Chronic kidney disease and valvular heart disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference

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Chronic kidney disease (CKD) is a major risk factor for valvular heart disease (VHD). Mitral annular and aortic valve calcifications are highly prevalent in CKD patients and commonly lead to valvular stenosis and regurgitation, as well as complications including conduction system abnormalities and endocarditis. VHD, especially mitral regurgitation and aortic stenosis, is associated with significantly reduced survival among CKD patients. Knowledge related to VHD in the general population is not always applicable to CKD patients because the pathophysiology may be different, and CKD patients have a high prevalence of comorbid conditions and elevated risk for periprocedural complications and mortality. This Kidney Disease: Improving Global Outcomes (KDIGO) review of CKD and VHD seeks to improve understanding of the epidemiology, pathophysiology, diagnosis, and treatment of VHD in CKD by summarizing knowledge gaps, areas of controversy, and priorities for research.

Valvular heart disease (VHD) is highly prevalent in patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD). This association with VHD is prognostically important, being associated with poor outcomes and higher mortality.[1] The 5-year mortality rate among patients with at least mild aortic stenosis or mitral regurgitation is more than 50% greater than in persons without CKD.[1]

Epidemiology

CKD. The first detectable stage of VHD involvement in CKD is calcification. The prevalence of aortic valve (AV) calcific abnormalities ranges from 28% to 85%.[2] This prevalence is significantly higher than in the general population, where calcific aortic sclerosis is observed in about 25% of people ≥65 years and severe aortic stenosis (AS) is found in about 3% of persons ≥75 years.[3] AV calcification increases as estimated glomerular filtration rate (eGFR) decreases.[4,5]

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The conference agenda, discussion questions, and plenary session presentations are available on the KDIGO website: https://kdigo.org/conferences/controversies-conference-on-coronary-artery-valvular-disease/.

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Administrative data from the US Renal Data System in 2017 showed that the prevalence of VHD diagnoses was 14% among patients with CKD compared with 7% in the Medicare survey of patients aged >65 years.[6] More specifically, functional evidence of aortic stenosis (as opposed to aortic calcification) was present in 9.5% of patients with CKD, compared with 3.5% of the general population (Figure 1[1]), with similar patterns for mitral regurgitation (43% vs. 24%), mitral stenosis (2% vs. 1%), and aortic regurgitation (19% vs. 10%).[1] Even when taking account of age, year of echocardiogram, race, sex, history of hyperlipidemia, hypertension, congestive heart failure, diabetes mellitus, and prior coronary revascularization, patients with CKD had a 1.2- to 1.3-fold increased odds of aortic stenosis and 1.3- to 1.8-fold odds of mitral regurgitation.[1] The prevalence increased in parallel with the progression to more advanced kidney disease (Figure 2).[1] In particular, aortic stenosis progressed more rapidly among CKD patients; the decline in AV area was estimated to progress at ∼0.2 cm^2 per year in patients with CKD, compared with ∼0.1 cm^2 per year among patients without CKD.[7] The 2-year survival of patients with CKD who had valvular disease was 72% compared with 86% in the general population. Mortality was highest among patients who had more advanced CKD, with a 2-year survival of 62% in persons with CKD G4 and G5.

ESKD. The prevalence of diagnosed VHD in the United States was found to be 14% in patients receiving hemodialysis (HD), 12% in patients receiving peritoneal dialysis, and 7.4% after renal transplantation.[6] Further, the 2-year survival of patients with VHD and ESKD was >30% lower compared

with persons without these conditions. Importantly, even in the absence of significant valvular dysfunction, the echocardiographic identification of valvular calcification in 35% to 40% of patients with ESKD (Figure 3)[8,9] was independently associated with adverse cardiovascular outcomes.[10]

Aortic stenosis is the most prevalent valvular problem among patients with ESKD. Its *prevalence* was found to be 6% to 13%,[2] and patients with ESKD had accelerated progression of this problem.[11] Aging and exposure duration of dialysis predict the prevalence of AV disease in most studies, with an association with increased calcium and phosphate levels rather than lipid disorders.[12] A change in AV area of –0.19 cm^2/year has been reported among patients undergoing HD (compared with –0.07 cm^2/year among control subjects),[7] and in the Action in Diabetes and Vascular disease: PreterAx and DiamicroN Controlled Evaluation (ADVANCE) trial, aortic calcification increased by 52% and mitral calcification increased by 54% over a span of 1 year among HD patients with secondary hyperparathyroidism who had calcification at baseline.[13] Over a 7-year follow-up of 110 patients undergoing HD, the annual *incidence* of aortic stenosis was 3%.[14] Significant predictors for development of aortic stenosis were older age, higher phosphate levels and calcium-phosphorus product, and vitamin D levels.

Pathophysiology
There are important analogies between the development of valvular and vascular disease in CKD. Even after adjustment for age, dialysis duration, diabetes, and calcium-phosphate product, mechanical and shear stress are important
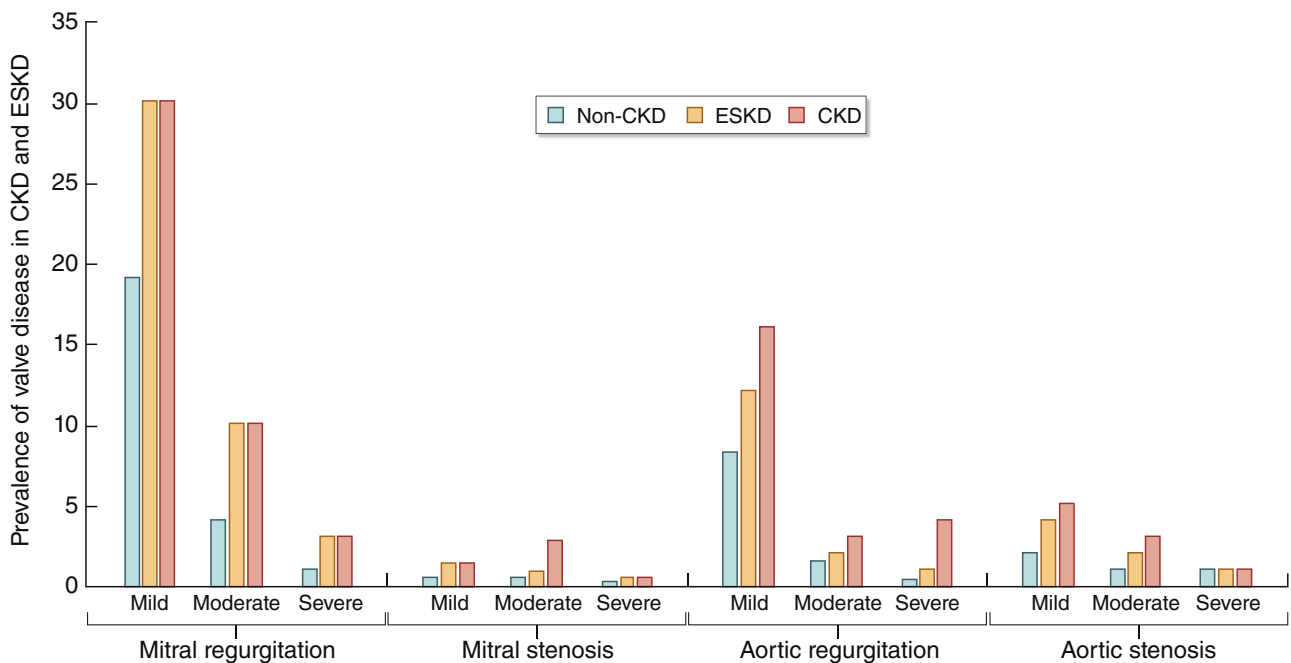

Figure 1 | Prevalence of left-sided valvular heart disease in patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) compared with the general population.[1]
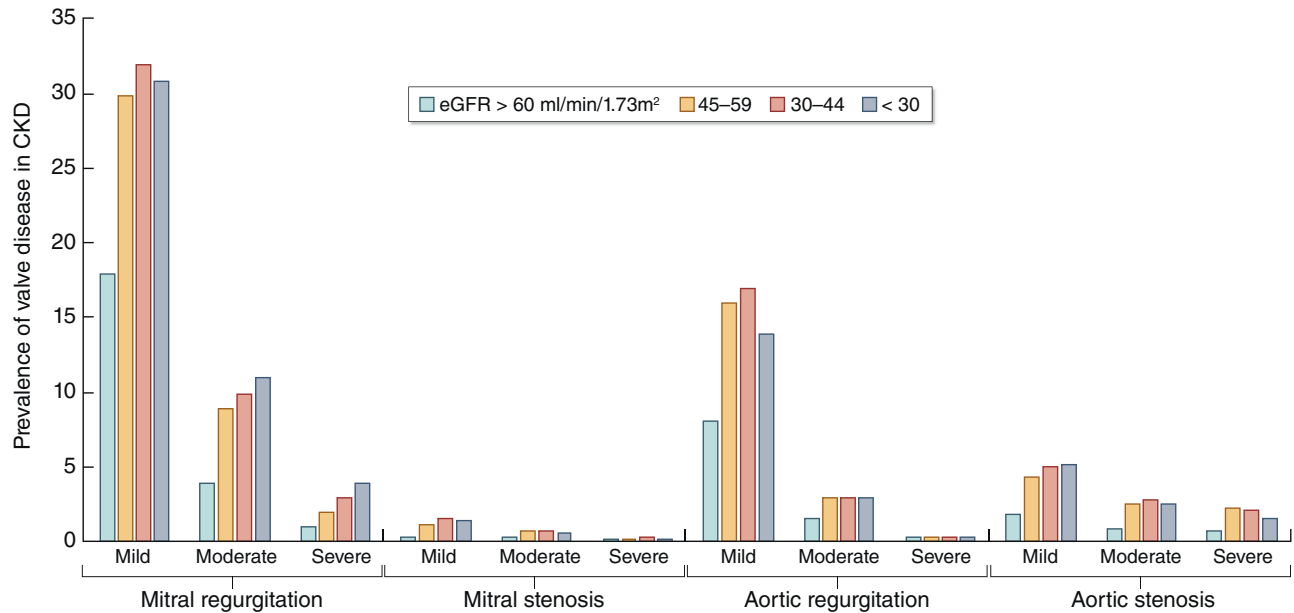
Figure 2 | Prevalence of left-sided valvular heart disease in patients with chronic kidney disease (CKD) of increasing severity. eGFR, estimated glomerular filtration rate. Adapted from Samad Z, Sivak JA, Phelan M, et al. Prevalence and outcomes of left-sided valvular heart disease associated with chronic kidney disease. *J Am Heart Assoc.* 2017;6(10): pii: e006044.[1] Copyright © 2017 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley.

correlates of valve calcification,[15] as are inflammation (assessed by C-reactive protein) and malnutrition (based on serum albumin).[16]

Metabolic milieu. Calcification of the interstitial cells of the valve leaflets (and the annulus and subvalvular apparatus of the mitral valve) are the unifying pathophysiological features of valvular stenosis and/or insufficiency secondary to CKD and ESKD. The contributors to valve calcification in CKD are numerous and complex (Figure 4[15]). Although multiple contributors (hyperphosphatemia, calcium-phosphate product, parathyroid hormone, and β2-microglobulin) have been identified, the exact contribution of each component and their synergy remains to be understood. Abnormal calcium and phosphate metabolism likely predispose to the development of valvular calcification in these patients.[12] Low vitamin D levels are associated with vascular calcification,[17] and in elderly patients with aortic stenosis, renal insufficiency, and low vitamin D levels, aortic stenosis progression has been associated with secondary hyperparathyroidism.[18] Excessive vitamin D supplementation is also associated with valve calcification in animal models,[19] although epidemiologic data in humans have focused more on the association with vascular calcification. Warfarin use is associated with calcification of the valves,[20] peripheral vasculature,[21] and coronaries,[22] and patients treated with warfarin who are undergoing HD are prone to vertebral fractures and mortality.[23] Possibly as a consequence, warfarin use is associated with increased mortality in persons with ESKD.[24] Amyloid protein deposition in calcific AVs could be a contributing factor.[25] The available literature mostly pertains to high-income regions, where degenerative calcification

predominates; data are more sparse from regions where rheumatic heart disease is common. Furthermore, congenitally abnormal valves, such as a bicuspid AV, can progress to calcification and stenosis at a faster rate. Valve and aortic calcification often co-exist and may occur at a young age, being present in about a third of young (19- to 39-year-old) patients with childhood-onset kidney disease who required dialysis or kidney transplantation, often in association with coronary artery calcification.[26] Among patients undergoing long-term dialysis, the number of calcified valves was associated with all-cause mortality and cardiovascular death; 1-year all-cause mortality was 57% with calcification of both aortic and mitral valves, 40% with either valve calcified, and 15% for persons in whom neither was valve calcified (Figure 5).[27]

Hemodynamic milieu. Whereas increased shear stress has been associated with the initiation and progression of aortic stenosis, the specific role of arteriovenous fistulae in the progression of valve leaflet damage is unclear. However, fistula flow may have other effects. The presence of a volume load contributes to cardiac chamber enlargement, which may worsen mitral and tricuspid valve regurgitation. Second, the additional load of fistula creation can lead to cardiac decompensation.[28]

Mitral regurgitation has many potential causes in persons with CKD and ESKD, but a critical distinction is between functional (potentially reversible) and degenerative dysfunction. Mitral valve regurgitation in patients undergoing HD may be partly or completely functional as a result of dilatation of the left atrium and mitral annulus, both of which can be related to volume overload.[29]
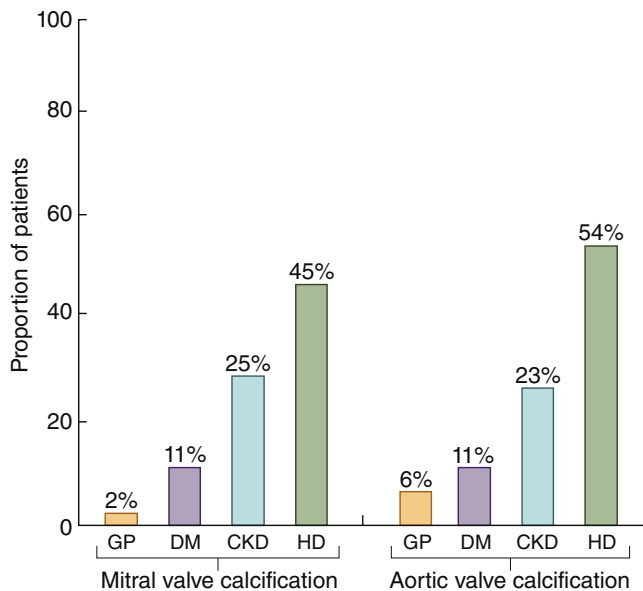
Figure 3 | Prevalence of valvular calcification in the general population and in patients with kidney disease.[8,9] CKD, chronic kidney disease; DM, diabetes mellitus; GP, general population; HD, hemodialysis.

Whereas the most common sites of valvular involvement are left-sided, right-sided valvular dysfunction, in particular tricuspid regurgitation, may be equally common, and its severity may significantly vary, depending on the patient's volume status. Right-sided valve disease can be associated with progression/deterioration of kidney disease, as well as risk for right-sided endocarditis.

Clinical assessment

Preclinical valve disease. VHD guidelines recognize that symptomatic valve disease is preceded by a potentially long preclinical phase, during which the patient is unaware of symptoms.[30] This phase may be compounded by inactivity in CKD. In addition, arteriovenous fistula may contribute to the challenges of assessing severity of VHD in patients undergoing HD.[31]

Echocardiographic screening is widely used for the early detection of VHD in persons with CKD. Use of this screening is often based on the rationale that knowledge of the presence and severity of valvular disease, left ventricular (LV) dysfunction, and LV hypertrophy (LVH), along with the estimation of pulmonary pressure, may all influence noncardiac aspects of care, including dialysis management or transplant candidacy. Annual surveillance has been suggested for persons with moderate VHD.

The application of screening findings to valve management is more problematic. No medical intervention has been shown to alter progression or outcomes of VHD. Nonetheless, valve interventions may be considered in the absence of symptoms when severe regurgitant lesions, or very severe aortic stenosis (i.e., peak AV jet velocity >5.5 m/sec) or rapidly progressive aortic stenosis (>0.3 m/s per year) are identified from testing triggered by physical examination

findings, or even when found coincidentally. It has been proposed that patients with ESKD who have moderate aortic stenosis are equivalent to "rapid progressors" who warrant a yearly echocardiogram and monitoring for early symptoms.[32]

Symptomatic valve disease. The effects of CKD and ESKD on the circulation can significantly confound the evaluation of VHD. Symptoms such as muscle weakness and fatigue may be attributed to anemia and frailty. Dyspnea may be attributed to pulmonary congestion due to fluid overload. A high-output state may be present as a result of anemia and magnified by the presence of an arteriovenous fistula. Systolic murmurs resulting from increased stroke volume, clinical evidence of LVH and fluid overload, and disturbances of vascular function all may increase suspicion of valvular disease but also may compromise its detection and the assessment of its severity. Even after LVH or elevated biomarkers are identified on the basis of an electrocardiogram or simple laboratory testing, dyspnea may be attributed to heart failure with preserved ejection fraction. Accordingly, imaging evaluation is essential; the first clinical imaging assessment for VHD is transthoracic echocardiography, which should be readily accessible to clinicians involved in the care of these patients.

Valvular regurgitation. Mitral and tricuspid regurgitation are often functional and potentially reversible—worsened by uncontrolled blood pressure and/or intravascular volume expansion, both of which occur in persons with advanced CKD and during the HD cycle. Echocardiography is best attempted on a postdialysis day with the patient at "dry weight" and with better blood pressure control. Although it seems intuitive that this would ensure more accurate determination of LV mass and systolic and diastolic function by minimizing variability in the severity of filling pressures, pulmonary pressures, and valvular regurgitation, specific evidence for this supposition is weak.[33] Furthermore, no evidence exists regarding whether, in patients undergoing HD, adjustment and estimation of dry weight using a combination of echocardiographic and biomarkers could lead to improvement in valvular regurgitation severity and symptoms.

Aortic stenosis. The assessment of aortic stenosis severity requires consideration of both the AV and left ventricle, but it is also important to remember that afterload is dependent not only on the valve but also on blood pressure. Classically, severe aortic stenosis is characterized by an AV area ≤ 1.0 cm^2 and mean AV gradient ≥ 40 mm Hg,[34] but these observations may be discordant (Figure 6).[35] Inconsistent severe aortic stenosis grading by AV area (≤ 1 cm^2) with mean gradient ≤ 40 mm Hg and maximum velocity ≤ 4 m/sec can be seen in up to 30% patients with preserved left ventricular ejection fraction, and for a left ventricle with normal function, the generation of a mean gradient of >40 mm Hg requires a valve area closer to 0.8 cm.[2,35] Discordance as a result of technical factors may be particularly problematic in persons with CKD and ESKD; body habitus not only can compromise image quality but also make parallel alignment of the Doppler beam and aortic stenosis jet more challenging than usual. Hypertension is a common comorbidity and can increase the
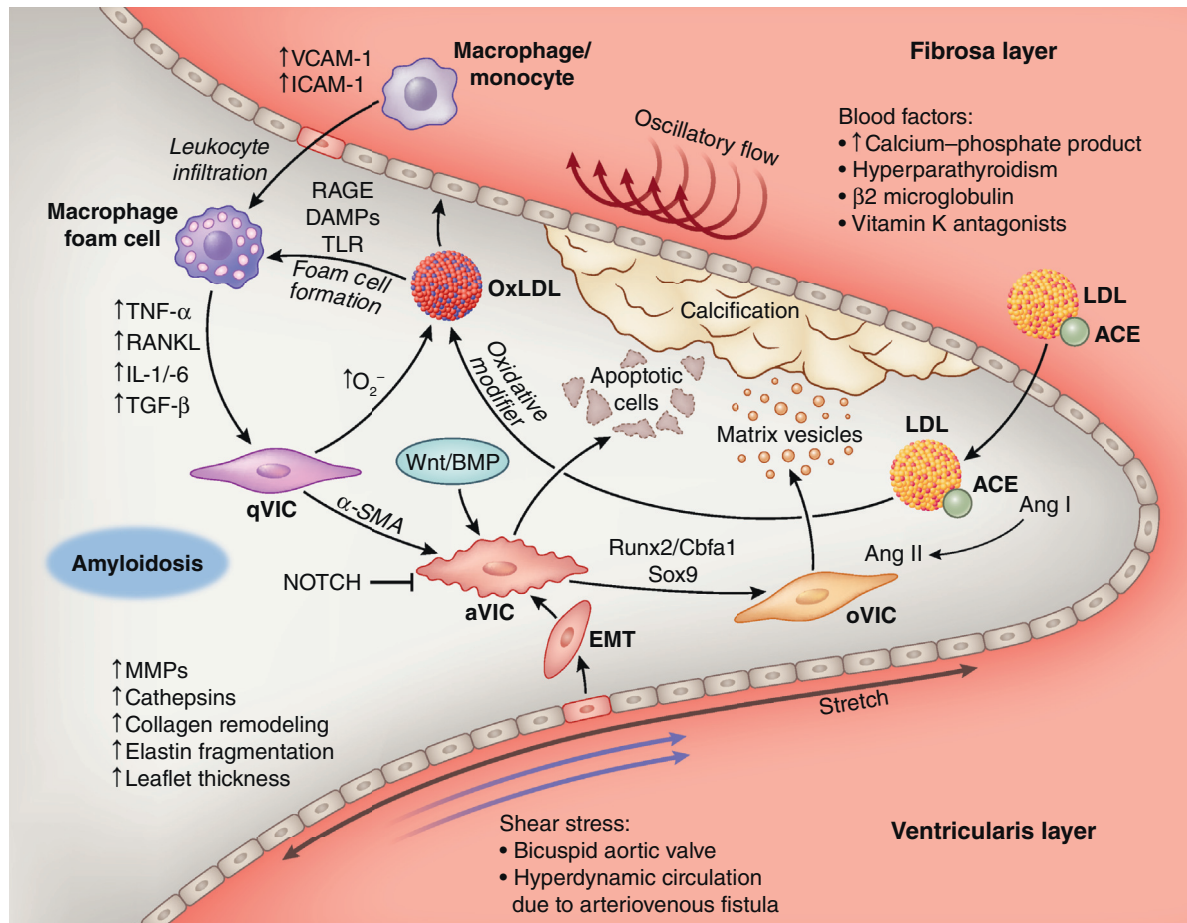
Figure 4 | Molecular, cellular, and biomechanical mechanisms of calcified aortic valve disease. In addition to generic factors related to valve calcification (shear stress, inflammation, adhesion molecules, and lipids), chronic kidney disease (CKD)–specific factors are suspected. ACE, angiotensin-converting enzyme; Ang I/II, angiotensin I/II; aVIC, activated valve interstitial cell; BMP, bone morphogenetic protein; DAMPs, damage-associated molecular patterns; EMT, endothelial-to-mesenchymal transition; ICAM-1, intracellular adhesion molecule-1; IL-1/-6, interleukin-1/-6; LDL, low-density lipoprotein; MMPs, matrix metalloproteinases; oVIC, osteogenic valve interstitial cell; OxLDL, oxidized low-density lipoprotein; qVIC, quiescent valve interstitial cell; RAGE, receptor for advanced glycation endproducts; RANKL, receptor activator of nuclear factor-κB ligand; Runx2, runt-related transcription factor 2; α-SMA, alpha smooth muscle actin; TGF-β, transforming growth factor-β; TLR, toll-like receptor; TNF-α, tumor necrosis factor-α; VCAM-1, vascular adhesion molecule-1. Adapted with permission from Yutzey KE, Demer LL, Body SC, et al. Calcific aortic valve disease: a consensus summary from the Alliance of Investigators on Calcific Aortic Valve Disease. *Arterioscler Thromb Vasc Biol.* 2014;34:2387–2393.[15] Copyright © 2014 American Heart Association, Inc. Available at: https://www.ahajournals.org/journal/atvb.

complexity of aortic stenosis assessment. Calculation of the valve area is based on the continuity equation (based on the assumption that flow through the outflow tract and AV are equal), and this is subject to error when septal hypertrophy invalidates the assumption that the LV outflow tract is circular. Because all stenotic indices, including gradients, are flow dependent, the transvalvular gradient may overestimate AV area and underestimate stenosis severity in the presence of a high-flow state, such as in a patient with arteriovenous fistula. Temporary arteriovenous fistula compression might be required to decrease transvalvular flow and to better evaluate aortic stenosis severity.[36]

Patients with significant aortic stenosis and reduced stroke volume typically have low gradient (i.e., <40 mm Hg). This is a heterogeneous group (Table 1),[37] and it is important to correctly classify whether the problem is

the ventricle, the AV, or a combination of both. When reduced stroke volume is due to low ejection fraction, this is known as "classical" low-flow low-gradient stenosis (Figure 7). The response to low-dose dobutamine stress can help elucidate whether the primary problem is aortic stenosis (reduction of valve area remains severe and gradient increases in parallel to stroke volume) or "pseudostenosis" (increasing stroke volume produces increased valve area and no increment of gradient). Moreover, the presence of LV contractile reserve suggests potential improvement of LV systolic function after surgical aortic valve replacement (AVR). Nonetheless, this may be less relevant in the transcatheter AVR (TAVR) era; in the True or Pseudo-Severe Aortic Stenosis (TOPAS)–TAVR registry, contractile reserve status did not predict outcomes and/or LV ejection fraction recovery after TAVR.[38]
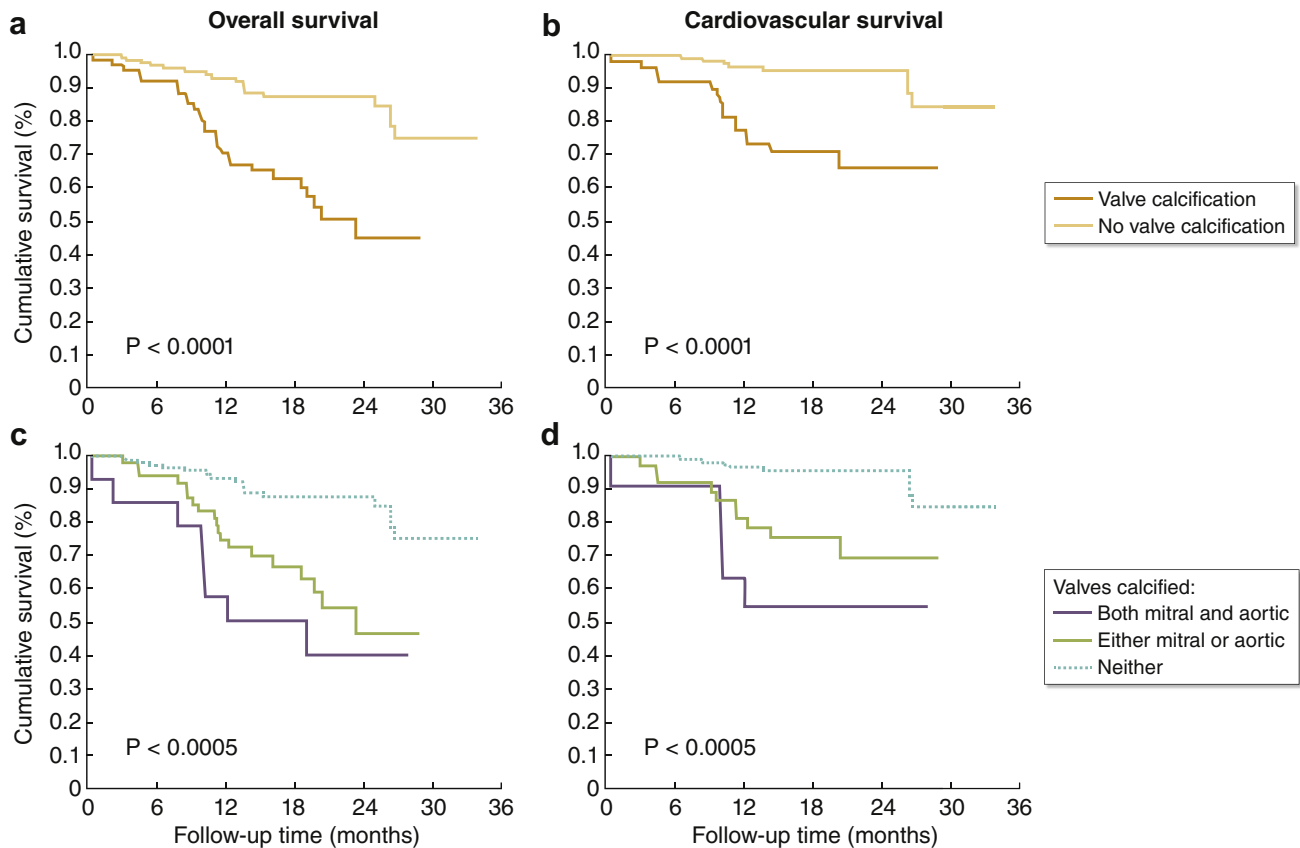
Figure 5 | Prognostic significance of valvular calcification in end-stage kidney disease. Both the presence and the extent of calcification are associated with overall (**a,c**) and cardiovascular outcome (**b,d**). Republished with permission of the American Society of Nephrology from the *Journal of the American Society of Nephrology*. Cardiac valve calcification as an important predictor for all-cause mortality and cardiovascular mortality in long-term peritoneal dialysis patients: a prospective study. Wang AY, Wang M, Woo J, et al. *J Am Soc Nephrol*. 2003;14:159–168.[27] Copyright © 2002. Permission conveyed through Copyright Clearance Center, Inc.

The flow dependence of the valve gradient also underlies "paradoxical" low-flow low-gradient stenosis, i.e., the mismatch between reduced valve area and a low gradient in the setting of a normal ejection fraction and reduced stroke volume (Figure 7).[39] This entity characteristically involves elderly persons and may be considered as a combination of aortic stenosis with heart failure with preserved ejection fraction.

Among patients with poor visualization of the AV, high cardiac output, and/or discrepancies between AV area and gradients, 3 other pieces of evidence may be of value. The first is the dimensionless severity index—a ratio between the proximal (LV outflow tract) and the distal (AV) velocities to cancel out the potential high-flow state. A dimensionless severity index of <0.25 (i.e., a 4-fold acceleration in velocity) implies severe aortic stenosis. The dimensionless severity index is not only more reproducible than AV area[40] but also less variable,[41] and importantly is linked with outcomes.[42] The second piece of evidence is direct evaluation of valve structure and function with transthoracic echocardiography, transesophageal echocardiography for left-sided valves, or retrospectively gated computed tomography angiography. The third piece of evidence is the use of a flow-independent metric

for severe aortic stenosis, based on AV calcification from noncontrast gated chest computed tomography. The cutoff AV calcium score for severe aortic stenosis (≥2000 Agatston units in men and ≥1200 in women) identifies severe aortic stenosis with an area under the curve ≥0.89, sensitivity ≥86%, and specificity ≥79%.[43] Sex-specific cutoffs (>2000 Agatston units in men and >1300 in women)[43] recently were shown to be more closely associated with outcomes than echocardiographic parameters of aortic stenosis severity in a large multicenter registry.[44] Furthermore, the additional information obtained from a computed tomography study (severity of calcification of the valves, aortic annulus, aorta, mitral annulus, and coronary vessels) is important for procedural planning and for the assessment of other potential complications that can arise from valve interventions.

Mitral annular calcification. Similar to aortic stenosis and aortic calcification, mitral annular calcification (MAC) shares biological links with atherosclerosis and is very common in patients with CKD[45,46] and aortic stenosis. MAC is particularly prevalent and extensive in patients undergoing HD. MAC progression appears to be more closely associated with the extent of baseline MAC and its inflammatory component,
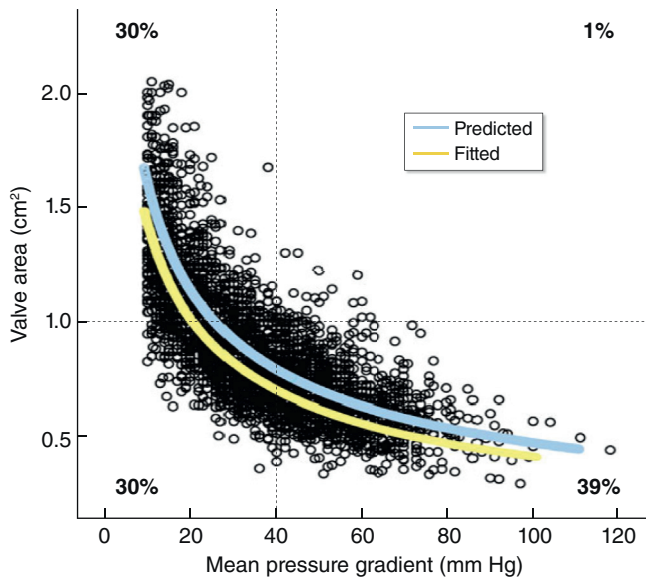
Figure 6 | Discordance of gradient and valve area in aortic stenosis. Reprinted with permission from Minners J, Allgeier M, Gohlke-Baerwolf C, et al. Inconsistencies of echocardiographic criteria for the grading of aortic valve stenosis. *European Heart Journal.* 2008;29:1043–1048, by permission of the European Society of Cardiology. All rights reserved. Copyright © The Author 2007.[35]

Table 1 | Contributors to low aortic valve gradients in aortic stenosis

Reduced forward stroke volume	LV abnormalities	• Concentric remodelling (LVH, cardiac amyloidosis) • Reduced diastolic filling
	Rhythm	• Atrial fibrillation
	Reduced transmitral flow	• RV dysfunction • Tricuspid regurgitation • Mitral stenosis
	Mitral regurgitation	
Reduced transvalvular flow rate	Increased ejection time Paced rhythm	

LV, left ventricular; LVH, left ventricular hypertrophy; RV, right ventricular.

assessed by ^{18}F-fluorodeoxyglucose activity, than with eGFR.[47] The presence of MAC has been associated with mitral regurgitation, stenosis, or mixed valvular disease. In addition, MAC is associated with greater cardiovascular risk, and higher risk for endocarditis, and atrial arrhythmias. Mitral interventions (either surgical or transcatheter therapies) remain challenging with high morbidity and mortality in the presence of MAC.[48]

Management

Prevention. Valvular calcification is an important contributor to VHD among patients with CKD and ESKD, particularly among patients with rapidly progressive aortic stenosis.

Delaying the onset of valvular calcification may be a means of delaying the development or progression of VHD. Unfortunately, there is a dearth of high-quality evidence of benefit from this strategy in randomized trials. The Action in Diabetes and Vascular disease: PreterAx and DiamicroN Controlled Evaluation (ADVANCE) study tested the use of a calcimimetic drug (cinacalcet, Amgen, Thousand Oaks, CA) in patients with ESKD. The study reported significant retardation of the progression of valvular calcification among patients randomized to calcimimetic therapy and low-dose vitamin D supplementation.[13] Cinacalcet also may retard progression of LVH in this population.[49] Whether there could be a beneficial and protective effect of cinacalcet on the progression of aortic stenosis and hypertrophic response is unknown. The use of cinacalcet at least merits consideration for the treatment of patients with secondary hyperparathyroidism and

rapidly progressive aortic stenosis and consideration for a specific clinical trial.

Despite the analogies between vascular and valvular injury, statin therapy has been ineffective in preventing the progression of aortic stenosis in the general population in 2 landmark trials.[50,51] Nonetheless, there may be a difference in the effect of low-density lipoprotein cholesterol control between AV sclerosis and stenosis, implying the intervention was too late. Alternatively, the type of intervention may have been inappropriate; the ongoing Study Investigating the Effect of Drugs Used to Treat Osteoporosis on the Progression of Calcific Aortic Stenosis (SALTIRE-2) trial ($n = 150$) is randomizing patients with aortic stenosis to alendronate versus denosumab (NCT02132026).

Medical management. Medical therapy options for the management of symptomatic valve disease are limited. Control of volume status with diuretics and hemofiltration may control congestive symptoms in the setting of regurgitant valve lesions and reduce functional regurgitation by allowing reverse remodeling. For patients undergoing HD, echocardiography could improve the estimation and adjustment of dry body weight, preventing the progression of chamber dilation and LV hypertrophy.[52] Whether this could also improve the severity of valvular regurgitation remains to be seen. Based on modest evidence in the general population, vasodilators are used to unload the left ventricle in the presence of aortic regurgitation or functional mitral regurgitation, although their use with primary mitral regurgitation is controversial.[53] Among patients undergoing HD in the setting of significant aortic stenosis, large volume removal over a short period and rapid changes in blood pressure should be avoided.

General considerations of surgical management. Valvular interventions are commonly considered in CKD, and knowledge of the specific challenges should inform access to nephrology expertise at cardiothoracic centers. Nonetheless, among patients with CKD and ESKD, evidence about whether, when, or how to intervene remains limited. Most data are derived from retrospective registry analyses,[54] and comparisons have been performed with propensity score matching. Relevant considerations
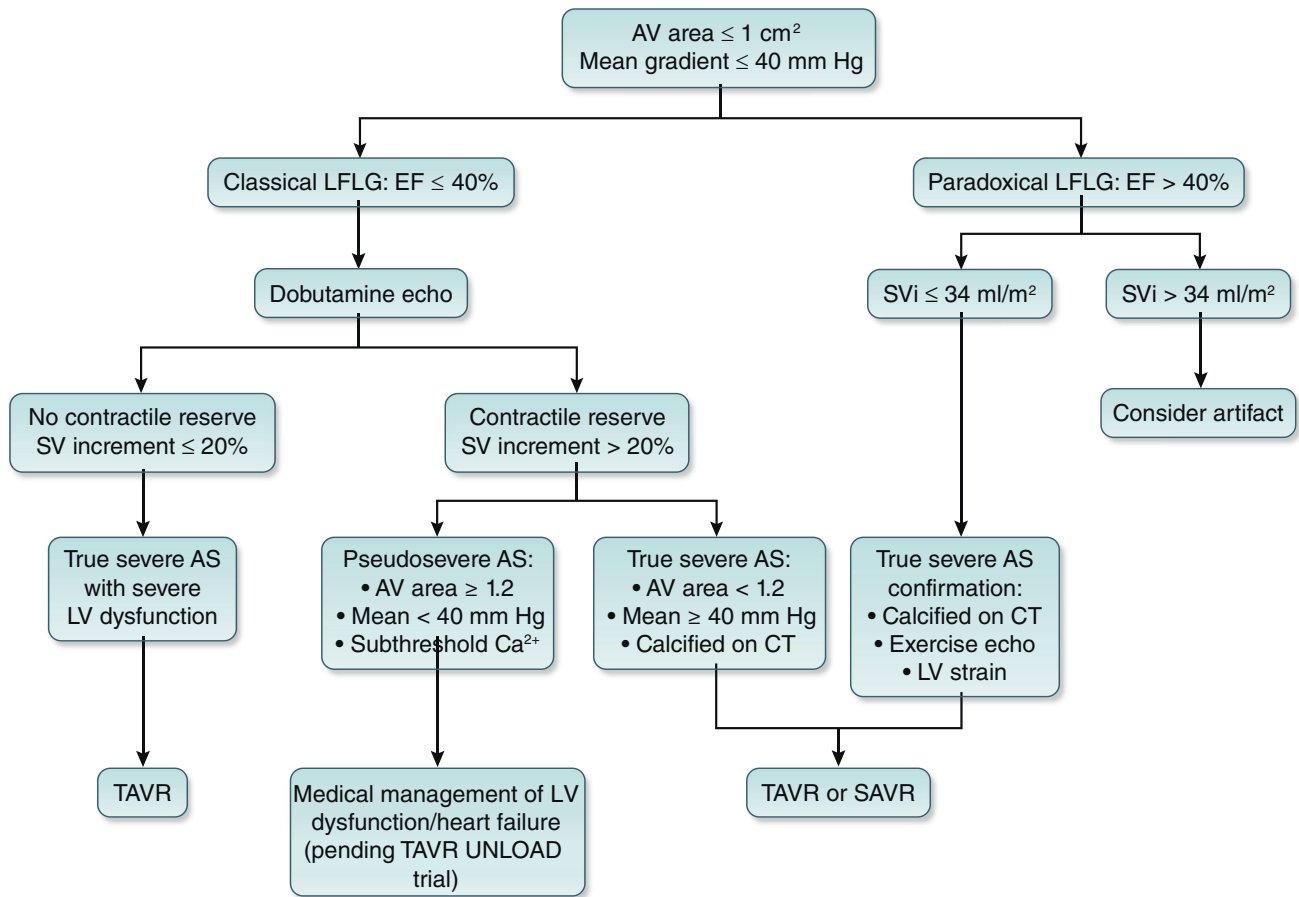
Figure 7 | Distinction of classical and paradoxical low-flow, low-gradient aortic stenosis (aortic stenosis). Dobutamine echocardiography may be useful to distinguish true and pseudostenosis in low-flow low-gradient aortic stenosis with reduced ejection fraction. AS, aortic stenosis; AV, aortic valve; CT, computed tomography; EF, ejection fraction; LFLG, low-flow, low-gradient; LV, left ventricular; SAVR, surgical aortic valve replacement; SV, stroke volume; SVi, stroke volume index; TAVR, transcatheter aortic valve replacement; TAVR UNLOAD, Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure trial.

include age, comorbidity, and life expectancy, choices between surgical and percutaneous valve delivery, consideration of goals of care (symptomatic benefits and survival), and caution regarding the potential side effects of warfarin (not only bleeding, but also the risk of calciphylaxis and calcification). In the past decade we have seen the rapid development of TAVR but also parallel improvements in cardiothoracic surgery (e.g., in perfusion, valves, surgical technique, and approaches). Calcification, especially annular calcification, poses specific issues for surgery and percutaneous intervention and is the major difference between CKD/ESKD and non-CKD.

Among patients with mild to moderate CKD, the benefits and risks of valve surgery are similar to those for the general population. However, the risks in persons with advanced CKD and ESKD are greater (Figure 8), with increasing mortality with worsening eGFR.[55] Despite the fact that outcomes of valve survival are poor in persons with ESKD, no studies have been performed that compare intervention with palliative or medical management.

AV replacement. In persons with early stage CKD, younger patients, and potential transplant candidates, management strategies for valvular disease should follow the guidelines in the general population. These guidelines include surveillance of both the progression of symptoms and the progression of the severity of VHD, leading eventually to valve intervention.[56] On the other hand, among older patients, specifically those with comorbidity, and patients with advanced CKD and ESKD, survival is markedly reduced. This information is important, because a median survival >2 years is considered the threshold for cost-effectiveness of TAVR in the general population.[57]

Valve intervention in persons with CKD has been studied most frequently for aortic stenosis, albeit in *post hoc* or registry analyses, with attempts to minimize selection bias by propensity matching. The currently available interventions are surgical AVR (biological or mechanical) and TAVR. Developments of both treatments in the past 15 years (particularly TAVR) have extended valve replacement to patients with advanced age and with comorbidities (including CKD/ESKD) previously considered inoperable. However, data on the management of VHD in CKD and ESKD are sparse, and no studies have compared interventional treatment with medical management, at a time when conservative (nondialysis) management of patients with CKD is gaining popularity.[58]
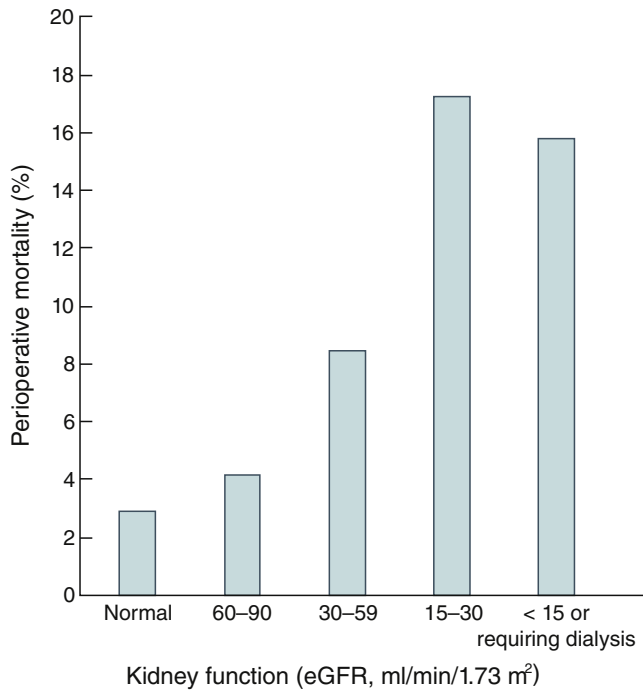
Figure 8 | Surgical aortic valve replacement mortality in chronic kidney disease.[55] This experience from Emory University (1996–2009) shows that mortality increases with worsening estimated glomerular filtration rate (eGFR).

For surgical AVR, there is a progressive increase in complication rates such as major bleeding and reoperation and mortality when comparing patients with moderately reduced kidney function (GFR between 30–60 ml/min per 1.73 m^2) versus those without kidney disease.[59] Mortality after surgical AVR increases with worsening eGFR (Figure 8).[55] Patients undergoing HD represent a more challenging group, given their higher burden of comorbidities. Although there has been an increase in the utilization of surgical AVR between 2005 and 2014 for these patients, along with a decrease in their mortality over time, in-hospital mortality in these patients remains twice that of their non-HD counterparts (8.1% vs. 3.9%, $P < 0.001$) even after propensity matching.[60] Recent reviews[61] have emphasized the role of biological and mechanical valves[62]; the current consensus is that survival is similar.[63] The On-X® mechanical AVR has lower anticoagulation requirements and may be

attractive in persons with CKD, but no analysis of this valve has been performed in persons with CKD.[64]

TAVR represents a potentially less invasive alternative for management of aortic stenosis in persons with CKD. Similar to what was seen with surgical AVR, there are parallel increases in risk associated with advanced CKD in patients undergoing catheter-based interventions. Specifically, there is a graded response of TAVR outcomes, in particular higher mortality and complication rates with progressive CKD (Table 2).[65–71] In the Placement of Aortic Transcatheter Valves (PARTNER) trial, there was a 10.7% 30-day and 34.4% 1-year mortality for patients with severe CKD.[72] Compared with patients who were not undergoing dialysis, patients with ESKD were younger (76 vs. 83 years; $P < 0.01$) and had higher rates of comorbidities leading to a higher Society of Thoracic Surgeons predicted risk of mortality (median 13.5% vs. 6.2%; $P < 0.01$). Likewise, patients undergoing dialysis had a higher 1-year mortality (37% vs. 19%; $P < 0.01$) and a higher rate of major bleeding (1.4% vs. 1.0%; $P = 0.03$) in 3053 (4.2%) of >72,000 patients in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies registry.[73] Analogous findings were identified in another group of dialysis patients undergoing TAVR, who had a 1-year mortality rate of 39%, compared with a 17.5% rate in those with CKD G3a (eGFR between 45–59 ml/min per 1.73 m^2).[65] This mortality rate appears to be further amplified by the presence of atrial fibrillation, with 1-year mortality rates as high as 71%.[66] The development of acute kidney injury in the peri-procedural TAVR setting is also associated with worse outcomes,[74,75] especially if post-TAVR HD is required.[76] Thus, while clear evidence exists that TAVR outcomes have been improving as the technique has become more established (rates of TAVR are increasing rapidly and have surpassed surgical AVR in some jurisdictions[77]), there is a persistent signal of adverse outcomes in patients with ESKD. Thus, whereas the procedure is not necessarily futile—a small study has documented better 1-year outcomes for dialysis patients with severe aortic stenosis undergoing surgical or transcatheter aortic valve repair compared with balloon aortic valvuloplasty[78]—there are possibilities for harm, especially in the presence of comorbid disease.[79]

The longevity of TAVR and biological prostheses in patients with advanced CKD and ESKD is an important source

Table 2 | Mortality in patients with reduced GFR after TAVR[66]

	CKD G1-G2 ≥60 ml/min per 1.73 m^2	CKD G3a-G3b 30–60 ml/min per 1.73 m^2	CKD G4 15–30 ml/min per 1.73 m^2	CKD G5-G5D <15 ml/min per 1.73 m^2 or dialysis
30-d mortality	6.0	7.7	10.4	11.9
Late (>30-d) mortality	21.4	25.1	32.5	44.1
Cardiovascular	12.1	14.0	20.0	11.9
Noncardiovascular	9.3	11.1	12.5	32.2

CKD, chronic kidney disease; GFR, glomerular filtration rate; TAVR, transcatheter aortic valve replacement.
Data are presented as percentages.
Adapted with permission from Allende R, Webb JG, Munoz-Garcia AJ, et al. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. *European Heart Journal*. 2014;35:2685–2696, by permission of the European Society of Cardiology. Copyright © The Author 2014.[66]
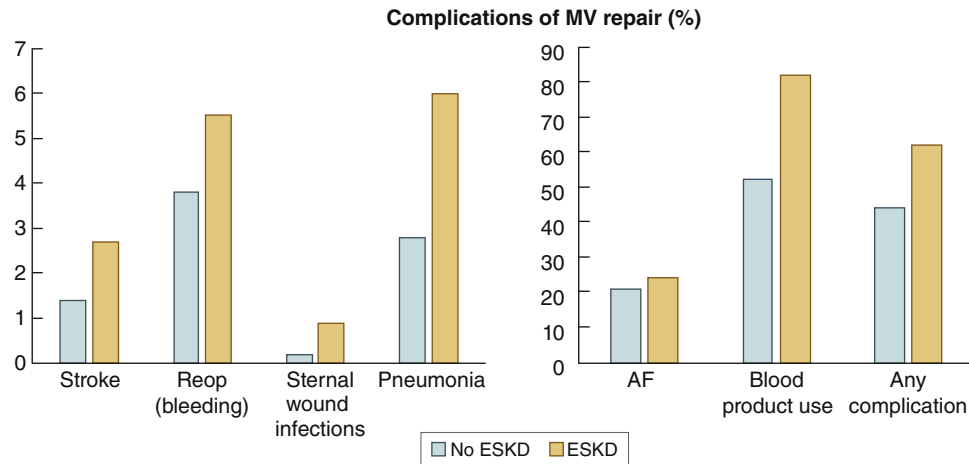
Complications of MV repair (%)

Figure 9 | Postoperative morbidity of primary mitral valve surgery in patients with and without end-stage kidney disease (ESKD).[82] AF, atrial fibrillation; MV, mitral valve; Reop, reoperation.

of uncertainty regarding the best choice of intervention. Given the limited survival in this group of patients, the long-term TAVR prosthesis durability and whether early degeneration can occur remain unanswered questions, but at least at 1 year, results appear promising for durability.[66] Results of attempts to compare TAVR with surgical AVR must be viewed carefully. Overall, surgical AVR is performed in younger and fitter patients and in those undergoing coronary artery bypass graft, whereas TAVR is reserved for inoperable, older patients with comorbidity. Propensity score matching compares the "best" of the TAVR group with the worst of the surgical AVR group. Nonetheless, limited, nonrandomized, propensity-matched data comparing surgical versus transcatheter AVR for patients with advanced CKD suggest that apart from a higher postprocedural need for a pacemaker with TAVR, mortality and periprocedural complications are significantly less common with that approach.[80] In particular, the potential need for dialysis appears to be lower among patients with advanced CKD receiving TAVR versus surgical AVR.[81] However, despite the best efforts, the development of acute kidney injury on top of CKD requiring dialysis is a real risk that is associated with high short-term mortality.[67,81]

A third of patients with CKD G4 who undergo valve replacement will be dead within 1 year, with roughly 1 in 6 requiring dialysis. In patients with CKD G5, more than one third will require kidney replacement therapy within 30 days; nearly two thirds will require kidney replacement therapy at 1 year. These data provide the context for discussion about goals of care and inform shared decision making in elderly patients with advanced CKD.[67] Nonetheless, functional class and symptomatic improvements are noted across all the CKD stages and even in those undergoing HD.[66,69]

Surgery for mitral regurgitation. The presence of kidney disease with severe mitral regurgitation leads to an almost 3-fold increase in mortality.[1] Advanced CKD is associated with increased risk of side effects and mortality with either mitral

replacement or repair (Figure 9[82]). Among the 86,563 mitral interventions reported by Vassileva *et al.*,[82] 1480 patients were undergoing dialysis. Dialysis-dependent patients had a lower propensity for mitral repair (44.6% vs. 61.5%; $P = 0.0010$; adjusted odds ratio, 0.69; 95% confidence interval, 0.61–0.78). No difference was reported in procedural success between repair and replacement in patients undergoing dialysis. For all mitral operations, 30-day mortality was 9.3% (compared with 2.3% for patients not undergoing dialysis), and 30-day mortality or major morbidity was 40.9% (vs. 15.9% for patients not undergoing dialysis).

Of particular interest is the possibility of percutaneous transcatheter mitral valve repair with the MitraClip™ device (Abbott Vascular, Menlo Park, CA), in select candidates. The observation of improvement in kidney function after device implantation has generated the hypothesis that hemodynamic improvements resulting after percutaneous mitral valve repair may improve kidney function.[83] Percutaneous mitral valve repair has been reported to have a high mortality at 1 year in patients with CKD G4–G5.[84] Further studies of kidney function after cardiac interventions and the influence on clinical outcome are needed.

Endocarditis

The risk of endocarditis increases with each step in the progression of CKD, with a dramatic increase among patients receiving HD.[85] In the latter group, the annual risk of bacterial endocarditis is almost 1%, especially during the first 5 months of HD.[85] This is approximately 100 times that of the unselected general population (including other high-risk groups). The risk is greatest among patients with ESKD and prosthetic or structurally abnormal valves, who have an HD catheter as their dialysis access.[86] Although infection of access grafts is nearly 10 times greater than the fistula infection rate,[87] it is not known that this is matched by differences in the frequency of endocarditis. Endocarditis involving TAVR

Table 3 | Evidence gaps and future needs

Topic	Research questions
General	• Analysis of surrogate outcomes in patients with valvular heart disease with CKD/ESKD—specifically, regression of LVH following intervention • Use of frailty scores in perioperative evaluation • The impact of CKD/ESKD on structural valve deterioration • Incidence of valve disease among CKD • Role of dialysis mode (HD vs. PD) and kidney transplantation on valve disease • Studies of valve disease that address feeling better rather than living longer
Aortic valve	• Relation between aortic stenosis and risk of sudden death in ESKD • Trials comparing TAVR, SAVR in CKD, and between TAVR/SAVR and medical management in patients with advanced CKD and ESKD • Timing of AVR in CKD to delay or prevent dialysis • Attempts to target inflammation (and senescence) in CKD to prevent aortic valve disease • Trials of medical therapies, including cinacalcet, to alter the progression of valvular calcification • Trials of TAVI vs. SAVR on left ventricular mass regression in CKD/ESKD
Mitral valve disease	• Analysis of the prevalence of mitral valve disease, interventions, and outcomes in CKD/ESKD • Understand the determinants of MAC and its progression • A study of intervention (surgical or percutaneous) vs. medical management of mitral regurgitation • A study for management (surgical or percutaneous) of patients with advanced MAC and mitral valvular disease.
Clinical trials (all valves)	• RCT in valvular heart disease interventions for patients with CKD (e.g., surgical bioprosthesis vs. mechanical [On-X®])
Right-sided heart disease	• Determinants of right-sided valvular abnormalities and the association of secondary right heart problems, including pulmonary hypertension, right ventricular failure and tricuspid regurgitation on outcomes • Additional epidemiological studies on right sided heart disease
Calcification	• Factors affecting progression of valvular calcification in CKD, ESKD • Best methods to monitor progression (CT, PET-CT, echocardiography vs. biomarkers)
Endocarditis	• Subacute bacterial endocarditis prophylaxis • Treatment approaches with antibiotics alone vs surgery • Role of PET-CT

AVR, aortic valve replacement; CKD, chronic kidney disease; CT, computed tomography; ESKD, end-stage kidney disease; HD, hemodialysis; LVH, left ventricular hypertrophy; MAC, mitral annular calcification; PD, peritoneal dialysis; PET-CT, positron emission tomography–computed tomography; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

has a particularly adverse profile,[88] occurring at a median time of 5 months from TAVR, with a mortality rate of 36%.

The pattern of organisms identified is also unlike the general population, with a preponderance of staphylococcal infections in patients with ESKD.[85] This phenomenon likely reflects contamination by skin organisms in patients with i.v. access. Avoidance of dialysis catheters is sensible and is a strong argument for preplanned permanent dialysis access in patients approaching ESKD. Patients who have ESKD and require valve replacement after treatment for endocarditis have a very poor outcome, with a 1-year mortality of about 50%.[86]

In the evaluation of suspected endocarditis, particularly involving prosthetic valves, transesophageal echocardiography is essential and should be readily accessible in the management of patients receiving HD and other patients with ESKD receiving kidney replacement therapy. Repeat transesophageal echocardiography may need to be considered in patients whose echocardiographic findings are negative or indeterminate, but clinical suspicion remains high. In addition, a growing body of literature on the potential role of positron emission tomography fused with computed tomography is available to help in the diagnosis of such cases.[89]

Conclusions

The prevalence of VHD is increased in patients with CKD compared with the general population, especially in patients with ESKD. In addition, the progression of VHD is faster in patients with CKD/ESKD when compared with the general population. The primary pathophysiological process involves calcification of valves and associated structures. While it is well established that VHD is associated with increased mortality, the optimal management of the excess CV risk due to valvular (rather than coronary artery or cardiomyopathic) heart disease in advanced CKD and ESKD remains unclear. Most of the literature is focused on aortic stenosis, with limited data on other valvular abnormalities. The role of medical therapies, such as cinacalcet, on development and progression of CKD-associated valve disease requires further study. Several evidence gaps and needs have been identified by the conference attendees that should help in the future design of studies to improve the understanding of diagnosis and management of VHD in this special population (Table 3).

Kenya; Charumathi Sabanayagam, Singapore; Catherine M. Shanahan, UK; Gautam R. Shroff, USA; Rukshana Shroff, UK; Angela C. Webster, Australia; Daniel E. Weiner, USA; Simon Winther, Denmark; Alexander C. Wiseman, USA; Anthony Yip, South Africa; Alexander Zarbock, Germany.

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