that the incidence of AKI at 30 days was lower after TAVR than after SAVR (7.1% versus 12.15%; odds ratio [OR], 0.52 [95% CI, 0.39–0.68]), but the incidence of dialysis-requiring AKI was similar (2.8% versus 4.1%; OR, 0.78 [95% CI, 0.49–1.25]).[114] Of note, in the low- to intermediate-risk patients in this analysis, TAVR was associated with reduced risk of AKI, including need for dialysis (OR, 0.57 [95% CI 0.38–0.85]).

AKI Reduction Strategies

Given the multifactorial risk model for AKI with TAVR, a cross-disciplinary approach to nephroprotective strategies is critical in ensuring optimal kidney outcomes.

- Ensuring euvolemia at the time of staged or ad hoc PCI with TAVR is critical in mitigating contrast-induced AKI. Standard nephroprotective volume infusion protocols or the use of high-urine-flow–maintaining devices[115] must be implemented with caution in the presence of critical AS. In a single-center randomized double-blind sham-controlled clinical trial involving 136 patients, forced diuresis with matched hydration was not shown to prevent AKI and needed to be terminated prematurely because of a higher risk of long-term mortality.[116] When volume expansion is indicated, crystalloids are fluids of choice.[117]

- In patients with evidence of congestion, appropriate decongestive therapies must be instituted before PCI and TAVR to achieve euvolemia, given the association between elevated right atrial pressures and AKI after PCI.[118] In this context, the use of bioimpedance plethysmography-based volume management may play a role in contrast-induced AKI reduction and can be considered in high-risk patients.[119]
- Iodinated contrast media minimization has not been demonstrated to be associated with a reduction in AKI after TAVR.[112] However, given the established relationship between contrast volume and AKI after PCI, use of contrast-sparing techniques such as zero-contrast PCI may be considered in patients with CKD undergoing staged PCI before TAVR.[120]
- The use of low-osmolar or iso-osmolar contrast media is also appropriate as part of a contrast-induced AKI reduction strategy.[106]
- As operator experience with the transradial approach increases, use of this vascular access route is preferred as a nephroprotective strategy, especially in patients with high preprocedural AKI risk.
- Appropriate cessation of concomitant nephrotoxins (eg, aminoglycosides, nonsteroidal anti-inflammatory agents, vancomycin) and optimization of calcineurin inhibitor drug levels (if applicable) are important preventive strategies for AKI reduction.

The study of biomarkers for periprocedural risk assessment and detection of AKI is an evolving field and represents another dimension in the ability to risk-stratify patients before AVR and to facilitate early AKI detection after AVR. Plasma metabolite signature profiling with 5-adenosylhomocysteine and β-2 microglobulin has shown great promise in predicting AKI and subsequent progression to CKD.[121,122] Similarly, urinary biomarkers of tubular injury such as neutrophil gelatinase–associated lipocalin, tissue inhibitor of metalloproteinase-2, and insulin-like growth factor binding protein-7 have demonstrated promise in predicting AKI after AVR in small studies.[123–125] As more consistent data become available on the validity of using biomarkers and metabolomic signatures, these will likely be routinely incorporated into clinical decision-making algorithms for best practices for AKI reduction with AVR.

RISK ASSESSMENT AND CHOICE OF INTERVENTION IN PATIENTS WITH CKD AND SEVERE AS

In 2 pivotal TAVR RCTs, PARTNER (Placement of Aortic Transcatheter Valves) and CoreValve US Pivotal Trials, ≈60% of patients had CKD.[126–131] These trials had a noninferiority design with primary efficacy outcomes that included a composite of mortality, stroke, and rehospitalizations for heart failure. In CKD, an expanded composite end point that includes both major adverse cardiovascular and kidney end points seems most appropriate.[132] Several post hoc analysis[132–137] of pivotal RCTs and observational studies have been published, although there are no RCTs directly comparing TAVR and SAVR in CKD. The subgroup analyses in CKD (summarized below) suggest tradeoffs between TAVR and SAVR that parallel the results of the overall trial results (ie, similar/lower procedural mortality and stroke; lower atrial fibrillation, bleeding, length of hospital stay, and AKI; but more pacemakers with TAVR relative to SAVR) and a higher absolute risk of periprocedural and long-term complications with either treatment modality relative to the general population without CKD.

Evidence From Pivotal RCTs

Those with eGFR <20 mL·min^{-1}·1.73 m^{-2} or CKD G5D were excluded from these RCTs; thus, evidence in this population stems largely from observational studies.

Self-Expanding Valves

Pineda et al[132] conducted a subgroup analysis of 797 patients randomized to TAVR (n=389) or SAVR (n=356) in the CoreValve US Pivotal High-Risk Trial stratified by eGFR. In this randomized trial of high-risk AS, prevalence of CKD G3 to G4 was 60.7% in SAVR versus 62.7% in TAVR. At the 3-year follow-up, among patients with CKD G3 to G4, the composite of major adverse cardiovascular and kidney end points was lower in TAVR than in SAVR (42.1% versus 51.0%; *P*=0.04); AKI occurred less frequently with TAVR (9.6% versus 18.2%; *P*=0.01), but rates of new hemodialysis were similar (TAVR, 7.2%; SAVR, 9.2%; *P*=0.23). Life-threatening or disabling bleeding was also lower among patients undergoing TAVR (20.7% versus 46.4%; *P*<0.001), with no difference in mortality (TAVR, 34.3%; SAVR, 41.7%; *P*=0.10), stroke/transient ischemic attack (TAVR, 15.8%; SAVR, 20.8%; *P*=0.23), or myocardial infarction (TAVR, 7.2%; SAVR, 9.2%; *P*=0.23). However, patients undergoing TAVR had higher rates of major vascular complication (6.7% versus 1.9%; *P*=0.01) and need for new permanent pacemaker (30.3% versus 16.5%; *P*<0.001).

Balloon-Expandable Valves

Thourani et al[133] evaluated the impact of CKD on clinical outcomes among 2531 patients undergoing TAVR with the SAPIEN balloon-expandable heart valve system in the PARTNER 1A (high-risk) and 1B (inoperable) cohorts. Of these patients, 1473 (58%) had CKD G3a or G3b, and 291 (12%) had CKD G4 or G5. Patients with CKD G3 or greater (versus no CKD or CKD G1 or G2) had increased 30-day mortality (no CKD/CKD G1/G2, 6.1%; CKD G3a/G3b, 6%; CKD G4/G5, 10.7%;

P=0.01) and 1-year mortality (no CKD/CKD G1/G2, 20.8%; CKD G3a/G3b, 21.5%; CKD G4/G5, 34.4%; *P*<0.001).[133] To date, subgroup analyses comparing the clinical outcomes of TAVR versus SAVR among patients with CKD in the PARTNER trials are not available. A recent subgroup analysis of all PARTNER trials in patients with CKD showed that kidney function remained stable or improved in 89% of patients undergoing TAVR and that <1% of patients progressed to CKD G5 within 7 days of the procedure.[138]

Evidence From Observational Registries

Observational studies used data from the National Inpatient Sample, a publicly available database, to examine patients with CKD undergoing TAVR versus SAVR. Mohananey et al[134] examined the outcomes of 42 189 patients with CKD (n=14 252, 33.7%) and CKD G5D (n=1708, 4%) undergoing TAVR in the United States between 2011 and 2014.[134] Patients with CKD had increased in-hospital mortality compared with those without CKD (4.5% versus 3.7%; *P*<0.001; adjusted OR [aOR] 1.34 [95% CI, 1.20–1.31]), increased hemorrhage requiring transfusion (13% versus 10%; aOR, 1.85 [95% CI, 1.63–2.11]; *P*<0.01) and increased permanent pacemaker implantation (11% versus 9.5%; aOR, 1.15 [95% CI, 1.07–1.23]; *P*<0.001). Similarly, patients with CKD G5D had increased hospital mortality (8.2% versus 3.7%; aOR, 2.51 [95% CI, 2.02–3.12]; *P*<0.001), hemorrhage requiring transfusion (17.5% versus 10.0%; aOR, 2.34 [95% CI, 2.01–2.73]; *P*<0.001), and permanent pacemaker implantation (12.6% versus 9.5%; aOR, 1.36 [95% CI, 1.17–1.58; *P*<0.001) compared with patients with no CKD. Kumar et al[135] performed a propensity-matched analysis of 1001 pairs of patients undergoing TAVR and SAVR using the National Inpatient Sample 2011 to 2014 data set. Compared with SAVR, TAVR was associated with lower in-hospital mortality (OR, 0.67 [95% CI, 0.45–0.99]; *P*=0.04), AKI (OR ,0.39 [95% CI, 0.32–0.46]; *P*<0.01), dialysis-requiring AKI (OR, 0.53 [95% CI, 0.35–0.81]; *P*<0.01), and postoperative stroke (OR, 0.46 [95% CI, 0.20–0.98]; *P*<0.01), shorter length of stay (OR, 0.35 [95% CI, 0.29–0.42]; *P*<0.01); and similar costs (OR, 1.05 [95% CI, 0.88–1.26]; *P*=0.57). Doshi et al[139] included patients with CKD G4 to G5. Results were similar, showing fewer in-hospital deaths and strokes with TAVR versus SAVR. TAVR also was associated with fewer complications such as AKI, dialysis requirement, blood transfusions, and longer length of stay. The need for a permanent pacemaker was higher with TAVR versus SAVR, although the difference was not statistically significant after multivariate adjustment in the study by Kumar et al[135] (11% versus 6.1%; *P*=0.39; OR, 1.01 [95% CI, 0.74–1.38]; *P*=0.93). Bhise et al[140] focused on patients with CKD G5D. Using propensity score–matching techniques, they found no significant differences in TAVR versus SAVR on in-hospital mortality or complications, but they did find shorter length of stay (8.3 days versus 17.1 days; *P*<0.001) and higher discharge disposition to home (56.3% versus 42.8%; *P*=0.10) with TAVR. In a much larger study, Mentias et al[141] evaluated 8107 patients with CKD G5HD (50% with TAVR, 31.6% with SAVR, 17.4% without AVR) and reported lower 30-day mortality with TAVR versus SAVR (4.6% versus 12.8%; *P*<0.01) with comparable outcomes at a median follow-up duration of 465 days.

Evidence From Meta-Analysis of Observational Studies

Cheng et al[136] performed a meta-analysis of 10 observational studies (N=9619) comparing TAVR and SAVR in CKD and reported early all-cause mortality and postoperative stroke from 2000 to 2018. TAVR was associated with lower early mortality (6.1% versus 10.2%; OR, 0.71 [95% CI, 0.51–0.98]), stroke (1.1% versus 2.2%; OR, 0.53 [95% CI, 0.37–0.75]), AKI requiring hemodialysis (OR, 0.66 [95% CI, 0.58–0.75]), and blood transfusion (OR, 0.50 [95% CI, 0.39–0.65]) but a higher risk of pacemaker implantation (OR, 2.06 [95% CI, 1.16–3.66]) compared with SAVR.

CHOICE OF MECHANICAL VS BIOLOGICAL VALVES IN PATIENTS WITH CKD UNDERGOING SAVR

In patients with CKD deemed suitable candidates for SAVR, choosing the appropriate prosthesis requires careful balance of the potential need for reintervention (bioprosthetic valve) and the risks of lifelong anticoagulation (mechanical valve). Evidence on this topic is derived from observational studies and limited by small sample sizes, precluding adjustment for differences in baseline characteristics. Hence, societal guidelines do not have any specific recommendations for CKD. It is imperative to consider life expectancy when recommending valve prostheses to patients with CKD; because they have reduced life expectancy and increased risk of bleeding,[142,143] they are probably less likely to derive the benefit of increased durability of mechanical valves. In general, the median time to bioprosthetic valve failure is reported to be ≈9 years,[144] and similarly, reoperation rates diverge between biological and mechanical valves at 8 years after the index AVR, coincident with separation of survival curves. These observations suggest that the mortality benefit of mechanical valves accrues only among patients with life expectancy beyond 8 to 10 years.[145] Another factor to balance is that the risk of major bleeding among patients with CKD is inversely related to eGFR and increases with microalbuminuria,

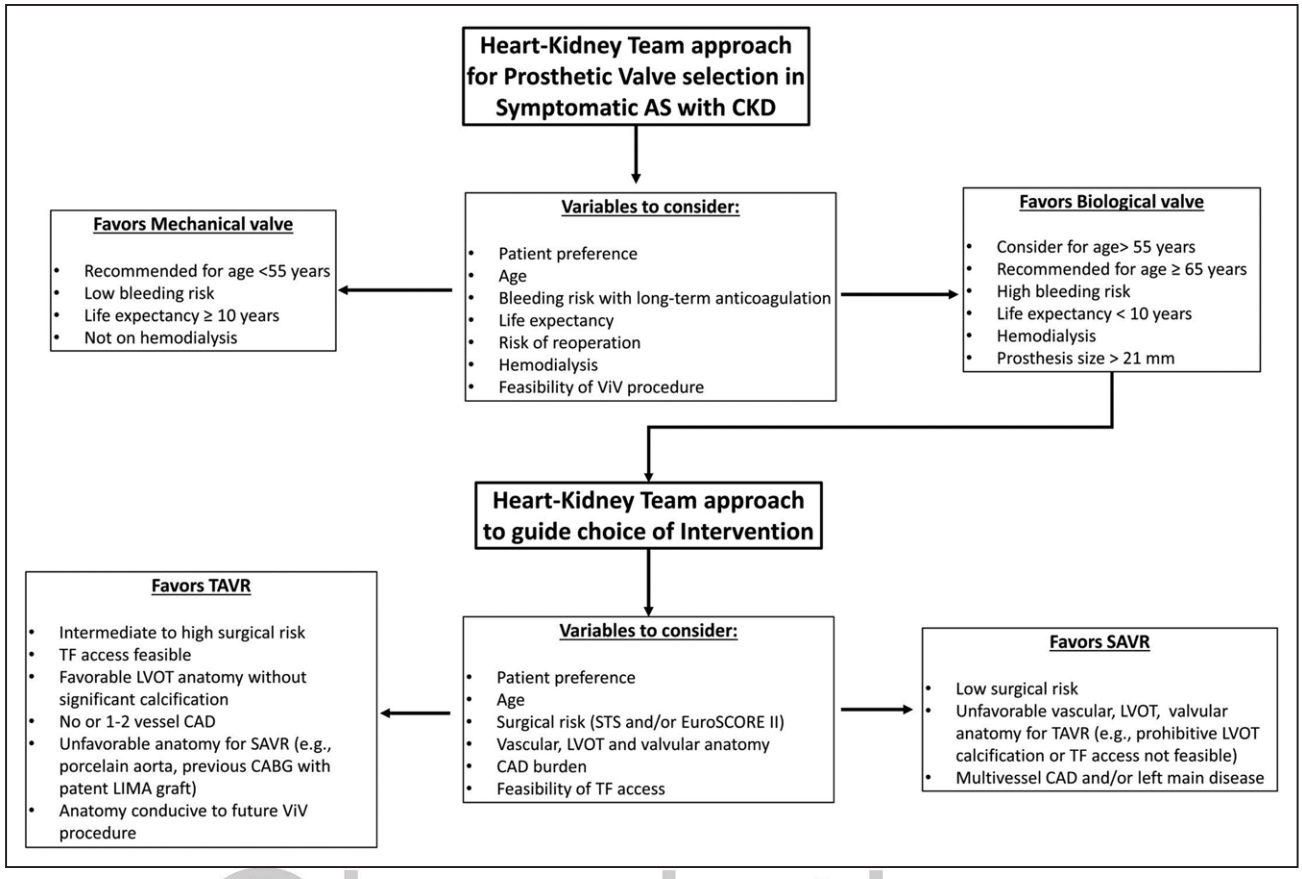

Figure 4. Suggested approach to valve selection and choice of intervention in patients with symptomatic aortic stenosis (AS) and chronic kidney disease (CKD).

CABG indicates coronary artery bypass graft; CAD, coronary artery disease; LIMA, left internal mammary artery; LVOT, left ventricular outflow tract; SAVR, surgical aortic valve replacement; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement; TF, transfemoral; and ViV, valve in valve.

age, and anticoagulant therapy.[143] Finally, the emergence of TAVR as a treatment option for patients with bioprosthetic valve degeneration needs consideration. This option is less invasive than redo surgery and is associated with lower periprocedural mortality, particularly when the mode of failure is stenosis and the surgical valve is >21 mm.[144,146] If valve-in-valve interventions are shown to have satisfactory long-term outcomes in CKD, the valve selection paradigm could be significantly affected.

Valve Selection in Patients With CKD G5D: Mechanical Versus Biological Valves

Patients with CKD G5HD require special attention, given their limited life expectancy and increased risk of bleeding with anticoagulation. Only 51% patients with CKD G5HD are alive 3 years after dialysis is initiated.[147] In addition, the risk of bleeding complications increases 3- to 10- fold among patients with CKD G5HD who receive warfarin, with annualized rates as high as 54%/y,[148,149] and an association between calcific uremic arteriopathy (previously calciphylaxis) and warfarin exposure has been reported.[150] Despite this background of significantly diminished life expectancy and increased risk of bleeding, the 1998 societal guidelines recommended mechanical valves for CKD G5HD based on case reports of early bioprosthetic valve failure attributable to accelerated tissue calcification.[151,152] A large (N=5858) analysis of the US Renal Data System database among patients with CKD G5HD undergoing SAVR between 1978 and 1998 showed no difference in 2-year survival with biological or mechanical valves (39±3.5% versus 39.7±1.4%; *P*=NS).[153] Of note, 5-year survival was only 14±1.3% after SAVR in this cohort. Multiple single-center studies and a meta-analysis have confirmed these observations.[154–156] As a result, the proscription of biological valves in patients with CKD G5D was rescinded in the 2006 societal guidelines, with no particular valve encouraged or discouraged since.[157,158]

TAVR VERSUS SAVR IN CKD

We recommend a multidisciplinary heart-kidney team approach to valve selection and choice of intervention in CKD, including shared decision making with the patient, and consideration of clinical risk predictors of adverse outcomes[159–162] (Figure 4 and Table 2).

Table 2. Factors Associated With Poor Outcome Among Patients Undergoing AVR That Likely Can Be Extrapolated to CKD

	TAVR	SAVR
Anatomic/procedural factors	Alternative (ie, nontransfemoral) access	Aortic calcification, porcelain aorta
	Polyvalvular disease (more than moderate mitral regurgitation or tricuspid regurgitation)	Concomitant severe mitral calcification and significant stenosis/regurgitation
	Perioperative atrial fibrillation	LV dysfunction
	LVOT calcification*	Longer cardiopulmonary bypass time
	Bicuspid valve*	Infective endocarditis
	Low coronary height*	Emergent nature of surgery
	Lower transaortic gradient	
Clinical factors	Advanced age	Advanced age
	High CAD burden, prior CABG	High CAD burden
	Dialysis	Dialysis
	Albumin <3.3 g/L	Severe pulmonary hypertension
	Body mass index <21 kg/m^2	Severe chronic obstructive pulmonary disease
	Home oxygen/oxygen-dependent lung disease	Home oxygen/oxygen-dependent lung disease
	Dependence on others for ADLs	
	Wheelchair dependency	
	Significant cognitive impairment	
	Frailty/futility	

ADL indicates activity of daily living; AVR, aortic valve replacement; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; CKD, chronic kidney disease; LV, left ventricular; LVOT, left ventricular outflow tract; SAVR, surgical aortic valve replacement; and TAVR, transcatheter aortic valve replacement.

*These factors influence valve selection and affect the choice of intervention but have not been shown to be independently predictive of poor outcomes.

1. Given the lack of a survival advantage and higher risk of bleeding/stroke with mechanical valves in patients >55 years of age at the time of surgery, biological valves may be preferred in these patients (Figure 4). The choice of intervention (SAVR versus TAVR) should be individualized after careful considerations of surgical risk, suitability for transfemoral access, coronary artery disease (CAD) burden, anatomic features detected on CT[163] (ie, LVOT calcification, coronary height, bicuspid anatomy), and patient preference (Figure 4 and Table 2). Because equivalent survival was demonstrated for mechanical and biological aortic prostheses in patients >55 years of age[145] and on the basis of superior major adverse cardiovascular and kidney outcomes of TAVR versus SAVR in CKD, we suggest that among patients with CKD who are ≥55 years of age with suitable transfemoral access and without prohibitive anatomic features on imaging, TAVR may be the preferred strategy.[131,132] Of note, transfemoral access is a preferred strategy because it has been shown in subgroup analysis to confer better outcomes than nontransfemoral access.[123,134] However, according to available evidence, nontransfemoral access should be considered noninferior to SAVR, although specific data in CKD are lacking.
2. Among elderly patients with CKD G4 to G5, the clinical decision making is particularly complex as a result of a finite risk of progression to dialysis after TAVR. This risk needs to be discussed specifically with the patient using a shared decision-making approach and appropriately reconciled with the patient's overall goals of care and life choices.
3. Given the attenuated survival of patients with CKD G5D and increased bleeding risk, a majority of these patients receive biological valves in the United States.[164] To date, these patients have been excluded from all pivotal clinical trials comparing TAVR and SAVR. However, a recent analysis revealed that 4.2% of commercial TAVR cases in the United States were performed on patients with CKD G5D.[165] Compared with patients not on hemodialysis, these patients were younger (mean age, 76 years versus 83 years) but had higher preoperative risk scores. The reported in-hospital mortality after TAVR was 5%, which compares favorably with historical data suggesting in-hospital mortality of 20% after SAVR. However, 1-year mortality after TAVR was 36%; thus, a third of all patients with CKD G5D undergoing TAVR in the United States will not be alive 1 year after the procedure. Judicious use of TAVR in patients with CKD G5D is required because of the diminished benefit and possible medical futility in some cases (Table 2).[160,161] Again, careful risk assessment by a multidisciplinary team that includes nephrologists, interventional cardiologists, cardiac surgeons, and likely palliative care is required for input before proceeding with TAVR in this high-risk subset of patients to ensure that patients will survive long enough to derive benefit from the procedure.

MANAGEMENT OF CONCOMITANT CAD IN PATIENTS NEEDING AVR

Management of stable CAD in the context of CKD G4 to G5D is quite complex in general, and the nuances with management of CAD in the context of AS/AVR are even more so. However, CAD is frequently coprevalent in patients with severe AS; the prevalence of CAD in RCTs that enrolled intermediate- to high-risk patients for TAVR ranged from 62% to 75%.[126,127] In the context of CKD G4 to G5D and AVR, the clinical impact of CAD

on periprocedural/long-term outcomes and the potential role and timing of revascularization require careful input from a multidisciplinary heart-kidney team.

Clinical Impact of CAD on AVR Outcomes

Among patients undergoing SAVR, simultaneous revascularization of significant CAD (defined qualitatively or with hemodynamic assessment) is the norm. Data on the impact of CAD on short- or long-term outcomes after TAVR from real-world registries are conflicting and controversial, likely driven by heterogeneity in definitions, study design, and patient selection.[166–169] In a meta-analysis involving 8334 patients, D'Ascenzo et al[170] reported that only more complex CAD (defined by SYNTAX [Synergy Between PCI With Taxus and Cardiac Surgery] score) was associated with higher 1-year mortality (OR, 1.71 [95% CI, 1.24–2.36]) in the context of TAVR, not any CAD. Unfortunately, no specific data are available to guide the impact of CAD in the context of CKD, although it is universally recognized that CAD tends to be more complex with progressive CKD.

Clinical Impact of Revascularization

Revascularization before TAVR may potentially be beneficial to prevent myocardial ischemia induced by rapid pacing during TAVR, thus improving procedural outcomes. However, among patients with CAD undergoing TAVR, no randomized data are available to guide the role of periprocedural revascularization compared with medical therapy only. A meta-analysis of 6 studies (N=3107 patients) reported that among patients undergoing TAVR, incomplete revascularization was associated with higher hazards of mortality compared with those without CAD.[171] However, a recent analysis found no benefit with respect to all-cause mortality at 30 days (OR, 1.30 [95% CI, 0.85– 1.98]) and 1 year (OR, 1.19 [95% CI, 0.92–1.52]) in patients who underwent TAVR with or without PCI.[172] Thus, the impact of PCI on TAVR outcomes in patients is uncertain, with a dearth of evidence in the literature to specifically guide management in CKD.

TAVR and Left Main Disease

Patients with left main disease are considered a unique subset because they are more vulnerable to hemodynamic compromise during procedural interventions, given the large myocardial distribution at risk. Furthermore, the anatomic proximity of the aortic valve annulus heightens the risk of occlusion of the left main ostium by the prosthesis/native leaflets during TAVR. The TAVR–left main registry evaluated 204 patients undergoing TAVR plus left main PCI and reported a 1-year mortality similar to that of a matched cohort undergoing TAVR without left main PCI (9.4% versus 10.2%; P=0.83).[173] The notable exception was patients who underwent unplanned/emergency left main PCI because of TAVR-related complications (such as left main dissection), in whom 30-day and 1-year mortality rates were significantly higher. In general, given this adverse outcome profile with unplanned left main revascularization with TAVR, prophylactic left main revascularization for protection during TAVR may be reasonable.

Timing of CAD Revascularization and TAVR

Once the decision to perform revascularization in patients undergoing TAVR is made, either a staged approach (PCI before TAVR) or a concomitant approach (PCI+TAVR) may be considered; PCI after TAVR is rarely preferable, given the limited data on and technical difficulties with this approach. In patients undergoing PCI before TAVR who are at high bleeding risk, a minimum of 3 months of dual antiplatelet therapy (DAPT) is generally indicated, although recent data may potentially support as short as 1 month of DAPT with newer-generation drug-eluting stents.[174,175] Notably, performing TAVR in the setting of recent PCI and DAPT would potentially increase the risk of periprocedural bleeding and transfusion requirements. Furthermore, a staged approach to multiple sequential percutaneous procedures may also be independently associated with an elevated risk of AKI attributable to multiple closely spaced nephrotoxic insults, particularly in subjects with CKD.[109] van Rosendael et al[176] compared the clinical outcomes of patients undergoing PCI >30 or <30 days preceding TAVR and noted a significant increase in post-TAVR minor vascular injury and bleeding when PCI was performed <30 days before TAVR. The elevated risk of AKI attributable to multiple vascular procedures (especially with femoral versus radial access), likely driven by higher rates of atheroembolic disease and bleeding, should be considered in patients with CKD undergoing TAVR with simultaneous PCI.[177] On the other hand, despite higher procedural complexity and contrast volume, the feasibility of simultaneous TAVR+PCI is established.[178,179] In composite, we recommend an individualized approach to balance the tradeoffs of staged PCI (before TAVR) to minimize the risk of AKI and simultaneous TAVR+PCI as an alternative option in patients who may be at higher risk for bleeding and vascular access complications from repeated cannulation. Higher adoption of transradial access and zero-contrast PCI could mitigate some of the risks of the latter strategy.

Specific Considerations for CAD/Revascularization in CKD

The literature on the role of revascularization for CAD among patients with CKD is sparse in general and

limited in the context of AVR. The recently published ISCHEMIA-CKD trial (International Study of Comparative Health Effectiveness With Medical and Invasive Approaches)[180] is the only RCT that has systematically evaluated the role of routine revascularization of stable CAD in CKD G4 to G5D and demonstrated no benefit of this strategy compared with medical therapy despite the presence of moderate to severe ischemia, but it excluded patients with severe AS. Given the absence of randomized data to guide the management of CAD among patients with CKD and severe AS, clinicians need to use their best judgment on the applicability of these findings in the context of procedural interventions such as AVR. This writing group recommends careful, individualized assessment of overall risks versus benefits of revascularization before TAVR and suggests that lack of benefit with routine revascularization of stable CAD in patients with CKD G4-5D in a well-conducted RCT be factored into the decision-making algorithm before TAVR. The decision on revascularization in these complex patients with CKD should account for higher-than-baseline risk of procedural complications (including AKI) but also reconcile the fact that PCI after TAVR can be complicated not only from usual procedural risks but also because of technical difficulties of accessing coronary ostia (particularly for self-expanding valves). We recommend the following:

- The decision to revascularize in CKD G4 to G5D should be made in collaboration by the multidisciplinary heart-kidney team, factoring in the symptoms, complexity of CAD, and ability to pursue complete revascularization while balancing the risk of AKI and vascular and other procedural risks.
- In general, given the complexities of CAD in this population, lack of definitive benefit, and potential harm with AKI, we suggest a conservative approach to revascularization before TAVR.
- As an extrapolation from the general population, revascularization of left main lesions may be a reasonable consideration, however, to increase the procedural safety of performing TAVR in these high-risk patients.

We anticipate that the ACTIVATION trial (Percutaneous Coronary Intervention Prior to Transcatheter Aortic Valve Implantation; ISRCTN75836930) will help shed light on the utility of routine PCI in subjects undergoing TAVR and, we hope, provide some guidance for the CKD population.

PERIPROCEDURAL MANAGEMENT AFTER AVR IN CKD/END-STAGE KIDNEY DISEASE

The periprocedural management of patients with CKD around the time of SAVR/TAVR for severe, symptomatic AS is critically important for optimal short- and long-term outcomes. We recommend the formulation of an individualized plan for these high-risk patients with multidisciplinary input from a heart-kidney team comprising cardiologists, cardiac surgeons, and nephrologists to carefully plan periprocedural management. In the absence of any specific evidence-based recommendations for perioperative management of the patient with CKD G4 to G5D for AVR, this writing group recommends careful consideration and anticipation of the following unique variables in this high-risk population to optimize periprocedural outcomes (Figures 4 and 5).

Hemodynamic and Volume Management

- It is important to diligently optimize volume status before AVR. Among patients with CKD G5D in particular, it is important to have the patient as close to their hemodynamic dry weight as possible. For those on hemodialysis, we would generally recommend a dialysis session on the day before AVR, whereas for those on PD, continuation of the regular schedule usually suffices. There is no specific evidence that intensification of the dialysis prescription improves outcomes.
- Among patients with complex hemodynamics, particularly in the context of pulmonary hypertension, polyvalvular involvement, and reduced cardiac output, a pulmonary artery catheter may be helpful in the perioperative setting to accurately assess volume status and to guide volume management.
- Among those with CKD G4 to G5, whose volume status and hemodynamics are not well optimized, an upfront discussion about the anticipated need for periprocedural dialysis is recommended as opposed to a "crash and burn" decision after the procedure.
- Similarly, there is a need to be thoughtful about fluid resuscitation postprocedurally in patients with CKD and to avoid "routine" maintenance fluid, particularly hypotonic fluids (eg, 1/2 NS), because of the risk of hyponatremia.
- In those with AS and concomitant congestive heart failure in particular, an astute balance of inotropes and vasopressors is necessary to ensure adequate cardiac output and maintenance of adequate kidney perfusion.

Dialysis Considerations With CKD G5D

Insufficient evidence exists in the literature to guide how best to manage dialysis/ultrafiltration in those with significant AS; anecdotally, PD may be better tolerated than hemodialysis. Adequate dialysis access is the lifeline of patients with CKD G5D; this writing group recommends

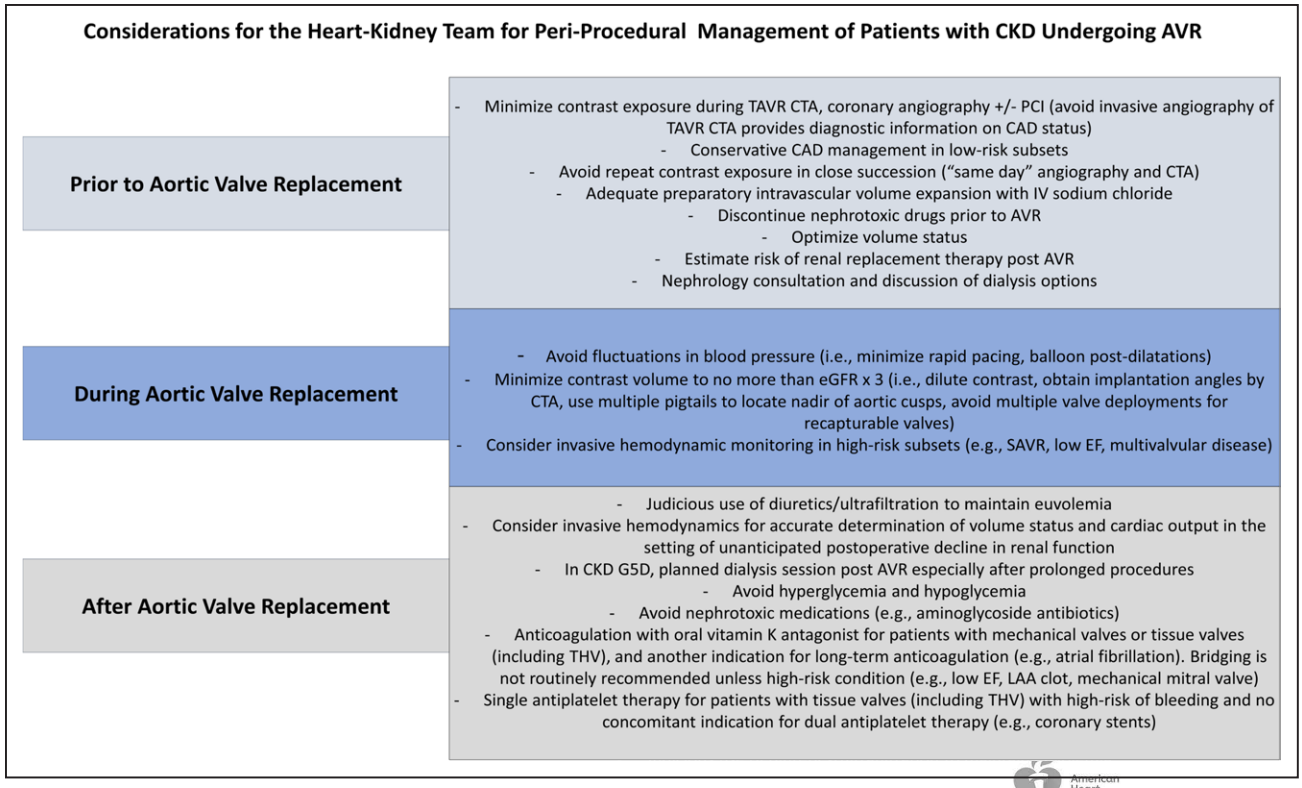

Figure 5. Specific considerations for the periprocedural management of patients with chronic kidney disease (CKD) undergoing aortic valve replacement (AVR).

CAD indicates coronary artery disease; CTA, computed tomography angiogram; EF, ejection fraction; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; LAA, left atrial appendage; PCI, percutaneous coronary intervention; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; and THV, transcatheter heart valve.

close attention in the preprocedural setting to ensure that dialysis access is adequate for anticipated postprocedural needs. Specifically, if patients with CKD G5D with an AVF are hemodynamically tenuous, it may be necessary to consider transitioning to continuous dialysis modalities such as continuous venovenous hemodialysis or filtration, necessitating placement of temporary dialysis access. Typically, PD can be continued in the context of most procedures (as long as the peritoneum is not violated) and provides adequate volume removal.

Electrolyte Management

In individuals with CKD G4 to G5D, periprocedural hyperkalemia is not uncommon because of various factors and should be anticipated. This makes it particularly important to ensure diligent periprocedural planning pertaining to dialysis access and management. In general, we recommend consideration of a hemodialysis session after the procedure in patients with CKD G5D, particularly after prolonged procedures such as a high-risk SAVR, for optimization of the hemodynamic and electrolyte milieu, especially if hyperkalemia is noted during the pump run in the operating room. It deserves mention that if PD is not deemed adequate to provide rapid management of hyperkalemia in a particular situation, placement of temporary hemodialysis access (possibly in the operating room to expedite dialysis on arrival to the intensive care unit) may be necessary for safe periprocedural management.

Periprocedural Considerations in Kidney Transplant Recipients

No specific recommendations for perioperative management of patients with CKD G5T undergoing TAVR or SAVR exist. Periprocedural immunosuppression should be performed in close conjunction with the transplantation nephrology consultant, with the use of stress-dose steroids as indicated. Mammalian target of rapamycin inhibitors such as sirolimus are linked to delayed wound healing compared with tacrolimus.[181,182] Therefore, it may be necessary to hold sirolimus around the time of SAVR, change to an alternative agent, or consider TAVR if transfemoral access is feasible to avoid sternotomy.

Optimization of Kidney Function and Prevention and Management of AKI

There is a close relationship between AS and kidney function; it has been suggested that AS may contribute

to impaired eGFR.[137,183] It is feasible that relief of AS may improve kidney flow; several groups have noted that 50% to 60% of patients have significant improvement in eGFR after AVR.[137,183,184] The risk of postoperative AKI generally has been higher in patients undergoing SAVR compared with those undergoing TAVR.[136,137] Unfortunately, some commonly used perioperative strategies have failed to show any consistent benefit in preventing AKI, including administration of dopamine, fenoldopam, atrial natriuretic peptide, and insulin-like growth factor-1.[185] However, diuretics were noted to be useful in managing volume overload, especially as is seen with those undergoing SAVR.[185] In addition to the cardiologist and surgeon, it is important to include a nephrologist as an integral component of the heart-kidney team in the periprocedural management of these patients. A variety of recommendations by the Kidney Disease: Improving Global Outcomes group are important to iterate[185]:

1. Isotonic crystalloids rather than colloids should be used for volume expansion,[186] and it is important not to use colloid preparations such as hyperoncotic starch that are associated with increased AKI.[187]
2. Plasma glucose levels of 110 to 149 mg/dL should be maintained without major swings of hypoglycemia, which can lead to an increased risk of death.[188]
3. Aminoglycosides should be avoided, but if they are required, single daily dosing with therapeutic drug monitoring is recommended.[185]
4. Liposomal amphotericin or azoles or echinocandins should be used for fungal or parasitic infections.
5. Oral and intravenous *N*-acetylcysteine has now been proven conclusively to be ineffective.[117,185]

Avoiding Contrast-Induced AKI

This is an important priority, as outlined previously, with potential impact of sequential exposure. Important recommendations by the Kidney Disease: Improving Global Outcomes group deserve reiterating.[185]

1. The risk for postoperative contrast-induced AKI should be assessed and screened by point-of-care creatinine testing or by questionnaire-based risk assessment for factors such as diabetes, cardiovascular disease, and CKD.
2. Use of contrast should be minimized in those at risk of contrast-induced AKI, and iso-osmolar or low-osmolar contrast should be used in those with increased risk. Specific strategies to minimize contrast exposure include the use of diluted contrast media (50:50), CT overlay to guide placement of embolic protection device and arterial access, and pigtail catheters in the noncoronary and right coronary cusps for valve alignment. Postimplantation angiogram could be replaced with an on-table TTE to assess for paravalvular leak.
3. Intravascular volume expansion with isotonic sodium chloride should be considered the standard of care for the prevention of adverse kidney outcomes.[117,189]
4. The PRESERVE study (Prevention of Serious Adverse Events Following Angiography) showed that among patients at high risk of kidney complications undergoing angiography or PCI, there was no benefit of intravenous sodium bicarbonate compared with intravenous sodium chloride or of oral *N*-acetylcysteine for the prevention of death, need for dialysis, or persistent decline in kidney function at 90 days or for the prevention of AKI.[117]
5. Studies have shown that there is no difference in oral versus intravenous fluids in contrast-induced AKI in CKD G3b or lower.[190,191] In outpatients, the use of oral fluid loading may be justified.
6. There is no role for prophylaxis hemodialysis/hemofiltration for contrast removal in those with increased risk of contrast-induced AKI.[192–194]

In conjunction with the nephrologist, operators of TAVR procedures should remain vigilant in maximizing preoperative and postoperative care and minimizing intraoperative contrast with the goals of preserving kidney function and preventing contrast-induced AKI.

Periprocedural Anticoagulation/Antiplatelet Management

In general, management of anticoagulation is particularly perilous among those with CKD G4 to G5D because the risks of thrombosis and bleeding tend to be higher relative to those without CKD. No specific evidence exists in the literature for anticoagulation management in CKD G4 to G5D after AVR. This writing group recommends that the risks versus benefits of anticoagulation be meticulously individualized in this high-risk population.

1. After mechanical AVR, targets for therapeutic anticoagulation in CKD are similar to those in the general population.[33] Mechanical SAVR with an On-X valve seems a particularly attractive option in this population because of a lower target international normalized ratio of 1.5 to 2.0 (in patients with no thromboembolic risk factors). It is reasonable to avoid postoperative bridging with heparin in the immediate postoperative period, instead allowing a few days for the VKA to become therapeutic, because the risk of thrombosis in the aortic position after mechanical SAVR is quite low and the risk of postoperative bleeding usually outweighs the risks of thrombosis in CKD G4 to G5D.
2. After bioprosthetic SAVR, anticoagulation with a VKA to achieve an international normalized ratio

of 2.5 is reasonable for 3 to 6 months at the discretion of the treating team. Aspirin 75 to 100 mg daily also is recommended after all SAVR.

3. After TAVR, the increased risk of bleeding in CKD needs recognition, as well as the fact that CKD itself is a risk factor for bleeding.[195] In a single-center study of patients undergoing TAVR, despite comparable antithrombotic regimens, patients with CKD had a significantly higher risk of bleeding at 1 year compared with those without CKD (9.2% versus 4.9%; *P*=0.32).[196] Bleeding in turn was associated with a nearly 2.5-fold higher hazard of subsequent mortality. Current guidelines recommend that anticoagulation with VKA to achieve an international normalized ratio of 2.5 may be reasonable for at least 3 months in patients at low risk of bleeding, but it is unclear whether this can be applied universally in all patients with CKD G4 to G5D. Alternatively, DAPT with clopidogrel 75 mg daily for the first 6 months in addition to lifelong aspirin 75 to 100 mg daily is considered reasonable. Certainly, in those undergoing PCI before TAVR, DAPT would be a more preferable option. In contrast, European guidelines recommend that single antiplatelet therapy may be considered if the bleeding risk is high,[37,157] which may be an attractive option in those with CKD G4 to G5D. Pivotal RCTs mandated DAPT with aspirin and clopidogrel for 6 months after the procedure; however, a meta-analysis of 3 randomized clinical trials (n=421) comparing dual and single antiplatelet therapy demonstrated increased hazards of life-threatening bleeding with DAPT.[197] In a recent pivotal RCT, aspirin monotherapy compared with DAPT for a duration of 3 months led to a reduction in overall bleeding (15.1% versus 26.6%; *P*=0.001) and nonprocedural bleeding over a period of 12 months.[198] On the basis of these data, we believe it is therefore reasonable to consider single antiplatelet therapy for patients with CKD G4 to G5D after TAVR.
4. A number of clinical trials comparing various novel oral anticoagulant agents and antiplatelet therapy or VKA (Supplementary Table D) will likely provide more information in the future, although it remains to be seen if they are adequately powered for deriving meaningful conclusions in the CKD population.

LONG-TERM ASSESSMENT OF PROSTHETIC VALVE FUNCTION AFTER SAVR/TAVR IN CKD/END-STAGE KIDNEY DISEASE

The pathophysiology of structural valve deterioration is not well understood, but patients with CKD,

Table 3. Opportunities for Research in the Diagnosis and Management of AS in CKD

Cardiovascular imaging	Should routine calculation of Z_{va} be performed in all patients with AS with CKD?
	What is the most optimal frequency of follow-up of asymptomatic AS with CKD G4–G5?
	What is the role of fistula occlusion (temporary) to assess the impact on hemodynamics in AS?
	Can native T1 mapping or late gadolinium enhancement provide prognostic information in patients with CKD/CKD G5HD with AS?
	Is there a need for alternative cut points of aortic valve calcium burden to predict risk in CKD?
	Is projected AVA (for normal flow rate) predictive of true AVA in patients with CKD G5HD with hemodynamically significant AVF or graft?
	Evaluate the correlation of AVA as calculated by the continuity equation vs planimetry (using 2D vs 3D techniques) in CKD in the context of higher calcific burden.
Hemodynamic management	How should hemodynamically significant AS be managed on hemodialysis? What hemodynamic effects should be anticipated when a patient with a low-flow state in CKD transitions to a high-flow state on dialysis vis-à-vis symptoms, hemodynamics, and LV and right ventricular function on echocardiography? Does this transition contribute to more rapid progression in AS?
	Does AS progress less rapidly with PD vs hemodialysis?
CAD	Does concomitant CAD affect short-term or long-term survival in those with CKD and severe AS?
	Does preemptive revascularization in asymptomatic patients with CKD undergoing TAVR or SAVR affect outcomes?
	Are there differences in clinical outcomes with pursuing staged PCI (before TAVR) vs simultaneous PCI and TAVR among patients with CKD deemed to need coronary revascularization?
AKI	Does the incidence of AKI defer with self-expanding vs balloon expandable TAVR systems vis-à-vis procedural considerations?
	Does albuminuria increase the risk of AKI after TAVR?
	Do serum or urinary biomarkers provide additional prognostic information beyond conventional risk factors?
AVR	Randomized study of major adverse cardiovascular and kidney outcomes in SAVR vs TAVR in CKD G4–G5.
	Randomized study of major adverse cardiovascular and kidney outcomes in SAVR vs TAVR in CKD G5HD.
	What are the prognoses/outcomes of valve-in-valve procedures in CKD?
	What is the optimal antiplatelet/anticoagulant regimen after TAVR in CKD, including CKD G5HD?
	Are there differences in degeneration between different bioprostheses in CKD vis-à-vis vulnerability to soft tissue calcification?
	Are there differences in outcomes between transfemoral and other approaches for TAVR in CKD?
Experimental research	Evaluate animal models of CKD that could be used when studying aortic valve pathology and aortic stenosis.

AKI indicates acute kidney injury; AS, aortic stenosis; AVA, aortic valve area; AVF, arteriovenous fistula; AVR, aortic valve replacement; CAD, coronary artery disease; CKD, chronic kidney disease; LV, left ventricular; PCI, percutaneous coronary intervention; PD, peritoneal dialysis; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; 2D, 2-dimensional; 3D, 3-dimensional; and Z_{va}, valvulo-arterial impedance.

especially those receiving dialysis, are at high risk for accelerated bioprosthetic valve structural valve deterioration and failure.[199,200] In addition, the high prevalence of atrial fibrillation and hemostasis disorders in this population increases the risk of valve thrombosis, which in turn, even if successfully treated with anticoagulation, may lead to accelerated structural valve deterioration.[201]

- All patients require lifelong follow-up by a cardiologist after AVR to monitor for or to detect structural or functional valve deterioration early.[37]
- Measurement of transvalvular gradients is recommended in the postoperative period, 30 days after valve implantation, and yearly thereafter, with TTE used to detect bioprosthetic-related complications.[202,203] This recommendation is even more important for patients with CKD, who are at higher risk for valve thrombosis or structural valve deterioration.
- The mechanism of degeneration of bioprosthesis (eg, leaflet tear, calcification, restriction, tear) can differ by the type of valve.[204] It is well recognized that CKD is a risk factor for accelerated degeneration, likely because of soft tissue calcification. Identifying bioprosthesis that may be less vulnerable to soft tissue calcification in CKD represents a potential area for future research.
- The use of advanced imaging (TEE, noncontrast CT) is usually reserved for patients with evidence of functional or structural valve deterioration to guide medical management.
- A multimodality imaging approach using TEE and contrast CT should be reserved in case of bioprosthetic structural valve deterioration to identify the cause of dysfunction and to distinguish structural (fibrocalcific remodeling or tear of valve cusps) from nonstructural (endocarditis, thrombosis, pannus, and paravalvular regurgitation) valve dysfunction[199,204] and to guide the timing of reintervention.

CONCLUSIONS

The diagnostic evaluation and management of AS in patients with CKD, particularly G4 to G5D, are complex and multifaceted and require multidisciplinary collaborative input. There are several facets in which this population differs quite remarkably from the non-CKD population and is therefore deserving of focused expertise and attention to the details outlined. This writing group strongly recommends a multidisciplinary heart-kidney team-based approach to this high-risk population and has identified several specific opportunities that will, we hope, inspire future research (Table 3) to enhance our clinical knowledge of this unique population and to improve their clinical outcomes.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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*Modest.

†Significant.

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