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Aortic Stenosis and Aortic Valve Replacement among Patients with Chronic Kidney Disease: A Narrative Review

Frederick Berro Rivera[a] Maria Victoria Valenzona Cu[b] Sharmaine Jesselyn Cua[b] Deogracias Villa De Luna[c] Edgar V. Lerma[d] Peter A. McCullough[e] Amir Kazory[f] Fareed Moses S. Collado[g]

[a]Department of Medicine, Lincoln Medical Center, Bronx, NY, USA; [b]University of the Philippines System, National Capital Region, Manila, Philippines; [c]Department of Internal Medicine, Danbury Hospital, Danbury, CT, USA; [d]Section of Nephrology, University of Illinois at Chicago College of Medicine/ Advocate Christ Medical Center, Oak Lawn, IL, USA; [e]Truth for Health Foundation, Tucson, AZ, USA; [f]Division of Nephrology, Hypertension, and Renal Transplantation, University of Florida, Gainesville, FL, USA; [g]Department of Cardiology, Rush University Medical Center, Chicago, IL, USA

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Transcatheter aortic valve replacement · Surgical aortic valve replacement · Chronic kidney disease · Outcomes

Abstract

Background: Aortic stenosis (AS) can present with dyspnea, angina, syncope, and palpitations, and this presents a diagnostic challenge as chronic kidney disease (CKD) and other commonly found comorbid conditions may present similarly. While medical optimization is an important aspect in management, aortic valve replacement (AVR) by surgical aortic valve replacement (SAVR) or transcatheter aortic valve replacement (TAVR) is the definitive treatment. Patients with concomitant CKD and AS require special consideration as it is known that CKD is associated with progression of AS and poor long-term outcomes. ***Aims and Objectives:*** The aim of the study was to summarize and review the current existing literature on patients with both CKD and AS regarding disease progression, dialysis methods, surgical intervention, and postoperative outcomes. ***Conclusion:*** The incidence of AS increases with age but has also been independently associated with CKD and furthermore with hemodialysis (HD). Regular dialysis with HD versus peritoneal dialysis (PD) and female gender have been associated with progression of AS. Management of AS is multidisciplinary and requires planning and interventions by the heart-kidney team to decrease the risk of further inducing kidney injury among high-risk population. Both TAVR and SAVR are effective interventions for patients with severe symptomatic AS, but TAVR has been associated with better short-term renal and cardiovascular outcomes. ***Implications for Practice:*** Special consideration must be given to patients with both CKD and AS. The choice of whether to undergo HD versus PD among patients with CKD is multifactorial, but studies have shown benefit regarding AS progression among those who undergo PD. The choice regarding AVR approach is likewise the same. TAVR has been associated with decreased complications among CKD patients, but the decision is multifactorial and requires a comprehensive discussion with the heart-kidney team as many other factors play a role in the decision including preference, prognosis, and other risk factors.

karger@karger.com
www.karger.com/crm

Correspondenec to:
Frederick Berro Rivera, frederick.berro.rivera@gmail.com

Introduction

Aortic stenosis (AS) is the most common primary valvular disease in developed countries, and its prevalence gradually increases with age, ranging from 0.2% in the 50–59 age group to 10% in the 80–89 age group [1, 2]. Studies have also shown an increase in prevalence of the entire spectrum of the disease from aortic sclerosis or asymptomatic mild thickening of the valve to severe symptomatic AS, as well as rate of progression of AS in chronic kidney disease (CKD) patients, particularly those undergoing dialysis [1, 3, 4]. When compared with patients with normal renal function, concomitant presence of AS with stage 4 CKD (i.e., an estimated glomerular filtration rate [eGFR] of 15–29 mL/min/1.73 m^2), stage 5 CKD (i.e., an eGFR of <15 mL/min/1.73 m^2), and those patients receiving maintenance dialysis results in rapid progression of AS, increased cardiac and all-cause mortality, and worse short-term and long-term outcomes after aortic valve replacement (AVR) [1, 3]. The 2020 American Heart Association (AHA)/American College of Cardiology (ACC) guideline for the management of valvular heart disease defined severe AS as having a maximum aortic velocity of ≥4 m/s, mean pressure gradient of ≥40 mm Hg, or aortic valve area of ≤1 cm^2, as shown in Table 1 [5]. Severe AS, if not addressed early on, can be fatal a few years after the onset of symptoms [2]. Studies have shown that medical treatment including statins or renin-angiotensin-aldosterone system inhibitors cannot slow the rate of progression of AS [2, 6]. Hence, AVR remains the definitive treatment for severe symptomatic AS [6]. Before the advent of transcatheter aortic valve replacement (TAVR), also known as transcatheter aortic valve implantation, in 2002, the standard treatment for severe AS was surgical aortic valve replacement (SAVR) [7]. With the development of TAVR, the choice of treatment now depends primarily on surgical risk. Various predictive risk stratification scoring systems have been developed to date. The most commonly used scoring system is the one from the Society of Thoracic Surgeons – Predicted Risk of Operative Mortality (STS-PROM) which classifies patients according to their risk of operative mortality (low risk <4%, intermediate risk 4–8%, and high risk >8%) [8]. In the 2017 AHA/ACC guideline for the management of valvular heart disease, a new subset of patients was included, namely, those at prohibitive surgical risk with the following inclusion criteria: 30-day all-cause mortality rate of >50%, multisystem organ involvement (≥3 major organ systems) that is unlikely to improve postoperatively, or the presence of anatomic factors that increase the risk of cardiac surgery [9]. For patients with severe AS and low-to-intermediate surgical risk, SAVR is recommended (class 1). For patients with high surgical risk, either SAVR or TAVR can be performed, taking into account patient-specific risks and individual preferences (class 1). On the other hand, for severe symptomatic AS with prohibitive surgical risk, TAVR is recommended (class 1) [9]. In a post hoc analysis of the landmark PARTNER (Placement of trial AoRtic TraNscathetER valves) trial by Thourani et al. in 2016 including severe symptomatic patients with high and prohibitive surgical risk who underwent TAVR, baseline renal dysfunction was found to be an independent predictor of 30-day and 1-year all-cause mortality [8]. This review aimed to provide an overview of AS in the context of CKD, including pitfalls in diagnosis, role of noninvasive studies in risk stratification, perioperative management, and preventive strategies to optimize kidney function before, during, and after AVR, with particular emphasis on short-term and long-term outcomes.

Prevalence of AS among Patients with CKD

AS progresses at a rapid and unpredictable rate in CKD [3]. A study using the Duke University Health System's Echocardiography Laboratory Database revealed higher prevalence of at least mild AS in patients with CKD compared to those without renal dysfunction (9.5% vs. 3.5%) [10]. The same study showed a higher risk of mild and moderate AS in patients undergoing hemodialysis (HD). Increased odds were also seen among females than males regardless of AS severity [10]. Patel et al. [1] analyzed echocardiographic data of more than 800 patients with CKD and AS. Out of 839 patients, 185 (22%) had mild, 355 (42%) had moderate, and 299 (36%) had severe AS [1].

Pathophysiology

Initially, AS was considered a passive disease associated with wear and tear of tissues due to aging. Later, it was discovered that it is due to active inflammatory processes influenced and accelerated by several factors. The natural course of progression of AS starts with endothelial damage due to mechanical stress, lipid penetration, and eventual accumulation in areas of inflammation. The various cells participating in the inflammatory processes will subsequently initiate fibrosis, leaflet thickening, and calcification. Shear stress from

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Table 1. Staging of AS based on valve anatomy and hemodynamics, hemodynamic and clinical consequences, caveats in the diagnosis and management of AS, and recommendations in CKD patients (adapted from [5])

Stage	Definition	Aortic valve anatomy	Aortic valve calcification	Aortic valve mobility	Aortic valve hemodynamics	Hemodynamic consequences	Clinical consequences	Caveats in the diagnosis and management of AS and recommendations in CKD patients
A	At risk of AS	Aortic valve sclerosis or bicuspid aortic valve	+	Normal	V_{max} <2 m/s	LVEF ≥ 50%	Asymptomatic	• Hypertension should be controlled according to standard guidelines (class 1), especially in CKD patients • Statin therapy is indicated for both primary and secondary prevention of atherosclerosis (class 1)
B	Progressive AS	Mild to moderate leaflet calcification with some reduction in systolic motion or rheumatic valve changes with commissural fusion	++	↓ to ↓↓	Mild AS V_{max} 2–2.9 m/s or mean ΔP <20 mm Hg Moderate AS V_{max} 3–3.9 m/s or mean ΔP 20–39 mm Hg	LVEF ≥ 50% Early LV diastolic dysfunction	Asymptomatic	• Periodic monitoring for symptom onset and hemodynamic changes in CKD patients • Hemodynamic progression leading to symptom onset occurs in almost all AS patients once V_{max} ≥2 m/s, although there is marked variability in disease progression
C: asymptomatic severe AS								
C1	Asymptomatic severe AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	+++	↓↓↓	Severe AS V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg AVA ≤1 cm^2 or AVAi ≤0.6 cm^2/m^2 Very severe AS V_{max} ≥5 m/s or mean ΔP ≥60 mm Hg	LVEF ≥ 50% LV diastolic dysfunction Mild LV hypertrophy	Asymptomatic	• CKD patients often present with discordant grading (e.g., mild to moderate AS with V_{max} and mean ΔP but severe AS with AVA) • Difficult AVA measurement in CKD patients due to extensive valvular calcification • Exercise testing with close monitoring of both BP and ECG may aid in determining severity of AS but should only be done in asymptomatic severe AS patients

Table 1 (continued)

Stage	Definition	Aortic valve anatomy	Aortic valve calcification	Aortic valve mobility	Aortic valve hemodynamics	Hemodynamic consequences	Clinical consequences	Caveats in the diagnosis and management of AS and recommendations in CKD patients
C2	Asymptomatic severe AS with LV dysfunction	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	+++	↓↓↓	V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg AVA ≤1 cm^2 or AVAi ≤0.6 cm^2/m^2	LVEF < 50%	Asymptomatic	• Periodic monitoring is warranted for all patients with asymptomatic severe AS, especially in CKD patients • AVR is indicated (class 1)
D: symptomatic severe AS								
D1	Symptomatic severe high-gradient AS	Severe leaflet calcification or congenital stenosis with severely reduced leaflet opening	++++	↓↓↓↓	V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg AVA ≤1 cm^2 or AVAi ≤0.6 cm^2/m^2 (larger if with mixed AS and AR)	LVEF may be normal or reduced LV diastolic dysfunction LV hypertrophy Pulmonary hypertension	Exertional dyspnea/poor exercise capacity (most common initial symptom) Exertional angina Syncope, presyncope, or dizziness Mid to late peaking systolic ejection murmur radiating to the right carotid artery	• Atypical symptoms in CKD patients and symptoms usually overlap with other common conditions in CKD patients • AVR is indicated (class 1)
D2	Symptomatic severe low flow/ low gradient AS with reduced LVEF	Severe leaflet calcification with severely reduced leaflet motion	++++	↓↓↓↓	AVA ≤1 cm^2 with resting V_{max} <4 m/s or mean ΔP <40 mm Hg Dobutamine stress echocardiography: AVA ≤1 cm^2 or AVAi ≤0.6 cm^2/m^2 V_{max} ≥4 m/s or mean ΔP ≥40 mm Hg MDCT: Aortic valve calcium score >1,200 AU in women or >2,000 AU in men and/or projected AVA is <1 cm^2	LVEF < 50% LV diastolic dysfunction LV hypertrophy	Heart failure symptoms Angina even at rest Syncope or presyncope Soft mid to late peaking systolic ejection murmur	• CKD patients are usually in a low-flow state but those with AVF may be in high-flow state • For CKD patients with reduced LVEF, low-flow, low-gradient AS, and discordant grading at TTE, dobutamine stress echo may be performed to confirm AS severity • If dobutamine stress echo is contraindicated or inconclusive, aortic valve calcium scoring by MDCT may be performed as an adjunct

Cardiorenal Med 2023;13:74–90
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Table 1 (continued)

Stage	Definition	Aortic valve anatomy	Aortic valve calcification	Aortic valve mobility	Aortic valve hemodynamics	Hemodynamic consequences	Clinical consequences	Caveats in the diagnosis and management of AS and recommendations in CKD patients
D3	Symptomatic severe low-gradient AS with normal LVEF or paradoxical low-flow severe AS	Severe leaflet calcification with severely reduced leaflet motion	++++	↓↓↓↓	AVA ≤1 cm^2 with V_{max} 4 m/s or mean ΔP <40 mm Hg AVAi ≤0.6 cm^2/m^2 and stroke volume index in a normotensive patient <35 mL/m^2	LVEF ≥ 50% Increased relative LV wall thickness Small LV chamber with low stroke volume Restrictive diastolic filling pattern	Heart failure symptoms Angina even at rest Syncope or presyncope Soft mid to late peaking systolic ejection murmur	• Since atrial fibrillation occurs in 20–50% of severe low-flow, low-gradient AS patients, an electrocardiogram may be performed as needed • AVR is recommended (class 1) • Patients with low-gradient AS are usually older adults with multiple comorbidities and these patients may present with symptoms consistent with AS despite not having concomitant AS (e.g., angina in CAD patients) • For patients with suspected low-flow, low-gradient severe AS but with normal LVEF, blood pressure must first be optimized before performing noninvasive studies for AS severity measurement • Caution in CKD patients maintained on diuretics since diuretics may reduce stroke volume, particularly in patients with baseline small LV chamber • AVR is recommended if the symptoms are likely due to AS severity (class 1)

AS, aortic stenosis; +, present (severity indicated by number of symbols); ↓, decreased (degree indicated by number of arrows); LV, left ventricular; LVEF, left ventricular ejection fraction; AVA, aortic valve area; AVAi, aortic valve area indexed to body surface area; AVR, aortic valve replacement; AR, aortic regurgitation; TTE, transthoracic echocardiography; MDCT, multidetector computed tomography; BP, blood pressure; AVF, arteriovenous fistula; CAD, coronary artery disease; DM, diabetes mellitus; LDL, low-density lipoprotein; V_{max}, maximum aortic velocity.

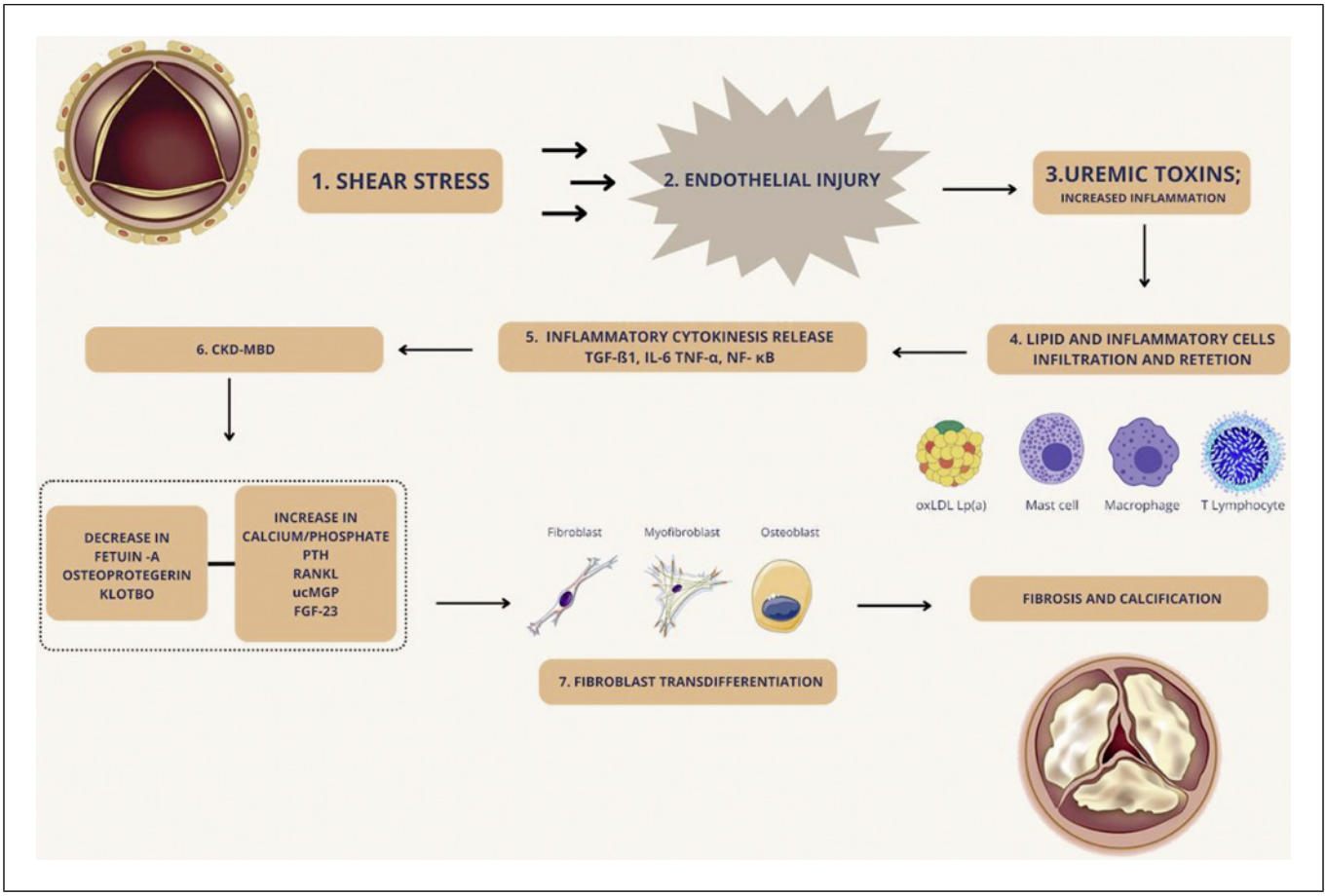

Fig. 1. Pathophysiology of the development of aortic stenosis in patients with CKD. Shear stress together with uremic toxins and mineral bone disease from CKD promote inflammation and fibroblast trans-differentiation, resulting in fibrosis and calcification of the aortic valve.

mechanical stimulation on the aortic valve may cause endothelial injury and deposition of oxidized low-density lipoprotein. These changes trigger infiltration of inflammatory cells and cytokines into the valvular tissue. The aortic valve structure is also affected by the imbalance in the expression of matrix metalloproteinases and associated substances. Eventually, there is osteoblastic differentiation in the valve interstitial cells caused by the increase in expression of bone-related proteins. Several signaling pathways have been shown to be involved in bone turnover and vascular calcification [11]. A declining kidney function creates a milieu that promotes the progression of AS [12]. The chronic inflammation and derangement in mineral metabolism in CKD enhance accelerated atherosclerosis and arteriosclerosis which eventually lead to progressive calcification [13]. Hyperphosphatemia, increased fibroblast growth factor-23, and hyperparathyroidism in patients with CKD appear to play a key role in the pro-calcification process, which includes complex interactions between a variety of promoters and inhibitors such as fetuin-A, matrix Gla protein, klotho, and osteoprotegerin [14]. Uremic toxins in CKD also promote further chronic inflammation. In AS, there is also a compensatory increase in left ventricular mass which serves to counteract the resistance to cardiac outflow by the diminished valve area (see Fig. 1).

Overlap of Symptomatology in AS and CKD: A Diagnostic Challenge

The typical history of AS is initiated by a prolonged asymptomatic period. During this period, the left ventricle gradually compensates for the increased workload brought about by the decreasing valve area. Because of this compensation and lack of any evident clinical

symptoms, the initial diagnosis of AS is typically delayed. The development of signs and symptoms such as exertional dyspnea, angina, syncope, and palpitations is an indicator of left ventricular decompensation. Symptom assessment remains challenging due to high prevalence of comorbidity [11]. With that said, dyspnea, a common symptom of AS, is also one of the most common symptoms in patients with CKD. In this population, dyspnea may be attributable to a number of potential causes such as anemia, protein-wasting energy syndrome, and pulmonary congestion [15]. In older patients with concomitant AS and CKD, symptoms are usually nonspecific due to high incidence of subclinical impairment of cardiac function [3]. In addition, subjective complaints such as dyspnea and chest pain may overlap with other conditions such as anemia, coronary artery disease, and fluid overload seen in advanced CKD, which could cloud the recognition of AS [3]. Signs such as intra-dialytic hypotension, abnormal atrial rhythms, and extreme fatigue can be a harbinger of a hemodynamically significant AS in the context of late-stage CKD [3]. In addition to the complexity of the clinical symptoms in CKD patients with AS, there are several considerations regarding common noninvasive diagnostic tests.

CKD and Acute Kidney Injury as Predictors of Adverse Outcome after TAVR

Acute kidney injury (AKI) is an important prognostic factor since it directly influences in-hospital and long-term outcomes among patients undergoing AVR. In the population-based study by Gupta et al. using the National Inpatient Sample database, they identified patients with no CKD, CKD (without chronic dialysis), or end-stage renal disease (ESRD) on long-term dialysis and examined in-hospital outcomes. They found out that AKI and AKI requiring dialysis were associated with several-fold higher risk-adjusted in-hospital mortality in patients in the no CKD and CKD groups [16]. On the other hand, CKD portends an increased risk of adverse outcomes in patients with AS who undergo TAVR. A meta-analysis in 2018 sought to determine whether advanced CKD is associated with increased mortality or greater incidence of major stroke, bleeding, and vascular complications in these patients. The analysis revealed an increased risk of short-term (in-hospital/30-day mortality) and long-term (1-year post-TAVR) mortality (hazard ratio [HR]: 1.51 and 1.56, respectively). There was no association identified, however, in low- to intermediate-risk patients [17]. This was corroborated by the recent meta-analysis by Rattawanong et al. [18] in which patients with CKD had a significantly higher risk of 30-day overall mortality (risk ratio [RR] = 1.56), long-term cardiovascular mortality (RR = 1.44), and long-term overall mortality (RR = 1.66), as well as procedural complications including pacemaker requirement (RR = 1.20) and bleeding (RR = 1.60). Table 2 provides a summary of studies including CKD patients with AS.

Predictors of mortality among patients undergoing TAVR include impaired left ventricular ejection fraction (LVEF) [19], poor functional class (NYHA class 3–4) [20], atrial fibrillation [21], and advanced CKD (CKD stage 4–5) [22, 23]. A multicenter international study group assessed the implications of baseline eGFR and dialysis therapy on the periprocedural and 1-year clinical outcomes in a large cohort of patients with severe symptomatic AS who underwent TAVR. The study identified baseline renal dysfunction as an independent predictor of morbidity and mortality. Specifically, baseline eGFR of ≤30 was associated with an increased risk of death (odds ratio = 3), bleeding (odds ratio = 5.2), and device implantation failure (HR = 2.28) [24]. The same study group published a second paper using the same population to assess the predictors of mortality in patients with TAVR distinguished by renal function. This study confirmed the results of their earlier paper, identifying advanced CKD as an independent predictor of adverse outcomes. Moreover, the study highlighted poor functional class and/or impaired LVEF in patients with advanced CKD are independently associated with an increased risk of death [25].

Gender Difference in Outcomes after TAVR among Dialysis Patients

It has been shown that more than half of women presenting for TAVR have concomitant CKD [26]. In recent years, there have been studies dedicated to exploring potential gender difference in TAVR outcomes. The baseline characteristics for men and women who received TAVR are variable, and they may experience distinct clinical outcomes at different time points post-procedure [27]. In most studies, women are likely to have less comorbidities. Male patients consistently show significantly worse baseline vascular disease and comorbidities such as hypertension, diabetes, coronary artery disease, and lower LVEF [28, 29]. In several studies, while men have been shown to have worse baseline vascular comorbidities, women tend to experience bleeding, vascular complications, and stroke more

Table 2. Summary of studies involving aortic stenosis patients with CKD

Primary author	Study population	Main inclusion criteria	Objective	Main findings
Szerlip et al. (2016)	ESRD patients	ESRD patients who underwent TAVR between December 2011 and February 2013	To examine whether TAVR is a safe and effective treatment option for aortic stenosis in patients with ESRD.	Operative mortality was 14.0% (6/43) with TF mortality 6.5% (2/31) and 33.3% (4/12) in non-TF patients. Six-month mortality was 11/43 (25.6%: 16.1% TF, 50.0% non-TF)
Codner et al.	AS patients who underwent TAVR	Patients with severe symptomatic AS who underwent TAVR from 2006 to 2015 with or without CKD	To evaluate outcomes within a large cohort of patients who underwent TAVR distinguished by renal function	All-cause mortality at 1 year was higher in patients with lower eGFR; every 10 mL/min decline in GFR leads to an increase in risk of death (35%, $p < 0.001$), cardiovascular mortality (14%, $p = 0.018$), major bleeding (35%, $p < 0.001$), and failure of transcatheter valve (16%, $p = 0.007$)
O'Hair et al.	AS patients and ESRD	Patients with senile degenerative aortic valve stenosis and ESRD requiring RRT or calculated creatinine clearance <20 mL/min but not requiring renal replacement therapy	To evaluate all-cause mortality or major stroke at 1 year and major adverse cardiovascular, cerebrovascular events of death, myocardial infarction, stroke, and reintervention	Rate of all-cause mortality or major stroke at 1 year was 30.3%; all-cause mortality was 5.3% at 30 days
Ruge et al.	TAVR patients with ESRD on HD	TAVR patients with ESRD on HD	To evaluate demographics, procedural details, clinical outcomes, mortality, and complications in TAVR patients with ESRD on HD	Estimated survival in 30 days is 83.3%, 1 year is 63.8%, 3 years is 37.3%, and 5 years is 18.9% Perioperative complications included stroke in 7.1%, major bleeding in 16.7%, and vascular complications in 7.1%
Gupta et al.	Post-TAVR patients with or without CKD	Post-TAVR patients ≥18 years old with no CKD, with CKD but not on dialysis, or ESRD patients on long-term dialysis	To assess the in-hospital outcomes among patients without CKD and with CKD including dialysis patients	Significantly higher in-hospital mortality in patients with CKD or ESRD (4.5% and 8.3%, respectively) versus no CKD (3.8%), $p < 0.001$; Higher incidence of MACE (8.3% vs. 9.0% vs. 11.8% in no CKD, with CKD, ESRD, respectively), $p < 0.001$ Higher MI incidence (2.5% vs. 2.9% vs. 3.6% in no CKD, with CKD, ESRD, respectively), $p < 0.001$
Khan et al.	ESRD patients who underwent AVR	AS patients >50 years old	To assess contemporary national trends of comorbidities, outcomes, and healthcare resource utilization in patients with AS and ESRD undergoing TAVR and SAVR	The median length of stay (13.9–6.5 days; $p < 0.001$) and cost of stay ($ 311,538.16 to $ 255,693.40; $p < 0.001$) are reduced with TAVR but remained unchanged with SAVR

Table 2 (continued)

Primary author	Study population	Main inclusion criteria	Objective	Main findings
Mentias et al.	ESRD patients who underwent AVR	ESRD-HD patients with AS	To evaluate and compare outcomes of ESRD-HD patients with AS managed with TAVR, SAVR, and conservative management	Thirty-day mortality was lower with TAVR compared with SAVR
Szerlip et al. (2019)	ESRD patients	ESRD patients with severe AS after TAVR	To determine the early and 1-year outcomes of TAVR in ESRD patients	Higher in-hospital mortality in ESRD patients (5.1% vs. 3.4%, $p < 0.01$) Higher rate of major bleeding (1.4% vs. 1.0%, $p = 0.03$) Higher 1-year mortality in dialysis patients (36.8% vs. 18.7%, $p < 0.01$)
Kawase et al.	HD and non-HD patients with severe AS with initial AVR strategy versus conservative strategy	Severe AS	Investigate the long-term outcomes of HD patients with severe AS and evaluate the effect of the initial AVR strategy relative to the conservative strategy in clinical outcomes of dialytic and nondialytic patients with severe AS	Higher 5-year incidence of all-cause mortality in HD patients versus non-HD patients (71% vs. 40%, $p < 0.001$) Among HD patients, the initial AVR group was associated with significantly lower 5-year incidence of all-cause death (60.6% vs. 75.5%, $p < 0.001$) and sudden death (10.2% vs. 31.7%, $p < 0.001$)
Samad et al.	CKD including dialysis patients and non-CKD	eGFR <60 with AS	To determine the prevalence and outcomes of aortic valve disease among patients with versus without CKD	5-year survival rates of mild, moderate, and severe AS for CKD patients are 40%, 34%, and 42%, respectively, and 69%, 54%, 67% for non-CKD patients
Thourani et al. (2016)	TAVR patients enrolled in PARTNER trial with different GFR stage	High or prohibitive surgical risk TAVR patients enrolled in PARTNER trial with severe symptomatic AS	To assess the impact of baseline renal function on 1-year clinical outcomes in TAVR patients enrolled in the PARTNER trial	Highest mean STS-PROM in those with severe RD Highest incidence of 30-day, 1-year all-cause mortality, and rehospitalization in severe RD
Nguyen et al.	TAVR and SAVR patients	TAVR and SAVR patients with GFR >60 mL/min, GFR 31–60 mL/min, or GFR 30 mL/min or less	To use GFR as measure of renal function to analyze short-, mid-, and long-term outcomes of TAVR and SAVR patients with varying extent of preoperative renal impairment	In SAVR patients, worsening preoperative renal dysfunction correlated with increased in-hospital mortality ($p = 0.004$), length of hospital stay ($p < 0.001$), and length of ICU stay ($p < 0.001$)

Table 2 (continued)

Primary author	Study population	Main inclusion criteria	Objective	Main findings
Perkovic et al.	Dialysis Patients	Dialysis patients with AS	To compare the rate of progression of aortic stenosis in dialysis patients with that in sex-matched control	More rapid progression of AS in dialysis patients in valve area (−0.19 vs. −0.7 cm^2/year; $p < 0.001$) and in peak transvalvular gradient (6.5 vs. 3.9 mm Hg/year; $p = 0.04$) There is also more rapid progression of mean transvalvular gradient (4.9 vs. 2.5 mm Hg/year; $p = 0.052$)
Kume et al.	Dialysis patients divided into 2 groups (non-calcification/no or mildly calcified aortic valve and calcification/moderate or heavily calcified aortic valve)	Dialysis patients without atrial fibrillation, moderate to severe valvular heart disease (except AS), systolic LV dysfunction (EF < 50%)	To compare the degree of aortic valve calcification and the progression of AS (progression of maximum aortic jet velocity and decrease in aortic valve area) in HD patients	More rapid rate of progression of maximum aortic jet velocity and decrease in aortic valve area in the calcification group versus non-calcification group (0.37±0.36 m/s vs. 0.17±0.29 m/s, $p = 0.027$ and 0.17±0.15 cm^2 vs. 0.04±0.07 cm^2, $p < 0.001$, respectively)
Ohara et al.	Dialytic and nondialytic CKD patients with AS	Dialytic and nondialytic CKD patients with valvular AS	To compare the rate of progression of AS, severity of aortic valve calcium deposition, and serological data between dialytic and nondialytic AS patients	Increased calcium-phosphate product in dialysis patients (49±14 mg/dL vs. 30±5 mg/dL, $p < 0.0001$) Lower peak transaortic gradient in dialysis patients (42±12 mm Hg vs. 57±22 mm Hg, $p < 0.05$) Higher rate of decrease in aortic valve area in dialysis patients (0.14±0.13 cm^2/year vs. 0.06±0.09 cm^2/year, $p < 0.05$) More severe aortic valve calcification at follow-up among dialysis patients
Wang et al.	Dialysis patients	Original observational cohort studies, ESRD patients on dialysis, studies evaluating the association between extent of CVC at baseline and cardiovascular or all-cause mortality	To investigate the association between CVC and risk of cardiovascular or all-cause mortality in dialysis patients	CVC was correlated with increased risk of cardiovascular mortality (HR 2.81, 95% CI: 1.92–4.10) and all-cause mortality (HR 1.73, 95% CI: 1.42–2.11)
Thourani et al. (2011)	ESRD patients post valve replacement	ESRD patients who underwent mechanical or bioprosthetic valve replacement	To investigate short-term and long-term outcomes in dialysis patients after cardiac valve surgery	19.9% 30-day mortality with no statistically significant difference between mechanical and bioprosthetic valve replacement; 18.1% overall 10-year survival irrespective of valve type

Table 2 (continued)

Primary author	Study population	Main inclusion criteria	Objective	Main findings
Kim et al.	ESRD patients	ESRD patients with mild to moderate AS	To investigate the progression of mild to moderate AS in ESRD patients and determine its metabolic and hemodynamic contributors and clinical outcomes	38% of ESRD patients had progression in the degree of AS versus 18% of controls ($p < 0.01$)
Thourani et al. (2015)	SAVR patients	Patients who underwent SAVR and risk-stratified by the Society of Thoracic Surgeons predicted risk of mortality (group 1, <4%; group 2, 4–8%; group 3, >8%)	To describe the outcomes of SAVR in low-risk, intermediate-risk, and high-risk patients	Lower than expected mean in-hospital mortality in all patients (2.5% vs. 2.95%)
Wongpraparut et al.	AS patients	Patients ≥40 years old with any degree of AS who had undergone ≥2 echocardiographic studies separated by minimum of 3 months	To compare the degree of AS progression with a number of clinical, biochemical, and echocardiographic variables	The presence and duration of HD, calcium supplementation, and serum creatinine correlated with rapid AS progression ($p < 0.05$, 0.05, and 0.005, respectively)
Okada et al.	AVR patients	Patients who underwent AVR between January 1996 and April 2010 at Nagoya Daini Red Cross Hospital	To clarify late clinical outcomes and discuss strategies for optimal valve selection in dialysis patients	No significant differences were observed according to the type of prosthesis between dialysis and nondialysis patients
Raggi et al.	Dialysis patients (double-blind, placebo-controlled phase 2b trial)	Patients 18–80 years old on HD for ≥6 months who had a CAC Agatston score between 100 and 3,500 at trial entry	To assess efficacy of SNF472 (intravenous myo-inositol hexaphosphate that selectively inhibits the formation and growth of hydroxyapatite) in attenuating CAC and aortic valve calcification in patients with end-stage kidney disease receiving HD in addition to standard care	SNF472 compared with placebo attenuated progression of calcium volume score in the aortic valve (14% [95% CI, 5–24] vs. 98% [95% CI, 77–123], $p < 0.001$)

ESRD, end-stage renal disease; TAVR, transcatheter aortic valve replacement; TF, transfermoral; AS, aortic stenosis; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular events; MI, myocardial infarction; SAVR, surgical aortic valve replacement; AVR, aortic valve replacement; HD, hemodialysis; CI, confidence interval; PARTNER, Placement of trial AoRtic TraNscathetER valves; MDRD, modification of diet in renal disease; NYHA, New York Heart Association; RD, renal dysfunction; ICU, intensive care unit; HR, hazard ratio; LV, left ventricular; EF, ejection fraction; AR, aortic regurgitation; CVC, cardiac valve calcification; EVOLVE, evaluation of cinacalcet therapy to lower cardiovascular events; SD, standard deviation; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Operative Mortality; CAC, coronary artery calcium.

often [28, 29]. The above findings contradict the findings from the Women's INternational Transcatheter Aortic Valve Implantation (WIN-TAVI) registry where women with advanced stage at baseline (moderate/severe CKD, stage ≥3b with eGFR <45 mL/min/1.73 m^2) were more likely to have multiple comorbidities such as hypertension, diabetes, atrial fibrillation, anemia, chronic lung disease, HD, prior percutaneous coronary intervention, and pacemaker implantation [30]. Furthermore, after multivariate adjustment, even moderate CKD was associated with a higher risk of 1-year Valve Academic Research Consortium (VARC)-2 safety

Table 3. AKI reduction strategies (Elmariah et al., 2016; Kornowski and Tang, 2021; Shroff et al., 2021)

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

AKI, acute kidney injury; TAVR, transcatheter aortic valve replacement; PCI, percutaneous coronary intervention; AS, aortic stenosis.

endpoints (HR = 1.68, 95% confidence interval [CI]: 1.10–2.60); all-cause death (HR 2.00, 95% CI: 1.03–3.90); and composite of death, myocardial infarction, stroke, or life-threatening bleeding (HR = 1.70, 95% CI: 1.04–2.76) [30].

Approach to the Perioperative Management

Management of AS in CKD patients requires an integrated, multidisciplinary team consisting of professionals with expertise in general cardiology, interventional cardiology, multimodality imaging, cardiac anesthesiology, cardiac surgery, nephrology, geriatrics, and other subspecialties as warranted, recently labeled as the "heart-kidney team." The collaboration of these healthcare professionals and shared decision-making with the patients are elements of optimal patient care and are of utmost importance in management of AS in the periprocedural period. Physicians are typically familiar with pathways for reducing AKI risk following TAVR because AKI is a well-established complication in other cardiovascular procedures such as percutaneous coronary intervention and cardiac surgery [27]. It is of paramount importance to identify patients at high risk for developing AKI and plan preoperative interventions to reduce AKI post-TAVR. Preprocedural interventions can be determined according to type of risk factor (i.e., modifiable such as volume of contrast to be used, prevention of hypotension, use of transfemoral approach and non-modifiable such as severity of peripheral arterial disease and baseline GFR) [27]. After TAVR, CKD patients should be managed carefully, avoiding any hemodynamic embarrassment that could worsen renal function (see Tables 3, 4).

Modality of Dialysis in Patients with AS

Among those with CKD, several studies showed that there is higher prevalence and faster progression of AS in patients undergoing HD compared to those undergoing peritoneal dialysis (PD) [31–33]. In a prospective study by Avila-Diaz et al., they found aortic valve calcification in less than one-third of 123 patients receiving PD therapy. This is consistent with the results of the study by Wang et al. in 2003 with 32% prevalence of AS among those receiving continuous ambulatory PD. This is lower than the reported 44–85% prevalence of AS among patients receiving HD in several studies [34–39]. As such, Candellier et al. [40] highlighted that PD is beneficial in slowing progress and symptomatology of AS in CKD patients. They proposed that this might be due to the slow continuous dialysis effect of PD, better maintenance of fluid balance, better control of serum phosphate, reduced inflammatory cytokine profile, and oxidative stress.

Table 4. Management of CKD patients after TAVR (adapted from Shroff et al.)

Avoid sustained hypotension
Judicial use of volume management
Correct electrolyte imbalances
Consider periprocedural RRT (may use SLED in setting of poor hemodynamics)
Use of anticoagulation and anti-platelet should be individualized
Appropriate threshold for blood transfusion for anemia

CKD, chronic kidney disease; TAVR, transcatheter aortic valve replacement; RRT, renal replacement therapy; SLED, sustained low-efficiency dialysis.

TAVR versus SAVR among Patients with CKD

There are only two recent studies comparing outcomes of patients with ESRD who underwent TAVR versus SAVR. Khan et al. [41], using National Inpatient Sample, determined the national trends of comorbidities, outcomes, and healthcare resource utilization among patients with AS and ESRD undergoing AVR. In that study period, the use of SAVR declined from 82.0 to 37.7%. On the contrary, there was an increased trend for TAVR from 18.0 to 62.3%; $p < 0.001$. Patients who received TAVR were older (74.6 [9.1] vs. 66.8 years [9.1]) and had a higher proportion of females (37.1 vs. 32.5%). TAVR patients, despite having higher comorbidity burden, had lower inpatient mortality and complications. The median length of stay (13.9–6.5 days; $p < 0.001$) and cost of stay ($ 311,538.16 to $ 255,693.40; $p < 0.001$) were low with TAVR but remained unchanged with SAVR. They concluded that in 12,550 ESRD patients who underwent AVR from 2012 to 2017, TAVR was associated with a lower short-term mortality rate and shorter hospital stay [41]. Similar results were reported in the study by Mentias et al. [42] when they analyzed 8,107 ESRD-HD Medicare beneficiaries who received dialysis and underwent TAVR, SAVR, and medical management only. They found that the 30-day mortality was lower with TAVR compared with SAVR (4.6% vs. 12.8%, $p < 0.01$), and after a median follow-up of 465 days on overlap propensity score weighting analysis, they found no difference in mortality between TAVR and SAVR (adjusted HR 1.02 [95% CI, 0.91–1.15], $p = 0.7$). Furthermore, mortality was lower with TAVR compared with conservative management (adjusted HR 0.53 [95% CI, 0.47–0.60], $p < 0.001$). Thus, short-term mortality is much higher with SAVR than TAVR, but there is a crossing of the curves at ~15 months in ESRD, resulting in net neutral outcomes at 2 years. They concluded that in ESRD-HD patients with AS, mortality was lower in the short-term with TAVR compared with SAVR but comparable in the mid-term. Finally, AVR is associated with an improvement in survival and reduction in heart failure hospitalizations compared with conservative management [42]. These findings were supported by the study by Pineda et al. [43] where they analyzed the impact of baseline CKD among patients who underwent TAVR from the CoreValve US Pivotal High Risk Trial. They found out that among high-risk patients with moderate to severe CKD, TAVR offered a lower 3-year major adverse cardiovascular and renal events rate compared with SAVR (42.1% vs. 51.0, $p = 0.04$) [43]. Structural valve degeneration is also a main issue among CKD patients. In the landmark study by Garcia et al. [44] wherein they assessed the 5-year cardiovascular, renal, and bioprosthetic valve durability among AS patients with CKD who underwent AVR, they found that SAVR cohort had the lowest rates of bioprosthetic valve failure (BVF) (0.8%) and structural valve degeneration-related BVF (0.3%). Furthermore, they found out that the third-generation SAPIEN 3 valve had comparable rates of BVF (2.4%; $p = 0.10$) and SVD-related BVF (0.0%; $p = 0.99$), whereas the second-generation SAPIEN XT valve had significantly higher rates of BVF (4.0%; $p = 0.02$) and numerically higher rates of SVD-related BVF (2.1%; $p = 0.10$) compared with SAVR. Hence, for patients who will undergo SAVR, careful selection of valve (bioprosthetic or mechanical) should be done, taking into account the patient's clinical status, overall prognosis, and potential need for reintervention with bioprosthetic valves versus the risks for lifelong anticoagulation with mechanical valves [44]. Finally, it should be emphasized that there are no RCTs in advanced CKD. These observational data have the potential for unmeasured confounders and selection bias, making it very difficult to recommend one approach versus another in this complex patient population based on associations. Taking all

Table 5. Summary of key findings from this review

Patients with CKD undergoing HD are at an increased risk of developing mild and moderate AS and is thought to occur due to chronic inflammation associated with CKD
All other factors adjusted, CKD is independently associated with higher overall risk in regard to short-term (30-day mortality), long-term (1- and 5-year mortality), and post-procedural complications (bleeding and requiring a pacemaker)
Among CKD patients with ESRD requiring dialysis, peritoneal dialysis has been shown to delay the progression of aortic stenosis. This is thought to occur due to the continuous dialyzing effect of PD along with a marked reduction in the inflammatory cytokines and oxidative stress
Although TAVR is associated with a lower rate of major adverse cardiovascular and renal events among patients with CKD undergoing surgery, other factors like age, functional status, and prognosis should also be considered. The approach on AVR should be individualized and should be handled by the heart-kidney team

CKD, chronic kidney disease; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; AS, aortic stenosis; ESRD, end-stage renal disease; AVR, aortic valve replacement.

Table 6. Knowledge gaps

Representation of CKD patients in randomized controlled trials
Lack of evidence from randomized trials regarding choice of mechanical versus bioprosthetic SAVR
Criteria for selection of asymptomatic CKD patients with severe aortic stenosis who would possibly benefit from early SAVR or TAVR
Criteria for choosing between TAVR and SAVR in eligible high-risk patients
Guidance on how to choose between various types of prosthesis among patients with advanced kidney disease
TAVR absolute and relative contraindications
Progression of AS in patients undergoing HD versus peritoneal dialysis
Surveillance of patients with asymptomatic AS with concomitant CKD G4/5/5D
Dose adjustment of anti-platelet/anticoagulant after TAVR in dialysis patients

CKD, chronic kidney disease; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; AS, aortic stenosis.

these into consideration, the working group of American Heart Association recommends a multidisciplinary approach comprising the heart-kidney team in determining what appropriate valve to use, whether TAVR or SAVR, involve patient and patient's family in decision-making, and considering the predictors of poor outcomes [3].

Prognosis

Several studies have concluded that the presence of baseline renal dysfunction in patients with severe AS is associated with poor prognosis and adverse short-term and long-term outcomes compared to those with normal baseline renal function, regardless of the choice of AVR procedure [1, 10, 45]. The retrospective cohort study by Bohbot et al. involving 4,119 patients with severe AS subclassified into 4 groups depending on their baseline eGFR level (no CKD – eGFR ≥60 mL/min/1.73 m^2; mild CKD – eGFR 45–59 mL/min/1.73 m^2; moderate CKD – eGFR 30–44 mL/min/1.73 m^2; and severe CKD – eGFR <30 mL/min/1.73 m^2) is the first to evaluate the effect of early AVR performed within the first 3 months on cardiac and all-cause mortality versus conservative treatment across the different CKD stages [46]. Their study revealed that the 5-year survival rate among severe AS patients correlates inversely with the severity of renal dysfunction (71%, 62%, 54%, and 34% among patients with no, mild, moderate, and severe CKD, respectively) and that early AVR leads to a significant reduction in 5-year cardiac and all-cause mortality across all stages of CKD, including dialysis patients, compared to conservative treatment [46]. In a post hoc analysis of the PARTNER trial by Cubeddu et al. [47] assessing the impact of TAVR on severity of renal dysfunction, several factors affecting the eGFR level within 7 days following TAVR were identified. Factors associated with improved outcomes with a higher eGFR include higher pre-procedural eGFR and baseline hemoglobin and platelet counts, as well as transfemoral TAVR approach. Meanwhile, factors associated with lower eGFR include higher body mass index, major bleeding episodes during hospital stay, presence of comorbidities such as diabetes, left ventricular hypertrophy, and history of prior myocardial infarction. They found that

following TAVR, the CKD stage either remained unchanged or showed improvement in 89% of patients.

Conclusion

There are special considerations for patients with both CKD and AS. CKD not only increases the risk of developing mild-moderate AS and its progression but is also associated with worse short- and long-term outcomes. Multiple studies highlighted the disparity between gender regarding the presence of comorbidities and poor outcomes, but the presence of conflicting results suggests that further research is needed to clarify this relationship. Although TAVR is associated with less short-term adverse cardiovascular and renal outcomes, long-term benefits and survival among CKD patients should be further elucidated as multiple studies have shown improved 5-year survival rates among those who undergo SAVR versus TAVR. As such, the presence of CKD should not be the only consideration in deciding course of treatment for patients requiring surgical intervention. The negative effect of CKD among patients with AS is clear. Hence, in the CKD population, it needs to be emphasized that the 2-year mortality is about 50% regardless of the modality of AVR. This highlights the high background risk of mortality and the need to bring up the notion of futility in decision-making among this group of patients (see Tables 5, 6).

Statement of Ethics

Ethics approval for this study was not required.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest relevant to the content of this manuscript.

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Author Contributions

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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