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Review

Chronic Kidney Disease and the Pathophysiology of Valvular Heart Disease

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ABSTRACT

Valvular heart calcification is common in patients with chronic kidney disease (CKD), especially in those receiving hemodialysis therapy, and it is associated with poor prognosis. Furthermore, progression of valvular heart disease (VHD) and structural valve deterioration of bioprosthetic valves are faster in these patients. Mechanisms involved in the pathophysiology of VHD are similar between patients with and without impaired kidney function, but CKD is associated with a bone metabolism dysregulation, which might lead to a procalcifying phenotype within vessels and heart valves. CKD is also associated with left ventricular remodelling and dysfunction, which might contribute to increase the risk of heart failure and death in patients with VHD. Even if promising pharmacotherapeutic avenues are in development, no medical treatment can prevent or reduce the valvular calcific process. Patients with advanced CKD should undergo transthoracic echocardiography for detection of VHD, and if present, follow-up should be more

RÉSUMÉ

Les calcifications valvulaires sont fréquentes chez les atteints d' isufisance rénale chronique, surtout en cas d'hémodialyse, et leur présence est associée à un mauvais pronostic. De plus, la progression des valvulopathies et la détérioration des bioprothèses sont accélérées dans cette population. Les mécanismes physiopathologiques impliqués dans le développement des valvulopathies sont similaires entre les patients avec et sans insuffisance rénale, cependant la dérégulation du métabolisme osseux est plus prononcée en cas de néphropathie, d'où un phénotype pro-calcifiant. L'insuffisance rénale entraine également un remodelage et une altération de la fonction du ventricule gauche, ce qui contribue à augmenter le risque d'insuffisance cardiaque et de décès en cas de valvulopathie. Même si des pistes thérapeutiques sont en développement, il n'existe aucun traitement médical permettant de prévenir ou de faire régresser les calcifications valvulaires. Chez les patients atteints d' insuffisance

Degenerative valvular heart disease (VHD) and left ventricular (LV) remodelling and dysfunction are common findings in patients with chronic kidney disease (CKD) who are hemodialysis (HD)-dependent. Valvular and annular thickening and calcification are observed in any of the heart valves but more frequently in the aortic and mitral valves, and especially in end-stage renal disease (ESRD) patients (ie, glomerular filtration rate < 15 mL/min/1.73 m^2 and/or patients receiving HD therapy). Subsequent valvular regurgitation and/or stenosis will develop in these patients. Thus, prevalence, progression, and severity of VHD increase with more advanced stages of CKD.[1] In addition, LV adverse remodelling and dysfunction become worse with CKD and VHD progression. In patients with ESRD treated with long-term HD, hemodynamically signicant aortic stenosis (AS) occurs 10 to 20 years earlier than in the general population.[2] A faster structural valve deterioration (SVD) of bioprostheses is also observed in patients with renal insufficiency.[3] Valve calcification and LV hypertrophy is a powerful risk marker for all-cause mortality with approximately 50% of patients with CKD dying from cardiovascular disease.[4-6]

AS has long been considered a passive and age-related disease. Albeit, aortic valve disease is not seen universally among the elderly population. According to recent pathophysiological studies, AS is not a single pathologic process but a combination of different processes that ultimately lead to severe valvular calcification and many pathways involved could be amplified in CKD patients.[7] Among these processes, inflammation and bone metabolism dysregulation have been shown to be impaired among patients with

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frequent than what is recommended in the guidelines. Transcatheter valve replacement might be preferred over surgical replacement in patients with CKD and severe aortic valve stenosis.

rénale avancée, il est important d'effectuer une échocardiographie pour le dépistage des maladies valvulaires et d'effectuer un suivi plus rapproché que ce qui est recommandé dans les lignes directrices. Le remplacement valvulaire par cathéter semble être préférable au remplacement chirurgical chez les patients atteints d' insuffisance rénale et de sténose aortique grave.

decreased renal function.[8,9] In particular, systemic calcium/phosphate imbalances, reduced expression of calcification inhibitors, elastic remodelling and osteogenic trans-differentiation of valvular fibroblasts could play a role during vascular/valvular calcification in these patients. The scope of this review is to expose and compare the pathophysiological processes involved in VHD and SVD in the general and in the CKD population. Perspectives of medical therapy are also discussed.

Valvular Calcification in Patients With CKD

CKD is common in the general population and is associated with an increased risk of cardiovascular complications, such as coronary artery disease, stroke, heart failure, and valvular calcification,[10] as well as cardiovascular and all-cause mortality. Strikingly, CKD patients are more likely to die of cardiovascular cause than of kidney failure. Aortic and mitral calcification (Fig. 1), including mostly mitral annulus calcification (MAC) and AS, are common in CKD, especially in ESRD patients who receive HD.[11] The prevalence of aortic and mitral valve calcification in CKD patients according to the main studies is presented in Table 1. At least mild AS or mitral regurgitation are more frequent in CKD patients and are associated with worse prognosis vs patients without renal insufficiency. In dialyzed patients, aortic valve calcification (AVC) and MAC are observed in 55% and 59% of patients, respectively,[12] and significant AS is observed in 6%-13% of patients.[11-28] Interestingly, Matsuo et al. reported severe AS in 4% of HD patients, including paradoxical low-flow low-gradient severe AS in 60% of these cases.[11] In addition, AS progression is accelerated (Table 2) and risk of major adverse cardiac events is higher in ESRD patients compared with those with normal kidney function.[13,29-34] However, the presence of valvular calcification, especially at the mitral level, is independently associated with a higher risk of cardiovascular and all-cause mortality in CKD patients.[5,30] Hence, the severity of CKD and duration of HD are strongly correlated with the progression of valvular calcific burden, and in turn, the magnitude of valvular calcification is strongly associated with the risk of cardiac events.[5] As for the clinical outcomes, recent results from the **C**ontemporary Outcomes After S**ur**gery and Medical T**rea**tme**nt** in Patients With Severe **A**ortic **S**tenosis (CURRENT AS) registry showed that aortic valve replacement compared with a conservative medical strategy is associated with lower long-term mortality risk in patients with HD.[35] However, in this same study, the surgery-related mortality was substantially higher in HD patients than in non-HD patients.[35] Importantly, a large proportion of the studies on VHD performed in the context of CKD involved HD-dependent patients, who are more exposed to the valvular calcific process than patients with moderate kidney dysfunction.

Risk Factors for Valvular Calcification in Patients With CKD

A limited number of studies reported risk factors for valvular calcification in patients with CKD. In a recent small Chinese study, the association of advanced age, higher blood cholesterol level, low-density lipoprotein (LDL) levels, and increased interventricular septum thickness with the presence of valvular calcification in patients with reduced renal function was reported.[28] Another study mentioned elevated serum phosphorus, albumin, and C-reactive protein (CRP) levels as well as dialysis duration as independent risk factors for valvular calcification.[36]

Mechanisms of Valvular Calcification in Patients With CKD

Endothelial dysfunction

In AS, early lesions are characterized by endothelial dysfunction associated with a subendothelial thickening and disruption of the overlying basement membrane in regions with low shear stress of the leaflets (Fig. 2).[37] These lesions are responsible for an alteration of the endothelial barrier function, which facilitates lipid infiltration and deposition as well as inflammatory cell infiltration processes (Table 3). The key initiating factor in the development of the early valvular lesions appears to be disturbance of flow patterns, which result in alteration of local endothelial shear stress, especially on the aortic side of the valve. These blood-flow perturbations can activate endothelial cells, tipping the balance of endothelial-derived factor and microparticles to alter the barrier function and enhance coagulation, leukocyte adhesion, and smooth muscular cell proliferation.[7,38-40] These activations are protective mechanisms, but an excessive response might induce abnormal fibroproliferation within valvular tissues.

The shear stress-related endothelial damage induced by the repeated turbulent blood flow crossing the valve is further exacerbated in HD-dependent ESRD patients. Indeed, fluid overload, anemia, and shunts across arteriovenous fistulae induce a state of high cardiac output, which leads to increased flow velocity and turbulence across the aortic valve and thereby predispose to valvular calcific process. In addition, CKD patients are more often exposed to cardiovascular comorbidities, especially hypertension, and to arteriosclerosis, which is responsible for vascular thickening, stiffening, and calcification. These 2 conditions increase the LV afterload, which further increases valvular endothelium damage and LV remodelling. To a lesser extent, LV dilatation and dysfunction related to afterload excess can result in the occurrence of mitral regurgitation.

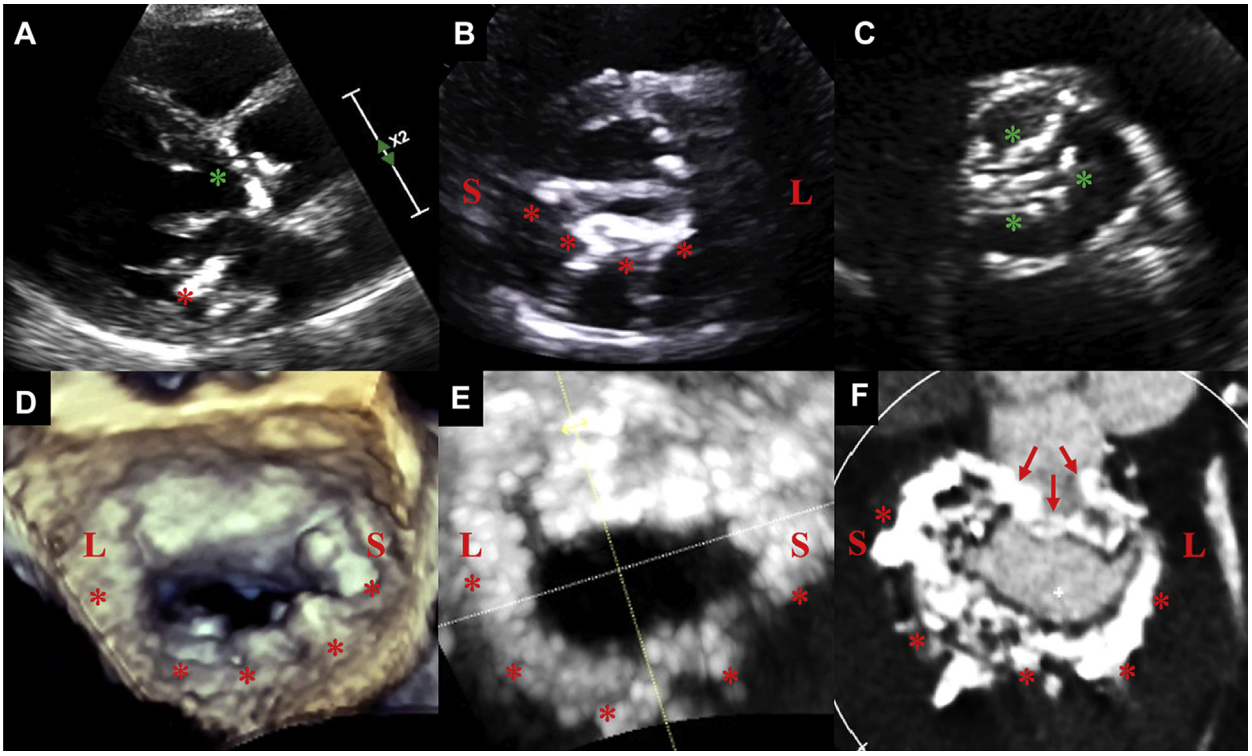

Figure 1. Illustrative example of aortic valve calcification and mitral annular calcification (MAC) in a patient with end-stage renal disease. (**A-C**) Transthoracic and (**D**, **E**) transesophageal echocardiographic views, and (**F**) cardiac computed tomography. (**A**) Aortic valve calcification (**green** star) and MAC (**red star**) from the parasternal long-axis view. (**B**) Extensive posterior MAC (**red stars**) from the parasternal short-axis view. (**C**) Calcification of the 3 aortic valve leaflets (**green stars**) from the parasternal short-axis view. (**D**) and (**E**) Extensive posterior MAC (**red stars**) from the left atrial en face view using 3-dimensional volume-rendering mode (**D**) and multiplanar reconstruction (**E**). (**F**) Extensive posterior (**red stars**) and anterior (**red arrows**) MAC from the left ventricular view using multiplanar reconstruction. L, lateral side; S, septal side.

Lipid infiltration

Lipid metabolism abnormalities are a central mechanism in the pathophysiology of atherosclerosis and AVC. Early lesions of calcific AS are characterized by the presence of intravalvular lipoproteins, especially oxidized dense LDL, which is not present in normal aged valves (Fig. 2).[37] Several studies have shown a strong association between increased circulating levels of LDL[41] or lipoprotein (a) (Lp[a]) and aortic valve disease

Table 1. Prevalence of aortic or mitral valve calcification in patients with and without CKD

Reference	Patients with CKD, n	Patients without CKD, n	CKD stage	Aortic/mitral valve calcification in patients with CKD, %	Aortic/mitral valve calcification in patients without CKD, %
Maher et al.[15]	87	NA	Hemodialysis	28/36	NA
Straumann et al.[16]	62	NA	Hemodialysis	55/40	NA
Braun et al.[12]	49	102	Hemodialysis	55/59	NM
Ribeiro et al.[17]	92	92	Hemodialysis	52/44.5	4.3/10
Ventura et al.[18]	135	NA	Hemodialysis	78/26	NA
Raggi et al.[19]	205	NA	Hemodialysis	34/45	NA
Wang et al.[20]	192	NA	Peritoneal dialysis	17.2/22.4	NA
Schönenberger et al.[21]	55	15	Hemodialysis	60/NM	12/NM
Varma et al.[22]	137	NA	Hemodialysis	36/39	NA
Kume et al.[13]	55	NA	Hemodialysis	47/NM	NA
Tarrass et al.[23]	90	NA	Hemodialysis	36/30	NA
Holden et al.[14]	108	NA	Hemodialysis	84/NM	NA
Ix et al.[24]	653	6132	Stage 3a or worse*	25/20	12/8
Adeney et al.[25]	439	NA	Stage 3a or worse*	25/20	NA
Ikee et al.[26]	112	NA	Hemodialysis	75/51.7	NA
Avila-Díaz et al.[27]	124	NA	Peritoneal dialysis	57.8/26.3	NA
Matsuo et al.[11]	315	NA	Hemodialysis	76.5/58.4	NA
Rong et al.[28]	288	NA	All stages	22.9/4.9	NA

CKD, chronic kidney disease; NA, not appropriate; NM, not mentioned.
*Glomerular filtration rate <60 mL/min/1.73 m^2.

Table 2. Summary of studies that identified an association between CKD and aortic stenosis progression or structural valve deterioration of bioprostheses

Reference	Patients with CKD, n	Patients without CKD, n	CKD stage	Valvular negative effect
Malergue et al.[34]	112	NA	Hemodialysis	AS progression: AVA reduction
Wongpraparut et al.[32]	58	NA	Hemodialysis	AS progression: AVA reduction > 0.25 cm^2/y
Perkovic et al.[33]	28	56	Hemodialysis	AS progression: faster AVA reduction (-0.19 vs -0.07 cm^2/y) and faster peak gradient increase (6.5 vs 3.9 mm Hg/y) in CKD patients
Ohara et al.[31]	16	82	Hemodialysis	AS progression: faster AVA reduction (-0.14 vs -0.06 cm^2/y) in CKD patients
Kume et al.[13]	55	NA	Hemodialysis	AS progression: AVA reduction
Kim et al.[29]	74	79	Hemodialysis	AS progression: faster progression (change in severity stage) in CKD patients
Lamberti et al.[91]	2	NA	NM	Accelerated SVD: calcific deposition
Brinkman et al.[92]	72	NA	Hemodialysis	Accelerated SVD: prosthesis dysfunction requiring surgery
Briand et al.[3]	217*		NM	Accelerated SVD: regurgitation worsening and/or $\geq$ 3 mm Hg/y increase in gradient
Okada et al.[90]	89	317	Hemodialysis	Accelerated SVD in CKD patients: 18% vs 0%, at 5 years
Salaun et al.[89]	1387*		NM	Accelerated SVD: $\geq$ 10 mm Hg increase in mean gradient or worsening of regurgitation $\geq$ 1/3 class

AS, aortic stenosis; AVA, aortic valve area; CKD, chronic kidney disease; NA, not appropriate; NM, not mentioned; SVD, structural valve deterioration; *When CKD was found as an independent factor associated with SVD in the global study population.

initiation and progression (Table 3).[42-44] Dyslipidemia was also identified as a risk factor for MAC.[45] Interestingly, patients with CKD, especially those who are HD-dependent, have higher level of Lp(a), which might increase the risk of coronary and heart valve diseases.[46] It is believed that dysfunction of the endothelial barrier facilitates the entry of circulating lipids into the aortic leaflets, which can thereafter trigger local modifications such as inflammation and cellular differentiation processes. Upregulation of the LDL receptor related protein-5 is involved in the activation of skeletal bone development and in the differentiation process of valvular myofibroblasts into osteoblasts.[47] In addition, angiotensin-converting enzyme is found in stenotic aortic valves, where it colocalizes with apolipoprotein B and angiotensin II.[48] This observation suggests a substantial role of the renin-angiotensin-aldosterone system (RAAS) in disease progression through the extracellular matrix remodelling and fibrosis process. These findings provide support to the concept that AVC is a lipid-driven process, which might be exacerbated in the setting of CKD.[41]

Reactive oxygen species

Increased oxidative stress in calcified and pericalcific lesions of the aortic valve has been documented in humans.[49]

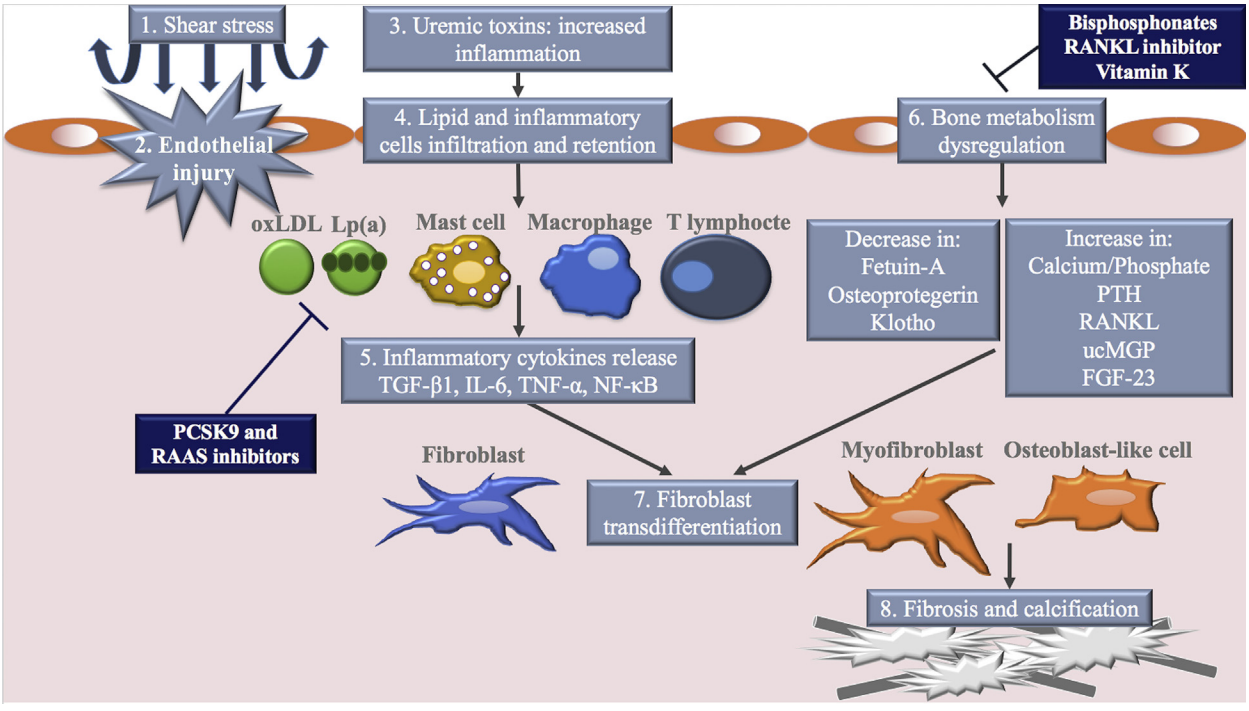

Figure 2. Pathways involved in valvular heart diseases and potential targets of medical therapy in patients with chronic kidney disease. FGF-23, fibroblast growth factor-23; GLA, gamma-carboxyglutamic-acid; IL-6, interleukin 6; LP(a), lipoprotein a; MGP, matrix GLA protein; NF-κB, nuclear factor kappa-B; oxLDL, oxidized low-density lipoprotein; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; RANKL, receptor activator of nuclear factor kappa-B ligand; TGF-β1, transforming growth factor-β1; TNF-α, tumour necrosis factor-α; ucMGP, uncarboxylated matrix-GLA-protein.

Table 3. Summary of the pathophysiology of valvular calcification process: involved mechanisms, valvular consequences, and effect of CKD

Pathophysiological mechanisms of AS	Valvular consequences	Effect of CKD
Endothelial dysfunction		
• Endothelial shear stress	• Barrier dysfunction with lipid and inflammatory cell infiltration • Valvular interstitial cells transdifferentiation and proliferation into smooth muscle-like cells	• Shear stress increase by fluid overload
Lipid infiltration		
• Oxidized LDL • Small circulating LDL particles • LP(a) • LDL receptor-related protein-5	• Local inflammation • RAAS activation • Valvular interstitial cells transdifferentiation and proliferation into osteoblastic like-cells	• Increase LP(a)
ROS		
• Increase in ROS production (superoxide and hydrogen peroxide) • Decrease in antioxidant defenses (NO, superoxide dismutase)	• Myofibroblast activation • Valvular interstitial cells transdifferentiation and proliferation into osteoblastic like-cells	• NOS uncoupling • NO reduction • Increased ROS production
Systemic and local inflammation		
• T lymphocytes, mast cells, and macrophages infiltration • Proinflammatory cytokines release (TGF-β1, IL-6, TNF-α, and NF-κB)	• Extracellular matrix remodelling with fibrosis • Inactivation of ROS production • Valvular interstitial cells transdifferentiation and proliferation into osteoblastic like-cells	• Increase in systemic inflammation related to production of uremic toxins (indoxyl sulfate) and malnutrition
Bone metabolism dysregulation		
• Calcium/phosphate imbalance • Increase in osteoblastic factors: osteopontin, osteocalcin, BMP-2, and Cbfa1/ Runt-related transcription factor 2 • RANKL/RANK/osteoprotegerin, and FGF-23/Klotho imbalance • Decrease in anticalcifying factors: fetuin-A and activated MGP (cMGP)	• Hyperphosphatemia • Apoptotic pathways activation • Osteoblastic cell differentiation • Soft tissue calcification	• PTH level increase with hyperphosphatemia • Decrease in fetuin-A • Decrease in osteoprotegerin and increase in RANKL • Decrease in Klotho and increase in FGF-23 • Increase in inactivated MGP (ucMGP) related to vitamin K deficiency

AS, aortic stenosis; BMP-2, bone morphogenetic protein 2; Cbfa1/Runt-related transcription factor 2, core binding factor 1/Runt-related transcription factor 2; CKD, chronic kidney disease; cMGP, carboxylated matrix-GLA-protein; FGF-23, fibroblast growth factor-23; GLA, gamma-carboxyglutamic-acid; IL-6, interleukin 6; LDL, low-density lipoprotein; LP(a), lipoprotein a; MGP, matrix-GLA-protein; NF-κB, nuclear factor κB; NO, nitric oxide; NOS, nitric oxide synthetase; PTH, parathyroid hormone; RAAS, renin-angiotensin-aldosterone system; RANK, receptor of nuclear factor κB; RANKL, receptor activator of nuclear factor κB ligand; ROS, reactive oxygen species; TGF-β1, transforming growth factor-β1; TNF-α, tumour necrosis factor-α; ucMGP, uncarboxylated matrix-GLA-protein.

Superoxide and hydrogen peroxide levels are markedly elevated in the calcified regions of the aortic valve, whereas antioxidant mechanisms are dysregulated as shown by the low expression and activity levels of superoxide dismutase enzymes (Table 3). Oxidative stress might also play a role in the early stage of AVC by driving activation of myofibroblasts, which are capable of transdifferentiation into osteoblast-like cells.[49] Asymmetric dimethylarginine (ADMA) and L-arginine are 2 molecules that compete for the activation of the endothelium-derived relaxing factor: nitric oxide. ADMA levels, which are abnormally elevated in CKD patients, is strongly associated with cardiovascular mortality.[50] Nitric oxide synthetase uncoupling, reduction of nitric oxide, and increase in reactive oxygen species production are related to increased ADMA generation and decreased antioxidant defense. In vitro studies showed that calcified valvular interstitial cells present a reduced expression of dimethylarginine dimethylaminohydrolase 1 and 2, the enzymes responsible for the control of ADMA levels.[51] ADMA circulating levels have also been associated with the presence of AVC,[52,53] however, this relationship has never been studied in patients with declined kidney function.

Systemic and local inflammation

Local inflammation related to lipid deposit, oxidative stress, and endothelial dysfunction is responsible for the release of proinflammatory cytokines, which enhance the recruitment and the infiltration of circulating inflammatory cells such as T lymphocytes, mast cells, and macrophages, including lipid-laden foam cells (Fig. 2).[37] Among the different cytokines involved in the early phase of aortic valve remodelling, tumour necrosis factor-α, transforming growth factor-β1, and nuclear factor-κB seem to be essential.[7]

Systemic uremic inflammation is a common condition in ESRD patients, a fortiori in case of HD,[54] mostly related to the inflammatory cytokines interleukin 6, tumour necrosis factor-α, and nuclear factor-κB. However, these cytokines are also involved in several organ dysfunctions, especially in the heart. Thus, this chronic microinflammatory state was shown to be associated with valvular calcification, accelerated atherogenesis, and adverse clinical outcomes. Several studies reported an association between the plasma level of CRP and interleukin 6 and the presence of aortic and mitral valvular calcification in CKD patients treated or not with dialysis.[55,56] In addition, Schönenberger et al. reported a higher CRP level in HD patients with significant AS.[21] Causes of this systemic inflammation in CKD patients are multifactorial.[54] Emerging evidence suggests that kidney dysfunction results in a serum accumulation of uremic toxins, such as indoxyl sulfate, which accelerate the progression of CKD and increases vascular cell proliferation, inflammatory cytokine release, and reactive oxygen species production. Indoxyl sulfate is produced by the liver from the proteins absorbed in the intestine, and it is normally excreted into urine. In a rat model, indoxyl sulfate induced calcification of the aorta through the activation of

osteoblastic proteins, such as osteopontin, osteocalcin, and core binding factor 1. Further studies focused on cardiac valves are needed to explore this hypothesis. Finally, ESRD patients are at high risk of malnutrition, which is itself a trigger for systemic inflammation and valvular calcification (Table 3).[56]

Bone metabolism dysregulation

Bone metabolism is a distinct contributor to AS (Table 3). Calcium deposit and mature bone formation are actively regulated in stenotic aortic valves (Fig. 2).[57] Histological analysis showed microscopic and macroscopic extracellular mineralization in advanced calcified leaflets, but also in early adjacent lesions that contain only inflammatory cells and lipid deposition.[37] The microcalcification formation might be mediated by cell death and the release of apoptotic bodies, which are similar to the matrix vesicles found in the bone. Moreover, explanted stenotic aortic valves express several osteoblastic markers as such as osteopontin, osteocalcin, LDL receptor-related protein-5, osteoprotegerin/ receptor activator of nuclear factor κB ligand (RANKL)/receptor of nuclear factor κB (RANK), bone morphogenetic protein 2, and core binding factor 1/Runt-related transcription factor 2.[9,49,58-60] In AS, RANKL/RANK to osteoprotegerin ratio is unbalanced to the detriment of osteoprotegerin, thus promoting calcifying processes.[61,62] Finally, fetuin-A, and matrix-carboxylation/gamma-carboxyglutamic (GLA)-protein (MGP) are other factors identified as powerful circulating inhibitors of vascular and soft tissue calcification[63] through the inhibition of transforming growth factor-β and bone morphogenetic protein 2 effects, the reduction of apoptosis-mediated calcification, and a direct prevention of calcification by binding to calcium crystals.

MGP. MGP is an extracellular protein expressed in several organs, which inhibits soft tissue calcification.[64] A recent in vitro study suggested that MGP directly acts as a negative regulator of AVC.[65] To be biologically active, MGP requires a γ-carboxylation, which is a vitamin K-dependent process. However, ESRD patients often have vitamin K deficiency, which leads to increased level of uncarboxylated (ie, inactive) MGP.[66] This imbalance between pro- and anticalcific mechanisms in CKD patients might accelerate the calcifying processes of the heart valves (Table 3). These findings also raise the issue of the use of vitamin K antagonist (VKA) therapy for anticoagulation, which might increase the risk of valvular calcification. Some retrospective and 1 prospective study suggested a higher risk of valvular calcification in patients who receive VKA for nonvalvular atrial fibrillation,[67] including HD-dependent ESRD patients.[14,68] In a retrospective study, Tastet et al. showed that patients with AS treated with VKA have faster hemodynamic (peak velocity) and anatomic (calcium score) progression of AS compared with those with non-VKA oral anticoagulants or with no anticoagulation.[69] The risk vs benefit ratio of VKA in patients with CKD requires further studies.

Fetuin-A. Fetuin-A is a circulating calcium-binding glycoprotein involved in the inhibition of tissue calcification.[63] Contradictory findings were reported regarding the relation between fetuin-A circulating levels and valvular calcification in patients with preserved renal function. Koos et al. reported that nondialyzed AS patients with a lower fetuin-A levels had faster AVC progression.[70] Similar results were observed in patients with MAC.[71] However, several studies showed an inverse correlation between fetuin-A level and cardiac valve calcification (ie, higher levels of fetuin-A being associated with more calcification).[72-74] In addition, fetuin-A deficiency was identified as a uremia-related and inflammation-related mortality risk factor in HD patients.[75] As for MGP, the imbalance between pro- and anticalcific mechanisms might explain the higher prevalence of valvular calcification in CKD patients (Table 3).

Osteoprotegerin/RANK/RANKL axis. The liaison of RANKL with RANK induces the osteoclast differentiation and maturation, and therefore bone resorption. Osteoprotegerin is a decoy receptor for RANKL, able to block its interaction with RANK, thereby inhibiting osteoclast differentiation.[76] In AS, RANKL/RANK to osteoprotegerin ratio is unbalanced to the detriment of osteoprotegerin procalcifying processes (Table 3).[61,62] Osteoclast activation related to imbalance in osteoprotegerin/RANKL ratio in CKD patients is not well known. Shuvy et al. reported an increased level of RANKL transcription in a rat model of renal failure.[9] Thus, further studies are necessary to determine the implication of RANKL in the setting of CKD.

Calcium/phosphate homeostasis. Alteration in calcium/phosphate homeostasis is a major complication of CKD. Kidney dysfunction and the associated vitamin D deficiency result in hypocalcemia and hyperphosphatemia. Hypocalcemia induces an increase in parathyroid hormone (PTH) plasma levels that stimulate bone resorption by osteoclasts and transform vitamin D in its active metabolite.[77] Hyperphosphatemia also increases PTH levels to facilitate its tubular excretion. However, the resulting secondary hyperparathyroidism induces osteoporosis and ectopic calcification (Table 3). This counterintuitive association between reduced bone mineralization and soft tissue calcification is also observed during osteoporosis and aging, and is often called the "calcification paradox." The mechanisms involved in this paradoxical process are not fully elucidated, but seem to be mainly related to the increase in phosphate plasma level and hydroxyapatite formation. Indeed, several authors showed a direct relation between valvular calcification and phosphate/PTH dysregulation.[9,11,25,78] In vitro studies showed that phosphate can induce matrix mineralization and is also able to activate apoptotic pathways in valvular interstitial cells,[79] which further increases the mineralization process. Hyperphosphatemia could also stimulate endothelial cells and then release of endothelial microparticles, leading to inflammation and endothelial cell apoptosis. In addition, elevated extracellular calcium and phosphate levels in CKD patients might induce the release of microvesicles from macrophages and vascular smooth muscle cells, which promote extracellular matrix microcalcification formation. In a rat model of adenine-induced renal failure with rapid hyperparathyroidism, rats fed with a high-phosphate diet developed AVC, whereas those with low-phosphate diet had minimal AVC.[9] Calcium/

phosphate homeostasis and secondary hyperparathyroidism are therefore major contributors to valvular calcification in CKD patients. Finally, the calcium/phosphate level regulation through the PTH axis is also a crucial contributor to the valvular calcification process, especially in the context of secondary hyperparathyroidism related to CKD.[9]

Fibroblast growth factor-23/Klotho axis. Fibroblast growth factor (FGF)-23 is a bone-derived hormone that contributes to maintain the mineral homeostasis by inducing urine elimination and lowering intestinal absorption of phosphate, and by reducing active vitamin D level.[80] FGF-23 level is regulated by calcium/phosphate modulators such as vitamin D and PTH. In CKD patients, FGF-23 level elevation correlates with the decline in kidney function and the increase in phosphatemia. FGF-23 also exerts a negative feedback control over PTH secretion. FGF receptors are ubiquitous, but the specific tissue action of FGF requires the presence of Klotho, which is a single pass membrane protein. In case of Klotho deficiency, the affinity of FGF-23 for its receptor is decreased, and FGF-23 alone cannot properly regulate phosphate homeostasis. Thus, FGF-23 might not be able to prevent secondary PTH elevation in patients with advanced CKD because of a possible Klotho downregulation in parathyroid glands. In CKD patients, FGF-23 is a powerful marker of renal disease progression, cardiovascular mortality, and all-cause mortality,[81] and seems to be involved in LV remodelling,[82] vascular damage, and AVC.[83,84] Klotho deficiency was also shown to be associated with aortic valve inflammation, osteogenic activation (ie, Runt-related transcription factor 2), and valvular fibrosis in mice and human models (Table 3).[85-87] Finally, it remains unclear if FGF-23, Klotho, or both are directly involved in valvular calcification in CKD patients.

CKD and SVD of Bioprostheses

According to current guidelines on VHD management, valve replacement or repair is the recommended therapy in symptomatic patients with severe VHD. Because "degenerative" VHDs are associated with calcific deposition, especially in CKD patients, the best treatment remains the replacement rather than the repair of the native valve.[88] Two types of prosthesis can be implanted according to patient age, comorbidity, life expectancy, surgical risk, personal choice, and probability of SVD. Bioprostheses are recommended in older patients (older than 60 years of age), when prolonged oral anticoagulation is not desirable, or when a percutaneous approach is used (patients with intermediate/high surgical risk). Conversely, bioprostheses are at high risk of accelerated SVD in young patients, patients with diabetes, or HD-dependent patients with CKDs. Several studies (Table 3) identified renal dysfunction as a powerful independent predictor of premature SVD.[3,89-92] The pathophysiology of SVD is not well understood, but it is assumed that mechanisms of SVD are similar to those involved in native VHD,[3] mainly because the background disease is still active (ie, blood flow-related shear stress, systemic inflammation, and metabolic disturbances; Fig. 2). Nevertheless, some studies suggest that it is reasonable to use bioprostheses in HD patients because the risk of accelerated SVD is offset by the risk thromboembolic events and anticoagulant-related bleeding events associated with mechanical prostheses.[93,94] Furthermore, the risk of reintervention because of SVD is relatively rare in these patients because of their short life expectancy, and these interventions can, nowadays, be performed via a transcatheter (valve-in-valve) procedure.[95,96] Finally, SVD could become a major concern in future years because of the rapid expansion of use of transcatheter valve therapies in high-risk populations including patients with advanced CKD.

CKD and LV Remodelling

Modification in LV geometry is an adaptive mechanism in response to physiological or pathological homeostasis change. Several conditions might induce LV structural changes and remodelling such as CKD and VHD (Fig. 2). Indeed, LV modifications in CKD patients are similar to those observed in VHD patients, and might be worsened when both diseases are concomitant. In addition, heart and kidney homeostatic functions are essential and inter-related. CKD induces volume overload, myocardial fibrosis, and increases the risk of coronary artery disease and pulmonary hypertension, which induce myocardial damage.[97] However, cardiac dysfunction impairs renal perfusion, which worsens kidney injury (cardiorenal syndrome). In CKD patients, the structural modifications of the myocardium begins in the early stage of disease and get worse in ESRD patients,[98,99] but seem to improve after kidney transplantation.[100] The early alterations of the myocardium include an increase in myocardial apoptosis and a change of cardiomyocyte and fibroblasts phenotypes toward a profibrotic phenotype.[101] These alterations induce LV myocardial dysfunction such as abnormal global longitudinal strain, increased LV filling pressure, and impaired LV relaxation even before significant LV dysfunction and hypertrophy develops.[98,99] Interestingly, an increase in FGF-23 and transforming growth factor-β levels, and Klotho deficiency in CKD patients seem to be related to the RAAS activation and are involved in the development of LV fibrosis.[102-104] Hence, there appears to be a cross-talk between mechanisms of valvular and myocardial dysfunction in CKD patients. These subclinical alterations evolve toward LV geometry changes including LV hypertrophy (concentric and eccentric), dilatation, and systolic dysfunction, which are strong predictors of adverse renal and cardiovascular outcomes.[6] In addition, history of cardiovascular disease is positively associated with the development of LV remodelling, especially in ESRD patients.[105] Interestingly, HD therapy might improve LV function and reverse LV remodelling by decreasing blood pressure level and volume overload, but the increase in fistula-related flow might also induce pulmonary hypertension and right ventricular dysfunction, which are associated with adverse outcomes.[106,107] Finally, LV alteration, remodelling, and dysfunction related to VHD might be amplified in the presence of CKD, which certainly contributes to increase the risk of heart failure and death in this population.

Perspective of Medical Therapies

There is no specific recommendation regarding the medical management of AS. However, several interesting pathways involved in the pathophysiology of VHD might be targeted by

therapies. Among them, the lipid infiltration and the calcium/phosphate metabolism are the main mechanisms targeted by therapeutic trials aimed at limiting or even reversing the process of calcification. Three randomized clinical trials have tested the benefit of statin treatment in AS progression, but all were negative despite a significant decrease in LDL plasma levels.[108-110] No significant interactions have been reported in these trials between lipid-lowering therapy and CKD with respect to AS progression rate and outcomes. However, the effect of Lp(a)-based therapies such as inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9) or hepatic expression of apolipoprotein (a) (apo(a)) (antisense oligonucleotides or small interfering RNA) is unknown and might offer unprecedented potential for significant reduction in progression of AS and ensuing risk of adverse events.[111] Recent studies suggest a possible beneficial effect of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on the aortic valve fibrotic process, calcification progression, and valve replacement, but the current evidence is overall weak.[112-114] RAAS inhibitors might also reduce the risk of adverse events in AS patients through its beneficial effects on hypertension, LV remodelling, and myocardial fibrosis, which might be even more important in patients with CKD.[115,116]

Calcium/phosphate metabolism dysregulation is common in older and/or CKD patients. Bisphosphonates have an anti-inflammatory effect and are a major regulator of bone turnover by limiting the osteoclastic resorption and calcium phosphate particles release. Thus, it was postulated that bisphosphonates could influence the course of AVC progression. This hypothesis was tested in elderly women with moderate AS without CKD but considered at higher risk of AVC progression because of osteoporosis.[117] Unfortunately, results were negative in this selected population. Conversely, a recent analysis of the **M**ulti-**E**thnic **S**tudy of **A**therosclerosis (MESA) showed a beneficial effect of bisphosphonates use by reducing the vascular and valvular calcification in older women.[118] Denosumab, a RANKL inhibitor (ie, osteoprotegerin-like), which has a similar action to bisphosphonates to treat osteoporosis, showed promising in vitro results by inhibiting the calcification of valvular interstitial cells.[119] Once again, no significant effect was observed on the degree of abdominal aortic calcification after 3 years of treatment in postmenopausal women with osteoporosis.[120] However, AVC progression was not investigated. A randomized controlled trial (**S**cottish **A**ortic Stenosis and **L**ipid Lowering **T**rial: **I**mpact on **Re**gression [SALTIRE] II) is ongoing to determine the effect of bisphosphonates and denosumab on AS progression. One explanation of these negative results could be (1) the presence of confounding factors such as osteoporosis; (2) the confounding effect of the concomitant use of procalcifying agents such as calcium and vitamin D supplements[117]; and/or (3) persistent elevation in plasma PTH level. In this regard, Di Lullo et al. showed impressive results using non-calcium-containing phosphate binders in CKD patients.[121] After 1 year of treatment, aortic and mitral calcification regressed significantly and the circulating levels of FGF-23 and CRP decreased.[121] Management of CKD bone mineral disorder is also essential to limit osteoporosis and soft tissue calcification, especially in patients receiving HD. Raggi et al. reported that the combination of calcimimetic agent cinacalcet with low-dose vitamin D is associated with slower progression of valvular calcification in patients with HD, compared with vitamin D supplementation alone.[122] Parathyroidectomy was also suggested by some authors to aggressively control calcium/phosphate-related complications in CKD patients, especially in cases of severe secondary hyperparathyroidism.[90] Another therapeutic way to limit valvular calcification could be to promote anticalcific agents such as MGP using vitamin K supplementation or to limit VKA prescription to patients not eligible for non-VKA oral anticoagulants (ie, glomerular filtration rate < 30 mL/min/1.73 m^2). Interestingly, recent data suggest that a reduced dose of apixaban might be used in patients with advanced CKD,[123] but this management is off-label and requires further validation. Other attractive therapeutic approaches could be to directly inhibit the cytokines responsible for the osteoblastic differentiation. However, because of the large overlap between factors involved in bone and valvular calcification, the major challenge is to slow or block the AVC process without compromising bone health.

Implications of CKD for the Management of Patients With VHD

Management of VHD in patients with nonsevere CKD (stage $\leq$ 3b: glomerular filtration rate ≥ 30 mL/min/1.73 m^2) should be similar to that in patients with normal kidney function (Fig. 3). However, because of the high prevalence of valvular calcification and cardiovascular events in patients with advanced CKD (stage ≥ 4: glomerular filtration rate < 30 mL/min/1.73 m^2),[124,125] a transthoracic echocardiography (TTE) evaluation should be performed during the course of the CKD, especially in case of symptoms or before HD initiation and renal transplantation (Fig. 3). Moreover, VHD progression is faster in ESRD patients who frequently fulfil the criteria for rapid progressor definition (≥ 0.3 m/s per year for AS).[13,31] Hence, follow-up in ESRD patients with known VHD should probably be more frequent than recommended by current guidelines,[88] and should be systematic before high-risk noncardiac surgery.[126] In addition, patients must be carefully educated about the importance of follow-up and rapid reporting of symptoms. Currently, there is a lack of data on therapeutic management of CKD patients with VHD. To our knowledge, no prospective study has been conducted in this population to determine the optimal timing and type of intervention in this population. Thus, therapeutic decision-making for intervention should comply with the current guidelines. The heart team should include an anaesthesiologist and nephrologist or geriatrician to assess the patient's frailty, surgical risk, and potential risk for periprocedural worsening of renal function. Despite a higher risk of death and complications in patients with advanced CKD,[127-130] invasive interventions are associated with better outcomes than medical therapy alone,[131] except when life expectancy is < 1 year. The optimal invasive approach to treat AS is a matter of debate[127,132] but recent retrospective data suggest better cardiovascular and renal outcomes using a transcatheter aortic valve replacement vs a surgical aortic valve replacement.[133-135] Indeed, transcatheter aortic valve replacement seems to be a lower risk for CKD worsening than surgery, which is a major concern in this population at high risk of subsequent cardiac

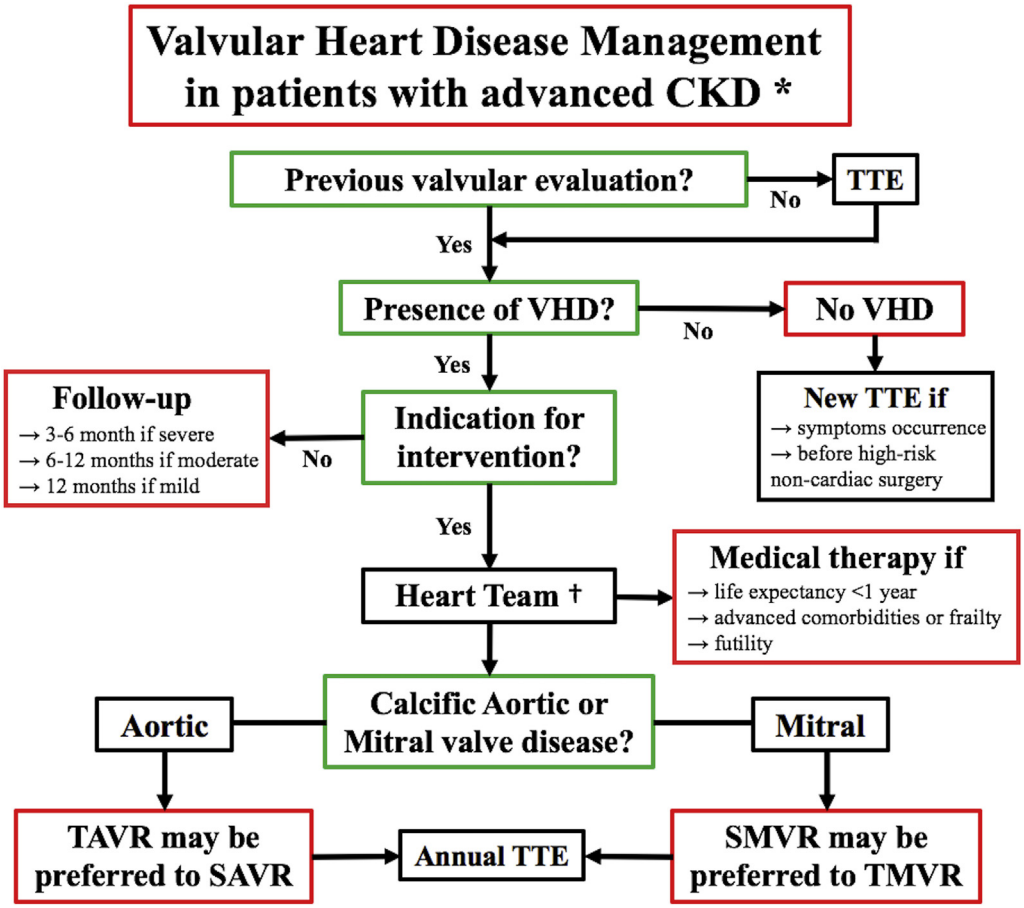

Figure 3. Proposed algorithm for the management of valvular heart disease in patients with advanced CKD. This algorithm is on the basis of the current but limited data published in the literature and will need to be further validated. * CKD ≥ stage 4 defined according to glomerular filtration rate < 30 mL/min/1.73 m^2. † Including anaesthetist and nephrologist. CKD, chronic kidney disease; SAVR, surgical aortic valve replacement; SMVR, surgical mitral valve replacement; TAVR, transcatheter aortic valve replacement; TMVR, transcatheter mitral valve replacement; TTE, transthoracic echocardiography; VHD, valvular heart disease.

and extracardiac interventions. For calcific mitral valve disease, a transcatheter valve-in-MAC procedure should be considered only in unoperable patients.[136] Finally, an annual TTE evaluation is recommended to assess onset and progression of SVD after valve replacement with a bioprosthesis.[18]

Conclusion

The pathophysiology of VHD is an active process, which involves several pathways such as lipid deposition, inflammation, and especially bone metabolism. The coexistence of these mechanisms highlight the presence of a temporal continuum from early aortic valve lesions to final calcified valve. CKD and HD therapy aggravate the progression of valvular calcification and promote SVD of bioprostheses, mainly by inducing hyperphosphatemia-derived lesions and by unbalancing the ratio of pro- and anticalcifying factors. Although several options are being investigated, no medical therapy has yet shown efficacy in slowing or preventing the progression of "degenerative" valvular disease. Patients with advanced CKD should undergo TTE examination for detection of VHD, and if present, follow-up should be more frequent than what is recommended in the guidelines. Transcatheter valve replacement might be preferred over surgical replacement in patients with CKD and severe aortic valve stenosis.

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References

1. Garland JS, Holden RM, Groome PA, et al. Prevalence and associations of coronary artery calcification in patients with stages 3 to 5 CKD without cardiovascular disease. Am J Kidney Dis 2008;52:849-58.
2. Baglin A, Hanslik T, Vaillant JN, et al. Severe valvular heart disease in patients on chronic dialysis. A five-year multicenter French survey. Ann Med Interne (Paris) 1997;148:521-6.
3. Briand M, Pibarot P, Després JP, et al. Metabolic syndrome is associated with faster degeneration of bioprosthetic valves. Circulation 2006;114: I512-7.
4. Fox CS, Larson MG, Vasan RS, et al. Cross-sectional association of kidney function with valvular and annular calcification: the Framingham heart study. J Am Soc Nephrol 2006;17:521-7.
5. Wang Z, Jiang A, Wei F, Chen H. Cardiac valve calcification and risk of cardiovascular or all-cause mortality in dialysis patients: a meta-analysis. BMC Cardiovasc Disord 2018;18:12.
6. Paoletti E, De Nicola L, Gabbai FB, et al. Associations of left ventricular hypertrophy and geometry with adverse outcomes in patients with CKD and hypertension. Clin J Am Soc Nephrol 2016;11:271-9.
7. Parolari A, Loardi C, Mussoni L, et al. Nonrheumatic calcific aortic stenosis: an overview from basic science to pharmacological prevention. Eur J Cardiothorac Surg 2009;35:493-504.
8. Rattazzi M, Bertacco E, Del Vecchio A, et al. Aortic valve calcification in chronic kidney disease. Nephrol Dial Transplant 2013;28:2968-76.
9. Shuvy M, Abedat S, Beeri R, et al. Uraemic hyperparathyroidism causes a reversible inflammatory process of aortic valve calcification in rats. Cardiovasc Res 2008;79:492-9.
10. Schiffrin EL, Lipman ML, Mann JF. Chronic kidney disease: effects on the cardiovascular system. Circulation 2007;116:85-97.
11. Matsuo H, Dohi K, Machida H, et al. Echocardiographic assessment of cardiac structural and functional abnormalities in patients with end-stage renal disease receiving chronic hemodialysis. Circ J 2018;82: 586-95.
12. Braun J, Oldendorf M, Moshage W, et al. Electron beam computed tomography in the evaluation of cardiac calcification in chronic dialysis patients. Am J Kidney Dis 1996;27:394-401.
13. Kume T, Kawamoto T, Akasaka T, et al. Rate of progression of valvular aortic stenosis in patients undergoing dialysis. J Am Soc Echocardiogr 2006;19:914-8.
14. Holden RM, Sanfilippo AS, Hopman WM, et al. Warfarin and aortic valve calcification in hemodialysis patients. J Nephrol 2007;20:417-22.
15. Maher ER, Young G, Smyth-Walsh B, Pugh S, Curtis JR. Aortic and mitral valve calcification in patients with end-stage renal disease. Lancet 1987;2:875-7.
16. Straumann E, Meyer B, Misteli M, Blumberg A, Jenzer HR. Aortic and mitral valve disease in patients with end stage renal failure on long-term haemodialysis. Br Heart J 1992;67:236-9.
17. Ribeiro S, Ramos A, Brandao A, et al. Cardiac valve calcification in haemodialysis patients: role of calcium-phosphate metabolism. Nephrol Dial Transplant 1998;13:2037-40.
18. Ventura JE, Tavella N, Romero C, et al. Aortic valve calcification is an independent factor of left ventricular hypertrophy in patients on maintenance haemodialysis. Nephrol Dial Transplant 2002;17: 1795-801.
19. Raggi P, Boulay A, Chasan-Taber S, et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol 2002;39:695-701.
20. Wang AY, Wang M, Woo J, et al. Cardiac valve calcification as an important predictor for all-cause mortality and cardiovascular mortality in long-term peritoneal dialysis patients: a prospective study. J Am Soc Nephrol 2003;14:159-68.
21. Schönenberger A, Winkelspecht B, Köhler H, Girndt M. High prevalence of aortic valve alterations in haemodialysis patients is associated with signs of chronic inflammation. Nephron Clin Pract 2004;96: c48-55.
22. Varma R, Aronow WS, McClung JA, et al. Prevalence of valve calcium and association of valve calcium with coronary artery disease, atherosclerotic vascular disease, and all-cause mortality in 137 patients undergoing hemodialysis for chronic renal failure. Am J Cardiol 2005;95: 742-3.
23. Tarrass F, Benjelloun M, Zamd M, et al. Heart valve calcifications in patients with end-stage renal disease: analysis for risk factors. Nephrology (Carlton) 2006;11:494-6.
24. Ix JH, Shlipak MG, Katz R, et al. Kidney function and aortic valve and mitral annular calcification in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Kidney Dis 2007;50:412-20.
25. Adeney KL, Siscovick DS, Ix JH, et al. Association of serum phosphate with vascular and valvular calcification in moderate CKD. J Am Soc Nephrol 2009;20:381-7.
26. Ikee R, Honda K, Ishioka K, et al. Differences in associated factors between aortic and mitral valve calcification in hemodialysis. Hypertens Res 2010;33:622-6.
27. Avila-Díaz M, Mora-Villalpando C, Prado-Uribe Mdel C, et al. De novo development of heart valve calcification in incident peritoneal dialysis patients. Arch Med Res 2013;44:638-44.
28. Rong S, Qiu X, Jin X, et al. Risk factors for heart valve calcification in chronic kidney disease. Medicine (Baltimore) 2018;97:e9804.
29. Kim D, Shim CY, Hong GR, et al. Effect of end-stage renal disease on rate of progression of aortic stenosis. Am J Cardiol 2016;117:1972-7.
30. Zentner D, Hunt D, Chan W, et al. Prospective evaluation of aortic stenosis in end-stage kidney disease: a more fulminant process? Nephrol Dial Transplant 2011;26:1651-5.
31. Ohara T, Hashimoto Y, Matsumura A, Suzuki M, Isobe M. Accelerated progression and morbidity in patients with aortic stenosis on chronic dialysis. Circ J 2005;69:1535-9.
32. Wongpraparut N, Apiyasawat S, Crespo G, et al. Determinants of progression of aortic stenosis in patients aged >= 40 years. Am J Cardiol 2002;89:350-2.
33. Perkovic V, Hunt D, Griffin SV, du Plessis M, Becker GJ. Accelerated progression of calcific aortic stenosis in dialysis patients. Nephron Clin Pract 2003;94:c40-5.
34. Malergue MC, Urena P, Prieur P, Guédon-Rapoud C, Pétrover M. Incidence and development of aortic stenosis in chronic hemodialysis. An ultrasonographic and biological study of 112 patients [in French]. Arch Mal Coeur Vaiss 1997;90:1595-601.
35. Kawase Y, Taniguchi T, Morimoto T, et al. Severe aortic stenosis in dialysis patients. J Am Heart Assoc 2017;6:e00496.

36. Tian Y, Feng S, Zhan Z, et al. Risk factors for new-onset cardiac valve calcification in patients on maintenance peritoneal dialysis. Cardiorenal Med 2016;6:150-8.

37. Otto CM, Kuusisto J, Reichenbach DD, Gown AM, O'Brien KD. Characterization of the early lesion of 'degenerative' valvular aortic stenosis. Histological and immunohistochemical studies. Circulation 1994;90:844-53.

38. Otto CM. Calcific aortic stenosis–time to look more closely at the valve. N Engl J Med 2008;359:1395-8.

39. Verrier ED, Boyle EM Jr. Endothelial cell injury in cardiovascular surgery. Ann Thorac Surg 1996;62:915-22.

40. Diehl P, Nagy F, Sossong V, et al. Increased levels of circulating microparticles in patients with severe aortic valve stenosis. Thromb Haemost 2008;99:711-9.

41. Côté C, Pibarot P, Després JP, et al. Association between circulating oxidised low-density lipoprotein and fibrocalcific remodelling of the aortic valve in aortic stenosis. Heart 2008;94:1175-80.

42. Stewart BF, Siscovick D, Lind BK, et al. Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. J Am Coll Cardiol 1997;29:630-4.

43. Capoulade R, Yeang C, Chan KL, Pibarot P, Tsimikas S. Association of mild to moderate aortic valve stenosis progression with higher lipoprotein(a) and oxidized phospholipid levels: secondary analysis of a randomized clinical trial. JAMA Cardiol 2018;3:1212-7.

44. Thanassoulis G, Campbell CY, Owens DS, et al. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med 2013;368:503-12.

45. Boon A, Cheriex E, Lodder J, Kessels F. Cardiac valve calcification: characteristics of patients with calcification of the mitral annulus or aortic valve. Heart 1997;78:472-4.

46. Hopewell JC, Haynes R, Baigent C. The role of lipoprotein (a) in chronic kidney disease. J Lipid Res 2018;59:577-85.

47. Caira FC, Stock SR, Gleason TG, et al. Human degenerative valve disease is associated with up-regulation of low-density lipoprotein receptor-related protein 5 receptor-mediated bone formation. J Am Coll Cardiol 2006;47:1707-12.

48. O'Brien KD, Shavelle DM, Caulfield MT, et al. Association of angiotensin-converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. Circulation 2002;106:2224-30.

49. Miller JD, Chu Y, Brooks RM, et al. Dysregulation of antioxidant mechanisms contributes to increased oxidative stress in calcific aortic valvular stenosis in humans. J Am Coll Cardiol 2008;52:843-50.

50. Böger RH. Asymmetric dimethylarginine (ADMA): a novel risk marker in cardiovascular medicine and beyond. Ann Med 2006;38:126-36.

51. Bertacco E, Millioni R, Arrigoni G, et al. Proteomic analysis of clonal interstitial aortic valve cells acquiring a pro-calcific profile. J Proteome Res 2010;9:5913-21.

52. Ngo DT, Heresztyn T, Mishra K, Marwick TH, Horowitz JD. Aortic stenosis is associated with elevated plasma levels of asymmetric dimethylarginine (ADMA). Nitric Oxide 2007;16:197-201.

53. Cagirci G, Cay S, Canga A, et al. Association between plasma asymmetrical dimethylarginine activity and severity of aortic valve stenosis. J Cardiovasc Med (Hagerstown) 2011;12:96-101.

54. Kooman JP, Dekker MJ, Usvyat LA, et al. Inflammation and premature aging in advanced chronic kidney disease. Am J Physiol Renal Physiol 2017;313:F938-50.

55. Leskinen Y, Paana T, Saha H, et al. Valvular calcification and its relationship to atherosclerosis in chronic kidney disease. J Heart Valve Dis 2009;18:429-38.

56. Wang AY, Woo J, Wang M, et al. Association of inflammation and malnutrition with cardiac valve calcification in continuous ambulatory peritoneal dialysis patients. J Am Soc Nephrol 2001;12:1927-36.

57. Mohler ER 3rd, Gannon F, Reynolds C, et al. Bone formation and inflammation in cardiac valves. Circulation 2001;103:1522-8.

58. Rajamannan NM, Subramaniam M, Rickard D, et al. Human aortic valve calcification is associated with an osteoblast phenotype. Circulation 2003;107:2181-4.

59. Aikawa E, Nahrendorf M, Sosnovik D, et al. Multimodality molecular imaging identifies proteolytic and osteogenic activities in early aortic valve disease. Circulation 2007;115:377-86.

60. Pohjolainen V, Taskinen P, Soini Y, et al. Noncollagenous bone matrix proteins as a part of calcific aortic valve disease regulation. Hum Pathol 2008;39:1695-701.

61. Bennett BJ, Scatena M, Kirk EA, et al. Osteoprotegerin inactivation accelerates advanced atherosclerotic lesion progression and calcification in older ApoE-/- mice. Arterioscler Thromb Vasc Biol 2006;26:2117-24.

62. Steinmetz M, Skowasch D, Wernert N, et al. Differential profile of the OPG/RANKL/RANK-system in degenerative aortic native and bioprosthetic valves. J Heart Valve Dis 2008;17:187-93.

63. Schafer C, Heiss A, Schwarz A, et al. The serum protein alpha 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. J Clin Invest 2003;112:357-66.

64. Schurgers LJ, Cranenburg EC, Vermeer C. Matrix Gla-protein: the calcification inhibitor in need of vitamin K. Thromb Haemost 2008;100:593-603.

65. Chiyoya M, Seya K, Yu Z, et al. Matrix Gla protein negatively regulates calcification of human aortic valve interstitial cells isolated from calcified aortic valves. J Pharmacol Sci 2018;136:257-65.

66. Shea MK, Holden RM. Vitamin K status and vascular calcification: evidence from observational and clinical studies. Adv Nutr 2012;3:158-65.

67. Yamamoto K, Koretsune Y, Akasaka T, et al. Effects of vitamin K antagonist on aortic valve degeneration in non-valvular atrial fibrillation patients: prospective 4-year observational study. Thromb Res 2017;160:69-75.

68. Di Lullo L, Tripepi G, Ronco C, et al. Cardiac valve calcification and use of anticoagulants: Preliminary observation of a potentially modifiable risk factor. Int J Cardiol 2019;278:243-9.

69. Tastet L, Pibarot P, Shen M, et al. Oral anticoagulation therapy and progression of calcific aortic valve stenosis. J Am Coll Cardiol 2019;73:1869-71.

70. Koos R, Brandenburg V, Mahnken AH, et al. Association of fetuin-A levels with the progression of aortic valve calcification in non-dialyzed patients. Eur Heart J 2009;30:2054-61.

71. Ix JH, Chertow GM, Shlipak MG, et al. Association of fetuin-A with mitral annular calcification and aortic stenosis among persons with coronary heart disease: data from the Heart and Soul Study. Circulation 2007;115:2533-9.

72. Kubota N, Testuz A, Boutten A, et al. Impact of fetuin-A on progression of calcific aortic valve stenosis - The COFRASA - GENERAC study. Int J Cardiol 2018;265:52-7.

73. El-Shehaby AM, Zakaria A, El-Khatib M, Mostafa N. Association of fetuin-A and cardiac calcification and inflammation levels in hemodialysis patients. Scand J Clin Lab Invest 2010;70:575-82.

74. Wang AY, Woo J, Lam CW, et al. Associations of serum fetuin-A with malnutrition, inflammation, atherosclerosis and valvular calcification syndrome and outcome in peritoneal dialysis patients. Nephrol Dial Transplant 2005;20:1676-85.

75. Ketteler M, Bongartz P, Westenfeld R, et al. Association of low fetuin-A (AHSG) concentrations in serum with cardiovascular mortality in patients on dialysis: a cross-sectional study. Lancet 2003;361:827-33.

76. Lacey DL, Timms E, Tan HL, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998;93:165-76.

77. Partridge NC, Li X, Qin L. Understanding parathyroid hormone action. Ann N Y Acad Sci 2006;1068:187-93.

78. Iwata S, Hyodo E, Yanagi S, et al. Parathyroid hormone and systolic blood pressure accelerate the progression of aortic valve stenosis in chronic hemodialysis patients. Int J Cardiol 2013;163:256-9.

79. Rattazzi M, Iop L, Faggin E, et al. Clones of interstitial cells from bovine aortic valve exhibit different calcifying potential when exposed to endotoxin and phosphate. Arterioscler Thromb Vasc Biol 2008;28:2165-72.

80. Zoppellaro G, Faggin E, Puato M, Pauletto P, Rattazzi M. Fibroblast growth factor 23 and the bone-vascular axis: lessons learned from animal studies. Am J Kidney Dis 2012;59:135-44.

81. Gutiérrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med 2008;359:584-92.

82. Kirkpantur A, Balci M, Gurbuz OA, et al. Serum fibroblast growth factor-23 (FGF-23) levels are independently associated with left ventricular mass and myocardial performance index in maintenance haemodialysis patients. Nephrol Dial Transplant 2011;26:1346-54.

83. Di Lullo L, Gorini A, Bellasi A, et al. Fibroblast growth factor 23 and parathyroid hormone predict extent of aortic valve calcifications in patients with mild to moderate chronic kidney disease. Clin Kidney J 2015;8:732-6.

84. Unsal A, Kose Budak S, Koc Y, et al. Relationship of fibroblast growth factor 23 with left ventricle mass index and coronary calcificaton in chronic renal disease. Kidney Blood Press Res 2012;36:55-64.

85. Chen J, Lin Y, Sun Z. Deficiency in the anti-aging gene Klotho promotes aortic valve fibrosis through AMPKalpha-mediated activation of RUNX2. Aging Cell 2016;15:853-60.

86. Chen J, Fan J, Wang S, Sun Z. Secreted Klotho attenuates inflammation-associated aortic valve fibrosis in senescence-accelerated mice P1. Hypertension 2018;71:877-85.

87. Li F, Yao Q, Ao L, et al. Klotho suppresses high phosphate-induced osteogenic responses in human aortic valve interstitial cells through inhibition of Sox9. J Mol Med (Berl) 2017;95:739-51.

88. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease: the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2017;38:2739-91.

89. Salaun E, Mahjoub H, Girerd N, et al. Rate, timing, correlates, and outcomes of hemodynamic valve deterioration after bioprosthetic surgical aortic valve replacement. Circulation 2018;138:971-85.

90. Okada N, Tajima K, Takami Y, et al. Valve selection for the aortic position in dialysis patients. Ann Thorac Surg 2015;99:1524-31.

91. Lamberti JJ, Wainer BH, Fisher KA, Karunaratne HB, Al-Sadir J. Calcific stenosis of the porcine heterograft. Ann Thorac Surg 1979;28:28-32.

92. Brinkman WT, Williams WH, Guyton RA, Jones EL, Craver JM. Valve replacement in patients on chronic renal dialysis: implications for valve prosthesis selection. Ann Thorac Surg 2002;74:37-42 [discussion: 42].

93. Bianchi G, Solinas M, Bevilacqua S, Glauber M. Are bioprostheses associated with better outcome than mechanical valves in patients with chronic kidney disease requiring dialysis who undergo valve surgery? Interact Cardiovasc Thorac Surg 2012;15:473-83.

94. Williams ML, Bavaria JE, Acker MA, et al. Valve selection in end-stage renal disease: should it always be biological? Ann Thorac Surg 2016;102:1531-5.

95. Kaplon RJ, Cosgrove DM 3rd, Gillinov AM, et al. Cardiac valve replacement in patients on dialysis: influence of prosthesis on survival. Ann Thorac Surg 2000;70:438-41.

96. Altarabsheh SE, Deo SV, Dunlay SM, et al. Tissue valves are preferable for patients with end-stage renal disease: an aggregate meta-analysis. J Card Surg 2016;31:507-14.

97. Bolignano D, Pisano A, Coppolino G, Tripepi GL, D'Arrigo G. Pulmonary hypertension predicts adverse outcomes in renal patients: a systematic review and meta-analysis. Ther Apher Dial 2019;23:369-84.

98. Edwards NC, Moody WE, Yuan M, et al. Diffuse interstitial fibrosis and myocardial dysfunction in early chronic kidney disease. Am J Cardiol 2015;115:1311-7.

99. Hung MJ, Yang NI, Wu IW, et al. Echocardiographic assessment of structural and functional cardiac remodeling in patients with predialysis chronic kidney disease. Echocardiography 2010;27:621-9.

100. Hawwa N, Shrestha K, Hammadah M, et al. Reverse remodeling and prognosis following kidney transplantation in contemporary patients with cardiac dysfunction. J Am Coll Cardiol 2015;66:1779-87.

101. Martin FL, McKie PM, Cataliotti A, et al. Experimental mild renal insufficiency mediates early cardiac apoptosis, fibrosis, and diastolic dysfunction: a kidney-heart connection. Am J Physiol Regul Integr Comp Physiol 2012;302:R292-9.

102. Leifheit-Nestler M, Kirchhoff F, Nespor J, et al. Fibroblast growth factor 23 is induced by an activated renin-angiotensin-aldosterone system in cardiac myocytes and promotes the pro-fibrotic crosstalk between cardiac myocytes and fibroblasts. Nephrol Dial Transplant 2018;33:1722-34.

103. Ky B, Shults J, Keane MG, et al. FGF23 modifies the relationship between vitamin D and cardiac remodeling. Circ Heart Fail 2013;6:817-24.

104. Xie J, Yoon J, An SW, Kuro-o M, Huang CL. Soluble Klotho protects against uremic cardiomyopathy independently of fibroblast growth factor 23 and phosphate. J Am Soc Nephrol 2015;26:1150-60.

105. Nubé MJ, Hoekstra T, Doganer V, et al. Left ventricular geometric patterns in end-stage kidney disease: determinants and course over time. Hemodial Int 2018;22:359-68.

106. Reddy YNV, Obokata M, Dean PG, et al. Long-term cardiovascular changes following creation of arteriovenous fistula in patients with end stage renal disease. Eur Heart J 2017;38:1913-23.

107. Alkhouli M, Sandhu P, Boobes K, et al. Cardiac complications of arteriovenous fistulas in patients with end-stage renal disease. Nefrologia 2015;35:234-45.

108. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis. Results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation 2010;121:306-14.

109. Cowell SJ, Newby DE, Prescott RJ, et al. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. N Engl J Med 2005;352:2389-97.

110. Rossebo AB, Pedersen TR, Boman K, et al. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008;359:1343-56.

111. Vuorio A, Watts GF, Kovanen PT. Lipoprotein(a) as a risk factor for calcific aortic valvulopathy in heterozygous familial hypercholesterolemia. Atherosclerosis 2019;281:25-30.

112. Bull S, Loudon M, Francis JM, et al. A prospective, double-blind, randomized controlled trial of the angiotensin-converting enzyme inhibitor Ramipril In Aortic Stenosis (RIAS trial). Eur Heart J Cardiovasc Imaging 2015;16:834-41.

113. Andersson C, Abdulla J. Is the use of renin-angiotensin system inhibitors in patients with aortic valve stenosis safe and of prognostic benefit? A systematic review and meta-analysis. Eur Heart J Cardiovasc Pharmacother 2017;3:21-7.

114. Côté N, Mahmut A, Fournier D, et al. Angiotensin receptor blockers are associated with reduced fibrosis and interleukin-6 expression in calcific aortic valve disease. Pathobiology 2014;81:15-24.

115. Nadir MA, Wei L, Elder DH, et al. Impact of renin-angiotensin system blockade therapy on outcome in aortic stenosis. J Am Coll Cardiol 2011;58:570-6.

116. Suematsu Y, Jing W, Nunes A, et al. LCZ696 (sacubitril/valsartan), an angiotensin-receptor neprilysin inhibitor, attenuates cardiac hypertrophy, fibrosis, and vasculopathy in a rat model of chronic kidney disease. J Card Fail 2018;24:266-75.

117. Aksoy O, Cam A, Goel SS, et al. Do bisphosphonates slow the progression of aortic stenosis? J Am Coll Cardiol 2012;59:1452-9.

118. Elmariah S, Delaney JAC, O'Brien KD, et al. Bisphosphonate use and prevalence of valvular and vascular calcification in women: MESA (The Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2010;56:1752-9.

119. Lerman DA, Prasad S, Alotti N. Denosumab could be a potential inhibitor of valvular interstitial cells calcification in vitro. Int J Cardiovasc Res 2016;6.

120. Samelson EJ, Miller PD, Christiansen C, et al. RANKL inhibition with denosumab does not influence 3-year progression of aortic calcification or incidence of adverse cardiovascular events in postmenopausal women with osteoporosis and high cardiovascular risk. J Bone Miner Res 2014;29:450-7.

121. Di Lullo L, Floccari F, Santoboni A, et al. Progression of cardiac valve calcification and decline of renal function in CKD patients. J Nephrol 2013;26:739-44.

122. Raggi P, Chertow GM, Torres PU, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrol Dial Transplant 2011;26:1327-39.

123. Kalra PA, Burlacu A, Ferro CJ, Covic A. Which anticoagulants should be used for stroke prevention in non-valvular atrial fibrillation and severe chronic kidney disease? Curr Opin Nephrol Hypertens 2018;27:420-5.

124. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296-305.

125. Go AS. Cardiovascular disease consequences of CKD. Semin Nephrol 2016;36:293-304.

126. Kristensen SD, Knuuti J, Saraste A, et al. 2014 ESC/ESA guidelines on non-cardiac surgery: cardiovascular assessment and management: the Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J 2014;35:2383-431.

127. D'Errigo P, Moretti C, D'Ascenzo F, et al. Transcatheter aortic valve implantation vs surgical aortic valve replacement for severe aortic stenosis in patients with chronic kidney disease stages 3b to 5. Ann Thorac Surg 2016;102:540-7.

128. Thourani VH, Forcillo J, Beohar N, et al. Impact of preoperative chronic kidney disease in 2,531 high-risk and inoperable patients undergoing transcatheter aortic valve replacement in the PARTNER trial. Ann Thorac Surg 2016;102:1172-80.

129. Gupta T, Goel K, Kolte D, et al. Association of chronic kidney disease with in-hospital outcomes of transcatheter aortic valve replacement. JACC Cardiovasc Interv 2017;10:2050-60.

130. Bhatia N, Agrawal S, Yang S, et al. In-hospital outcomes of transcatheter aortic valve implantation in patients with end-stage renal disease on dialysis from a large national database. Am J Cardiol 2017;120:1355-8.

131. Condado JF, Maini A, Leshnower B, et al. End-stage renal disease and severe aortic stenosis: does valve replacement improve one-year outcomes? Catheter Cardiovasc Interv 2017;89:1109-15.

132. Vindhyal MR, Ndunda P, Khayyat S, Boppana VS, Fanari Z. Transcatheter aortic valve replacement and surgical aortic valve replacement outcomes in patients with dialysis: systematic review and meta-analysis [e-pub ahead of print] Cardiovasc Revasc Med. https://doi.org/10.1016/j.carrev.2018.12.002.

133. Kumar N, Khera R, Garg N, et al. Comparison of outcomes of transcatheter vs surgical aortic valve replacement in patients with chronic kidney disease. Am J Cardiol 2018;121:343-8.

134. Pineda AM, Kevin Harrison J, Kleiman NS, et al. Clinical impact of baseline chronic kidney disease in patients undergoing transcatheter or surgical aortic valve replacement. Catheter Cardiovasc Interv 2019;93:740-8.

135. Alkhalil A, Golbari S, Song D, et al. In-hospital outcomes of transcatheter vs surgical aortic valve replacement in end stage renal disease. Catheter Cardiovasc Interv 2018;92:757-65.

136. Yoon SH, Whisenant BK, Bleiziffer S, et al. Outcomes of transcatheter mitral valve replacement for degenerated bioprostheses, failed annuloplasty rings, and mitral annular calcification. Eur Heart J 2019;40:441-51.