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CKJ Review

CKJ REVIEW

Valvular calcification in chronic kidney disease: new insights from recent clinical and preclinical studies

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ABSTRACT

Valvular calcification, developing either in the mitral or the aortic valve, is highly prevalent in patients suffering from chronic kidney disease (CKD), in whom their presence correlates with higher cardiovascular and all-cause mortality risk. To date, the exact mechanisms that promote heart valve calcification remain unclear, and none of the treatments tested so far have shown efficacy in preventing valvular fibrocalcific remodelling. It is therefore essential to improve our understanding of the mechanisms involved in the pathological process if we are to find new, effective therapies. The purpose of this review is to (i) summarize our current knowledge of the mechanisms by which CKD and related therapies affect valvular cell activity, (ii) present the latest therapeutic targets identified in preclinical studies, and (iii) discuss the most recent clinical trials evaluating the efficacy of therapies aimed at preventing valvular calcification in CKD.

Keywords: aortic valve calcification, chronic kidney disease, mitral valve calcification

INTRODUCTION

Cardiovascular calcification is a degenerative process characterized by the accumulation of calcium and phosphate salts in the form of hydroxyapatite within the intimal and/or medial layers of the vessel wall, and in the heart valves. Cardiovascular calcification is not only abundant in CKD patients, but has also been shown to have a faster rate of progression [1, 2]. Research has largely focused on the pathophysiology and consequences of vascular calcification; less attention has been paid to heart valve calcification and its impact on the survival of patients with CKD. Epidemiological data report that the aortic valve (AV) and mitral valve (MV) are most commonly affected in CKD patients, resulting in valve stenosis and/or regurgitation [3, 4]. In patients on maintenance haemodialysis (HD), the reported prevalence of AV and MV calcification varies between 25% and 59% [1, 5–7]. Overall, the prevalence of valvular calcification (VC) is eight times

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higher in patients undergoing HD than in the general population [7]. In HD patients, the presence of VC is correlated with higher cardiovascular and all-cause mortality risk [8–10]. The exact mechanisms that promote heart valve calcification remain unclear, and there is no pharmacotherapy specifically targeting VC to prevent progressive valvular fibrocalcific remodelling. It is therefore essential to improve our understanding of the mechanisms involved in the pathological process if we are to find effective therapies. The purpose of this review is to (i) summarize our current knowledge of the mechanisms by which CKD and related therapies affect valvular cell activity, (ii) present the latest therapeutic targets identified in preclinical studies, and (iii) discuss the most recent clinical trials evaluating the efficacy of therapies aimed at preventing VC in CKD.

VALVULAR CALCIFICATION: MAJOR MECHANISMS AND CONSEQUENCES

Overview of the main cellular and molecular mechanisms

Quiescent valvular interstitial cells (qVICs) are the prominent cell type in healthy valve cusps and leaflets, residing throughout the fibrosa, spongiosa, and atrialis (MV)/ventricularis (AV) layers. VICs are recognized as essential for the homeostasis and remodelling of layer-specific extracellular matrix but also play a key role in pathological leaflet remodelling [11]. In response to injury or altered mechanical forces, qVICs transition towards activated VICs (aVICs), displaying a myofibroblastic phenotype characterized by the expression of α-smooth muscle actin (α-SMA), leading to fibrosis, thickening, and increased valve stiffness. Alternatively, qVICs and aVICs can differentiate into osteoblast-like cells (obVICs). These cells express markers such as runt-related transcription factor 2 (RUNX2), a marker of terminal osteoblastic differentiation, and can secrete a bone-like matrix that can calcify. If not halted, this mineralization process can lead to the formation of bone- and cartilage-like tissues that dramatically decrease the elasticity of valve leaflets. Evidence from histological and *in vitro* studies suggests that valvular remodelling shares similarities with vascular atherosclerosis. The main cellular and molecular mechanisms leading to VC are summarized in Fig. 1.

AV calcification

In the AV, infiltration of red blood cells, oxidized lipids, and immune cell (monocytes/lymphocytes) following valvular endothelial injury is the initiating event [12–14]. Subsequent release of growth factors and pro-inflammatory cytokines by infiltrated macrophages and T cells have a profound impact on qVIC physiology. Indeed, secretion of TGF-β (transforming growth factor β) promotes qVIC transition towards pro-fibrotic aVIC. Local dysregulation in the mineral balance promotes the formation of obVICs expressing alkaline phosphatase (ALP), bone morphogenetic protein 2 (BMP2), MSX2, osteopontin (OPN), and RUNX2 [11, 15, 16]. Through a process known as endothelial-to-mesenchymal transition (EndMT), aortic valvular endothelial cells (VECs) can acquire a myofibroblastic phenotype and progressively develop an osteoblast-like phenotype, leading to calcification [17–19]. AV diseases preferentially occur in the aortic side of the valvular leaflets where they are exposed to complex and unstable haemodynamic conditions [20]. Similar to the vasculature, the altered haemodynamics can induce endothelial activation and inflammatory responses in AV leaflets [21], rendering them more prone to calcification and plaque formation [22].

MV calcification

As MV remodelling has been studied less than AV remodelling, it remains unclear to what extent the same mechanistic sequence is involved in the development of MV calcification. The process may be slightly different in the MV compared to the AV due to specific valvular architectures, overall cellular content, and different haemodynamic environments associated with their physical locations. Histologically, mitral annulus specimens show lipid deposition and inflammatory cell infiltration in the vicinity of calcification [23, 24]. Myofibroblastic differentiation of interstitial cells and the presence of lamellar bone have also been reported [25]. Stretching, mechanical stress, inflammation, or turbulent flow can trigger myofibroblastic differentiation of mitral qVICs either directly [26] or through the release of TGF-β [27]. *In vitro*, mitral qVICs exposed to osteogenic medium can undergo both myofibroblastic and osteogenic differentiation, and display the ability to calcify over time [28–31]. As with aortic VECs, mitral VECs showed a propensity for osteogenic, as well as chondrogenic differentiation [30].

Consequences for valvular phenotype and function

Process of AV remodelling

The gradual fibro-calcific remodelling of the AV leaflets, called calcific aortic valve disease (CAVD), represents the most prevalent valvular heart disease worldwide [32, 33]. In the early phase of the disease, called AV sclerosis, the valve thickens and calcifies slightly, but these changes do not impede blood flow. Over time, the disease can progress to severe calcification of the valve with impaired leaflet movement and progressive narrowing of AV opening that impedes left ventricular outflow. Without intervention, progressive ventricular hypertrophy ensues ultimately leading to heart failure and death. Patients can experience distressing symptoms such as shortness of breath, angina, and syncope. Calcific aortic stenosis (CAS), the late stage of CAVD, is associated with important cardiovascular morbidity and mortality. Without appropriate and timely treatment the risk of death at 2 years can increase to 50% in the presence of severe CAS [32, 34, 35]. Currently, aortic valve replacement (AVR), either through surgery (SAVR) or transcatheter means (TAVR), remains the mainstay of management for patients with progressive and symptomatic CAS.

Process of MV remodelling

MV calcification results from gradual calcification of the fibrous mitral annulus, predominantly developing along its posterior portion [36]. When the calcification is confined to the annulus, leaflet motion is preserved and ventricular filling is unimpeded. However, calcific degeneration tends to spread further into the leaflets over time, resulting in impaired leaflet mobility and distortion [37]. These anatomical changes can cause both mitral stenosis [37] and mitral regurgitation [38]. While either lesion may be dominant in a given patient, mixed disease is more common. Mitral annular calcification is associated with progressive gradients across the MV [39]. When mitral stenosis or mitral regurgitation becomes severe, symptoms of heart failure, including dyspnoea and exercise intolerance, may occur. Possible extension of calcification into the left ventricle, papillary muscle, chordae tendineae, and left ventricular outflow tract, with

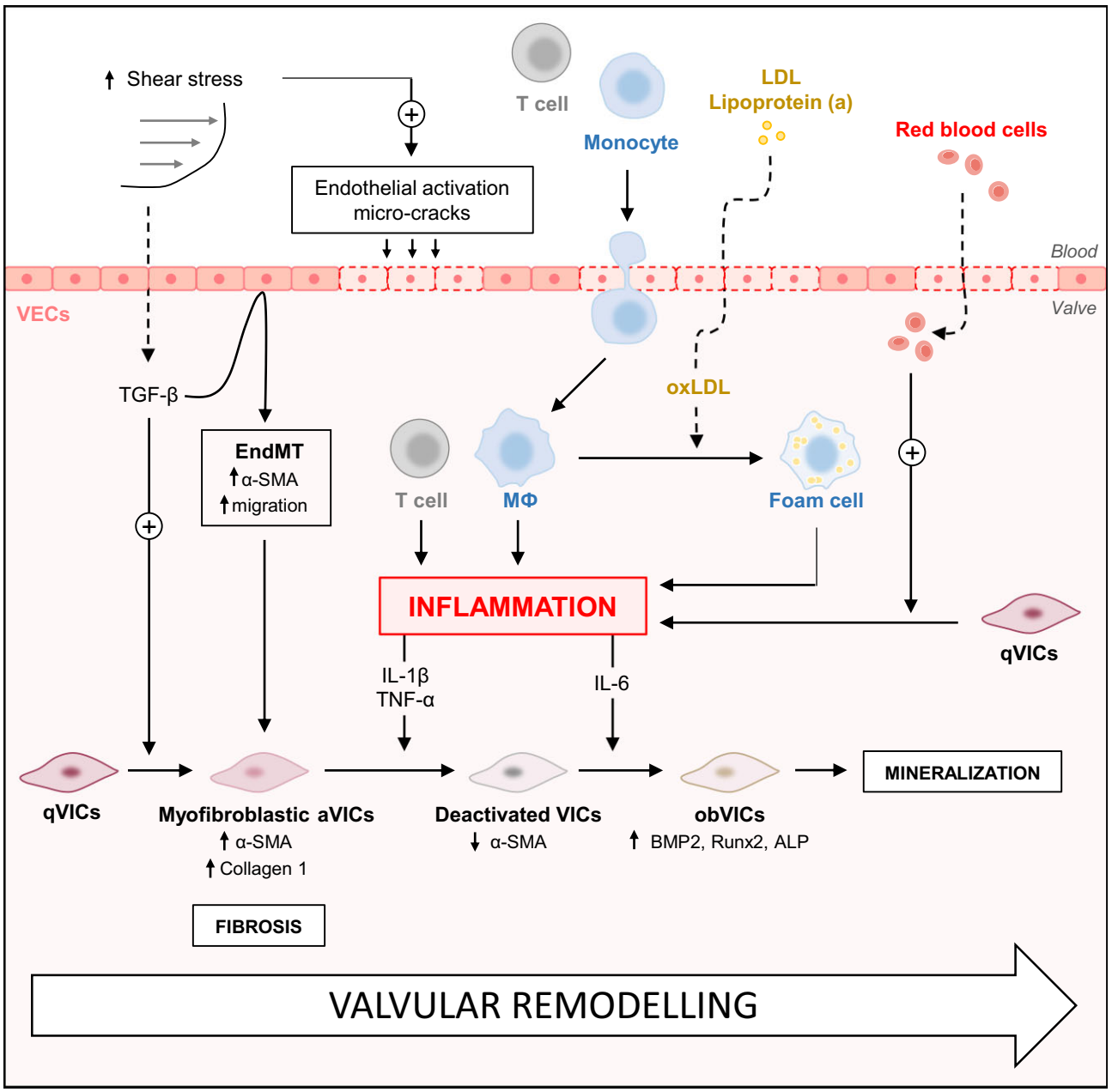

Figure 1: Overview of the main mechanisms leading to valvular remodelling. Among the main mechanisms involved in AV remodelling, shear stress can induce endothelial damage and TGF-β accumulation within the valvular tissue. TGF-β promotes the EndMT of VECs as well as the transformation of qVICs into myofibroblast-activated VICs (aVICs), which can secrete collagen and promote valvular fibrosis and thickening. VECs dysfunction favours the infiltration of oxidized LDL and inflammatory cells, including macrophages, thereby promoting foam cell formation and initiating a process that resembles vascular atherosclerosis. Macrophage secretion of TNF-α and IL-1β promotes the deactivation of aVICs. Subsequent exposure to IL-6 promotes their osteogenic transition towards obVICs capable of promoting the mineralization process. αSMA, α-smooth muscle actin; MΦ, macrophage; oxLDL, oxidized LDL; ALP: alkaline phosphatase.

occasional continuous calcification of the aorto-mitral curtain extending to the AV have been reported in the most severe cases [40].

VALVULAR CALCIFICATION IN CKD PATIENTS

Prevalence and outcomes

AV calcification

In CKD, the prevalence of CAS gradually increases as eGFR declines [41]. In this population, the pathological remodelling of the AV is more frequent [42], occurs earlier [4], progresses faster [43], and is associated with a worse prognosis [41, 43, 44] than in the general population. In CKD patients, most CAS are of degenerative origin (91%), with bicuspid-related CAS observed in only 7% of patients [45]. To date, the prevalence and progression of CAS in kidney transplant recipients has been poorly studied. Although the exact cellular and molecular mechanisms underlying AV remodelling in CKD patients remain unclear, multiple factors may account for the high prevalence and rapid progression of CAS in the CKD population. These include: the high calcium-phosphate product, accumulation of uremic toxins,

low-grade inflammation, and use of anti-vitamin K drugs, together with low levels of calcification inhibitors such as pyrophosphate and fetuin A.

MV calcification

MV calcification is also common in patients with CKD [5, 46, 47]. Interestingly, severe MV calcification predicts CKD [48]. In dialysis patients, the presence of MV calcification correlated significantly with ischaemic heart disease [49]. Mitral annular calcification is associated with increased mortality and significant coronary artery disease in end-stage kidney disease patients. These patients have increased left ventricular cavity size, worse left ventricular systolic function, and higher left ventricular filling pressures compared to patients without MV calcification [47]. MV calcification is highly prevalent in renal transplant patients, with reported rates ranging from 21.5% to 23% [50–52]. Among renal transplant recipients, the burden of pre-transplant MV calcification was reported to be an independent predictor of post-transplant risk of cardiac death and myocardial infarction [52]. Kidney transplantation, which reduces cardiac volume overload, leads to a significant improvement in mitral regurgitation [51]. In 2021, Daragó et al. reported that calcification of the mitral and aortic valves progressed steadily, although not significantly, after kidney transplantation. In this study, the presence of diabetes was significantly associated with the incidence of calcified valves after kidney transplantation.

Clinical and preclinical associations

The main factors associated with the risk of developing VC in patients with CKD and the general population are summarized in Table 1. The mechanisms of action are presented in Fig. 2.

CaxP product

Elevated CaxP (calcium-phosphate product) product is a strong predictor of VC in HD patients [10, 53, 54]. *In vitro*, calcium and phosphate, either alone [55–57] or in combination [58, 59], promote VICs osteogenic transition (evidenced by increased BMP2, OPN, RUNX2, SOX9 expression, and ALP activity), and mineralization [55, 60–62]. In rodents with induced renal disease, an increase in phosphate intake is required to induce VC [63–65]. Serum phosphate levels, even within the normal range, are significantly associated with the prevalence of VC both in the general population [66–68] and in patients with reduced renal function [69].

PTH

Elevated levels of PTH (parathyroid hormone) are associated with the presence of AV calcification in patients with preserved renal function [70], with mild to moderate CKD [71] and those receiving maintenance HD [72]. In preclinical studies, elevated PTH (either *in vitro* or in CKD mice) promotes VEC dysfunction and subsequent EndMT. This favours their transition towards osteoblast-like cells able to express BMP-2, bone sialoprotein, OPN, SOX9, and RUNX2 [73, 74]. The secretome of PTH-treated VEC promotes VICs osteogenic transition, evidenced by increased BMP-2/4 expression, increased secretion of osteocalcin and TGF-β1, and downregulation of collagen I and III [73]. The observation that Notch-1 inhibition in CKD mice prevents PTH-induced EndMT and subsequent AV calcification [74] suggests that targeting PTH or its associated signalling may protect against VC.

Table 1: Traditional and CKD-specific risk factors for VC. LDL, low density lipoprotein; ApoE, apolipoprotein E; ApoB, apolipoprotein B; ENPP1, ectonucleotide pyrophosphatase/phosphodiesterase 1; VDR, vitamin D receptor; ADMA, asymmetric dimethylarginine; UTs : uremic toxins; CRP: C-reactive protein.

Main risk factors for VC	
Traditional	CKD specific
Non-modifiable risk factors: Age Gender (AV: male; MV: female) Bicuspid AV Gene variants for Runx2, ApoE, ApoB, Notch1, ENPP1, VDR	**Disturbed mineral homeostasis:** ↑ Calcium-phosphate product ↑ Serum phosphate ↑ PTH ↑ FGF-23
Modifiable risk factors: Smoking	**Loss of calcification inhibitors:** ↓ Klotho ↓ Fetuin A ↓ Pyrophosphate ↓ Vitamin K
Comorbidity: Obesity Metabolic syndrome Hypertension Diabetes Familiar hypercholesterolaemia Kidney disease Osteoporosis History of chest irradiation Aortic stenosis (MV)	**Accumulation of UTs:** ↑ Indoxyl-sulfate ↑ Homocystein ↑ ADMA ↑ β2-microglobulin
Serum biochemistry: ↑ LDL and lipoprotein a ↑ triglycerides ↓ Vitamin K ↑ Homocystein ↑ Calcium ↑ Phosphate ↓ Magnesium	**Low-grade inflammation:** ↑ CRP ↑ IL-6

FGF-23

High C-terminal FGF-23 (fibroblast growth factor 23) is a determinant of VC in HD patients [75]. In patients with mild to moderate CKD, FGF-23 levels also correlate with the extent of AV calcification [71, 76]. In patients with CAS and preserved renal function, FGF-23 is the most important biomarker associated with the risk of adverse outcomes [77]. Elevated C-terminal FGF-23 levels are associated with increased 1-year mortality in patients undergoing TAVR with an eGFR $\geq$ 45 ml/min/1.73 m² [78]. However, the mechanisms linking FGF-23 to VC remain unclear.

Klotho

In patients with mild to moderate CKD, AV calcium score negatively correlates with circulating klotho levels [71]. Interestingly, lower klotho expression was observed in human calcified AV tissues [79]. Klotho-deficient mice show calcification at the hinge region of the fibrosa side of the AV [80]. When fed a high-fat diet, these mice show greater collagen levels in the AV than WT mice, indicating that klotho deficiency promotes AV fibrosis [81]. In SAMP1 mice, restoration of circulating klotho levels suppressed inflammation and subsequent myofibroblastic transition, thereby attenuating AV fibrosis [82]. *In vitro*, expression of klotho decreases in VICs exposed to high-phosphate [79]. Exposure to recombinant klotho markedly reduced phosphate-induced VICs osteogenic transition and

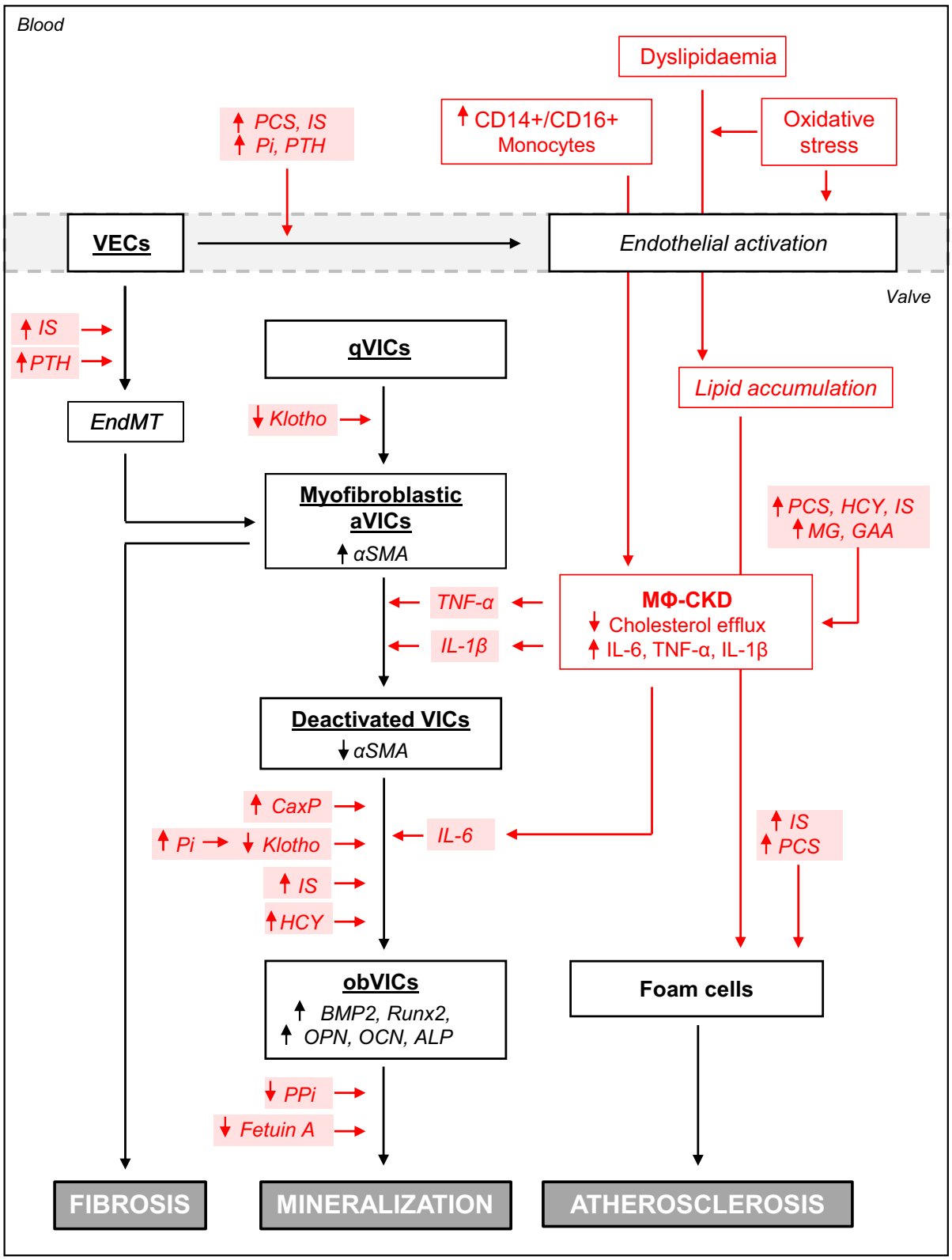

Figure 2: Main mechanisms by which CKD-related disorders promote VC. α-SMA, α-smooth muscle actin. GAA, guanidine acetic acid; HCY, homocysteine; IS, indoxyl-sulfate; PCS, paracresyl sulfate; Pi, inorganic phosphate; PPi, pyrophosphate; MG, methylguanidine; ALP: alkaline phosphatase.

mineralization. The observation that recombinant klotho reduces both RUNX2 and ALP basal levels in VICs isolated from calcified valves suggests that klotho may even reverse VIC pro-osteogenic activity [79]. Whether CKD-induced downregulation of klotho in VICs is linked to hyperphosphataemia and contributes to valvular remodelling remains to be investigated.

Loss of calcification inhibitors

AV explants cultured *ex vivo* secrete pyrophosphate, which effectively protects them against mineralization [83, 84]. Therefore, pyrophosphate deficiency in CKD [85, 86] may have an important impact on CAVD. In peritoneal dialysis (PD) patients, circulating fetuin A levels correlate with the presence of AV leaflet mineralization [87] and predict a worse prognosis [88]. Vitamin K deficiency is highly prevalent in CKD patients, and has been associated with vascular calcification [89–91], vascular stiffness [90, 92], mortality [93], and CV disease. To date, it is unclear whether vitamin K deficiency directly contributes to VC in CKD patients.

Inflammation

Inflammation is a potent inducer of VC. *In vitro*, macrophage secretion of TNF-α (tumour necrosis factor-α) or IL-1β (interleukin 1β) suppresses myofibroblastic activation of VICs from both aortic and mitral origin, which is necessary for IL-6 (interleukin-6) induced osteogenic transition [31, 95] (Fig. 1). Interestingly, macrophages from rats with CKD show enhanced pro-inflammatory properties when cultured *ex vivo* compared to those from control rats [96], and AV calcific remodelling in CKD rats is associated with macrophage infiltration and micro-inflammation, as evidenced by elevated NFkB activation [97]. Low-grade inflammation linked to CKD is associated with AV fibrocalcic remodelling and a higher prevalence of cardiovascular events [98–100]. In end-stage kidney disease patients with VC, inflammatory markers such as CRP (C-reactive protein) and IL-6 were shown to predict a worse prognosis [88, 100–102].

Uremic toxins

Uremic toxins (UTs) may play a key role in the onset, progression, and prognosis of VC in CKD. In patients with severe CAS and normal kidney function, serum asymmetric dimethylarginine activity is elevated and positively correlates with CAS severity [103]. Additionally, homocysteine levels are elevated in CAVD compared to those without CAVD [104]. *In vitro*, exposure to homocysteine promotes VICs osteogenic transition and mineralization. In mice, elevation of plasma homocysteine levels promotes AV fibrocalcic remodelling [105]. *In vitro*, indoxyl-sulfate promotes osteogenic transition and mineralization of human VICs [58] as well as VECs EndMT [106]. Whether a clinical association exists between circulating levels of asymmetric dimethylarginine, homocysteine, indoxyl-sulfate, and CAS in CKD patients has never been explored. Consistent with previous studies demonstrating a correlation between beta-2 microglobulin and VC [98, 107], Shen *et al*., recently reported beta-2 microglobulin to be a predictor of VC in HD patients [108, 109]. Given the key role played by UTs in endothelial activation [110, 111], monocyte inflammation [111–116], and foam cell formation [111, 117], it is plausible that UTs may predispose to valvular inflammation/atherogenesis by directly modulating the phenotype of monocytes and macrophages.

Hypomagnesaemia

Clinical studies in patients with advanced CKD have observed an association between low serum magnesium levels, increased vascular calcification, and cardiovascular mortality [118, 119]. Indeed, magnesium has been shown to prevent Pi-induced calcification of VSMCs *in vitro* through its ability to interfere with the process by which Ca and P crystallize into hydroxyapatite and to induce a signal in the cells that prevents their osteogenic transition [118, 119]. Low serum magnesium levels are recognized as a risk factor for cardiac valve calcification in patients with [120–124] and without renal disease [125]. Despite this association, it appears that the efficacy of magnesium in preventing *in vitro* the mineralization of aortic or mitral VICs has never been studied. To our knowledge, no interventional studies have been conducted to test the effect of magnesium supplementation on VC in CKD patients with low serum magnesium. Randomized clinical trials evaluating the effects of dietary magnesium supplementation, the use of magnesium-based phosphate binders, or the use of magnesium-enriched haemodialysis/PD solutions may be helpful in evaluating whether magnesium can be used as a therapeutic target to prevent VC in CKD.

Sclerostin

Sclerostin is an inhibitor of Wnt signalling [126] that has been reported to be cardioprotective [127]. In a cohort of 110 patients with CKD stages 3–5, sclerostin was identified as an independent risk factor for VC [128]. However, another study in 80 HD patients failed to demonstrate an association between serum sclerostin and VC [129]. Given that Wnt signalling is a key driver of BMP2-dependent osteogenic signalling in VICs [32], the downregulation of which reduces the osteogenic transition of VICs [130], the possibility that sclerostin elevation may protect against VC cannot be ruled out and needs further investigation.

Monocytes subsets

Three monocyte subsets have been defined in humans as a function of the cell surface expression of the lipopolysaccharide receptor CD14 and the FcIII receptor CD16: the classical (Mon1, $CD14^{++/}CD16^{-}$); intermediate (Mon 2, $CD14^{++}/CD16^{+}$); and non-classical (Mon 3, $CD14^{+}/CD16^{++}$) monocytes [131]. The proportion of pro-inflammatory $CD14^{+}/CD16^{+}$ monocytes (Mon2/Mon3) is abnormally high in both dialysed and non-dialysed patients with CKD [132] and closely associated with levels of high-sensitivity CRP and IL-6 [133]. *In vitro*, $CD14^{+}/CD16^{+}$ cells collected from CKD patients are more atherogenic [134] than Mon1, showing greater capacity to adhere to the endothelium [134], lower cholesterol efflux, avid oxLDL uptake, and potent intracellular production of IL-6, IL-1, and TNF-α [135]. Mon2 subset is increased in patients with CAS without renal impairment [136]. In these patients, high amounts of Mon2 before TAVR is associated with long-term mortality and worse functional outcomes post-TAVR [137]. In non-dialysed CKD patients, Mon2 monocytes are independently associated with cardiovascular events [135, 138]. If a similar association is found in patients with CKD, the measurement of Mon2 levels may be useful in the prediction of patients at risk of developing VC.

Clinical management

AV calcification

In patients with severe CKD, the diagnosis of CAS is challenging because patients remain asymptomatic for long periods and

typical symptoms such as dyspnoea or angina may be underestimated due to sedentary lifestyles and confounding factors such as anaemia and volume overload. In HD patients, subtle signs such as hypotension, arrhythmias, and angina should be monitored during the dialysis session to alert the clinician to the presence of haemodynamically significant CAS.

Transthoracic echocardiography is widely used for early CAS detection [139]. It allows accurate diagnosis of the cause of CAS, assessment of haemodynamic severity, measurement of left ventricular size, search for hypertrophy or systolic dysfunction, and can help determine prognosis and optimal timing of valve intervention. Annual monitoring has been suggested for individuals with moderate CAS [34]. However, interpretation of transthoracic echocardiography in patients with CKD is difficult. First, CAS is not the only factor influencing afterload, which may also be influenced by hypertension or arterial stiffness, which are classically high in CKD patients. In addition, systolic dysfunction may decrease the mean pressure gradient, which may lead to an underestimation of the severity of CAS [140]. Therefore, reassessment of CAS severity during the first few months of dialysis is essential. Second, it is important to note that the AV area calculation is based on the continuity equation, which assumes that flows in the outflow tract and AV are equal. Therefore, in patients with septal hypertrophy [141] or severe calcification of the aortic annulus extending into the outflow tract, the AV area calculation may be biased. Finally, the presence of an arteriovenous fistula in HD patients may increase preload, cardiac output, and transvalvular flow [142]. Therefore, measurement of mean transvalvular pressure gradient and AV area during temporary fistula occlusion may theoretically better reflect the severity of CAS. However, because these measurements may underestimate CAS-induced haemodynamic disturbances in the left ventricle, they are not recommended in clinical practice [143].

Other imaging modalities include cardiac computed tomography and cardiac magnetic resonance imaging. Given that VC is strongly correlated with the progression of CAS, the severity of haemodynamic disturbances and the clinical outcome of CAS [144, 145], the 2021 European guidelines recommend the use of cardiac computed tomography to assess the degree of VC in patients with low valve gradient [34]. However, no study has specifically validated this method in the CKD population. Recently, magnetic resonance imaging, which depicts patterns of left ventricular remodelling more accurately than echocardiography, has become the gold standard for non-invasive assessment of the left ventricle [146]. However, given the reluctance to use gadolinium in severe CKD, no study has specifically evaluated this population. In this context, T1 mapping, which can detect myocardial damage including diffuse fibrosis [147] without the use of gadolinium, may be a promising approach in CKD patients.

To date, there are no specific guidelines for the management of CAS in patients with CKD, a population which has been excluded from large randomized trials. In fact, there is no medical treatment and, similar to patients with normal renal function, intervention is recommended in symptomatic patients with severe, high-grade aortic stenosis [mean gradient $\geq$40 mmHg, peak velocity $\geq$4.0 m/s, and valve area $\leq$1.0 cm^2 (or $\leq$0.6 cm^2/m)] [34]. Moreover, if AVR is associated with improved outcomes in CKD patients, dialysis remains a preoperative predictor of in-hospital mortality after AVR (whether surgical or transcatheter), which remains twice as high in dialysis versus non-dialysis patients [148–150]. Nevertheless, retrospective studies have demonstrated the benefit of AVR over conservative treatment in CKD [44] and dialysis patients [151]. Although acute kidney injury is a common complication of AVR [152] and is associated with an increased risk of mortality [153, 154], fear of acute kidney injury should not be a deterrent to AVR. In a recent study derived from the PARTNER cohort (n = 5190), Cubeddu *et al.* provide reassurance by showing that in CKD patients with severe CAS undergoing TAVR, CKD stage is more likely to remain stable or improve than worsen [155]. This post-procedural improvement in renal function, probably related to cardio-renal crosstalk, has also been demonstrated after SAVR [156]. The recent development of contrast-free TAVR may also help reduce the risk of acute kidney injury [157]. To date, severe CAS remains a barrier to access to transplantation or major surgery, and evidence on outcomes with AVR in renal transplant patients remains limited. The increased risk of graft failure with SAVR compared to TAVR reported in retrospective studies may encourage the preference of TAVR in kidney transplant patients with CAS [158]. The benefit of AVR before transplantation needs to be studied.

MV calcification

MV calcification is often asymptomatic until the lesions become severe and lead to degenerative mitral stenosis. It causes dyspnoea, orthopnoea, and cardiac signs associated with right ventricular failure (peripheral oedema, hepatosplenomegaly) [159]. Echocardiography is the gold standard for diagnosis, but the usual parameters have not been validated [34]. Planimetry is less reliable due to diffuse calcium and irregular orifice. The mean transmitral gradient has been shown to have prognostic value [160], which encourages us to perform transthoracic echocardiography after dialysis when blood pressure is controlled in a 'dry weight' patient. Medical management of early MV stenosis consists of controlling congestive symptoms with diuretics or ultrafiltration in dialysis patients. Transcatheter and surgical approaches are high-risk procedures and evidence from randomized trials is lacking [161].

PREVENTING VC IN CKD

Over the last 15 years, several therapeutic strategies have been developed and used to prevent the development of VC. The most promising approaches are presented in Table 2.

SNF472

SNF472 is an intravenous formulation of the hexasodium salt of myoinositol hexaphosphate (phytate; IP6) that selectively and directly inhibits the formation and growth of hydroxyapatite crystals [189, 190]. SNF472 inhibited the calcification of human VICs [162] and pig AV leaflet cultured *ex vivo* [164]. Consistently, administration of SNF472 significantly attenuated the progression of AV calcification in HD patients [163]. Future studies are needed to assess the potential risks and benefits of this agent, particularly regarding its effect on bone mineral density [191].

Sodium thiosulfate

Several studies suggested that sodium thiosulfate (STS) may effectively prevent cardiovascular calcification linked to CKD by binding calcium ions in the circulation or soft tissues [192–196]. In addition, STS has antioxidant and anti-inflammatory properties that may help prevent tissue damage and remodelling [197]. In mice, targeted delivery of STS effectively reduced TNF-α, IL-6, and IL-1β in both serum and aorta and reduced the

Table 2: Main therapies under investigation to prevent VC. ApoE, apolipoprotein E; HDF, hemodiafiltration; ND, not determined.

		Evidence of efficiency			
Treatment	Mechanism of action	Preclinical	Reference	Clinical	Reference
SNF472	Inhibits crystal formation and growth	↓ VICs mineralization	[162]	Slowed the progression of AV mineralization in HD patients	[163]
		↓ Pig leaflet mineralization	[164]		
STS	Chelates precipitated calcium to form soluble calcium thiosulfate	In mice: ↓ Vascular calcifciation ↓ TNF-α, IL-1β, IL-6 in serum and aorta	[165]	Prevented VC in HD patients	[166]
Calcimimetics	Decreases serum PTH and CaxP	↓ PTH in rats, which prevented VECs EndMT, and VC	[74]	Slowed AV calcification in HD patients when given in combination with low-dose vitamin D	[167]
	Promotes PBMCs-induced decalcification	↑ CaSR expression in PBMCs from CKD patients, which rescues their capacity to prevent vascular calcification	[168]		
	Activation of CaSR in VICs and monocytes	Deleterious effect: ↑ VICs osteogenic transition and calcification	[56]		
		Deleterious effect: ↑ Monocytes/macrophages chemtaxis, infiltration, and inflammation	[169–171]		
Phosphate-lowering therapies	Decreases serum phosphorus	In ApoE KO mice with CKD, sevelamer, and lanthanum carbonate reduced valvular atherosclerosis and calcification	[172, 173]	Sevelamer and calcium-based phosphate binder slowed AV and MV calcification in HD patients	[174, 175]
Anti-IL-6	Neutralization of IL-6	Reduces indoxyl-sulfate-induced VICs mineralization	[58]	Subcutaneous administration of ziltivekimab (CKD stages 5–3) or clazakizumab (HD) reduced hsCRP Clazakizumab also reduced phospholipase A2 and lp(a)	[176–178]
HD					
HDF, HCO, and MCO dialysis	Improve clearance of uremic retention solute with middle-to-high molecular weight compared to standard high-flux dialysis	↓ Monocyte inflammation ↓ VSMC calcification (MCO/HCO)	[179–182]	Reduce systemic inflammation to a greater extent than conventional high-flux dialysis	[180, 183, 184]
Acetate-free, citrate-acidified bicarbonate dialysis	Reduces serum calcification propensity	Protects against calcium deposition in rat aortic rings cultured *ex vivo*	[185]	Improves serum calcification propensity, assessed by T50, in HD patients	[186]
Peritoneal dialysis	Greater preservation of residual renal function Improved CKD-MBD More physiological approach to volume removal Reduced valvular shear stress			ND	
Vitamin K	Carboxylation of matrix-gla protein	ND		Vit K1 improved vitamin K status and retarded thoracic aortic calcification progress but had no effect on VC in HD patients (Vitavask trial)	[187, 188]

progression of vascular calcification [165]. In HD patients, STS therapy was reported to prevent the development of VC [166] as well as the progression of calcification in both the coronary and iliac arteries [198–200]. However, a meta-analysis of 19 cohort studies concluded that intravenous STS was not associated with improvement of skin lesions or survival benefit in CKD patients with calciphylaxis [201]. Additional studies are needed to confirm whether STS can protect against VC.

Calcimimetics

CaxP product and PTH dramatically affect VICs/VECs osteogenic properties. In CKD rats, reduction of PTH level using cinacalcet prevented EndMT and subsequent VC [74]. In HD patients with secondary hyperparathyroidism, Cinacalcet given in combination with fixed low-dose vitamin D sterols slowed AV calcification, although the primary outcome of the study, coronary calcification, was barely significant at 0.07 [167]. These latter data suggest that different mechanisms of calcification may exist between valves and arteries. Consistent with this hypothesis, calcimimetic activation of the calcium-sensing receptor (CaSR) expressed by aortic vascular smooth muscle cells (VSMCs) protects against mineralization [57], whereas their activation of the CaSR expressed by human VICs promotes osteogenic transition and mineralization [56]. Interestingly, peripheral blood mononuclear cells (PBMCs) isolated from CKD patients display lower CaSR expression at their cell surface than PBMCs from healthy donors, which renders them less efficient *ex vivo* to resorb a pre-established calcification [202]. Pre-incubation of these PBMCs with a calcimimetic significantly rescued their capacity to prevent calcium deposition and to resorb a pre-established calcification [202]. In pro-inflammatory conditions, activation of the monocytes CaSR promotes chemotaxis [203], infiltration [203], and NLRP3-dependent inflammation [169–171]. These adverse off-target effects may partly explain why cinacalcet failed to prevent the risk of death or major adverse cardiovascular events in the CKD population [204].

Phosphate-lowering therapies

As pathophysiological [205] and epidemiological data suggest a role for phosphate in the development [68] and progression [206] of VC, targeting phosphate to slow down VC progression could be a promising avenue. Early studies showed that sevelamer and lanthanum (both non-calcium-based phosphate binders) decreased VC in Apolipoprotein E-deficient mice with CKD [172, 173]. In a randomized clinical trial, Raggi and colleagues treated 186 HD patients with either calcium-based phosphate binders or sevelamer. After 1 year of follow-up they observed that cardiovascular calcification (including AV and MV calcification) slowed in 45% of the patients treated with sevelamer and regressed in 26% compared with only 28% and 10%, respectively, in the calcium group [174]. In a recent cohort study of 1489 adult patients receiving maintenance dialysis, Zhang *et al.* showed that the use of calcium-based phosphate binders was associated with a higher risk of coronary artery calcification progression compared with the use of non-calcium-based phosphate binders [207], which is consistent with the findings of previous meta-analyses [208]. Some years ago, it was suggested that combined preparations of calcium and magnesium could be effective alternatives to calcium-based agents because the amount of calcium is reduced compared to calcium salt alone and replaced with magnesium, which is a natural antagonist of the mineralization process. In this context, Matias *et al.* reported that calcium acetate/magnesium carbonate therapy reduced pulse pressure, lowered ventricular mass index, and reduced the progression of AV calcification in HD patients on hemodiafiltration ($n = 36$) compared with sevelamer ($n = 30$) or no phosphate binder therapy ($n = 72$) after 48 months of follow-up [175]. Interestingly, in the randomized LANDMARK study, lanthanum-based treatment for hyperphosphataemia neither reduced the cardiovascular events [209], nor delayed the progression of coronary artery calcification [210] compared with calcium carbonate in haemodialysis patients. In the same vein, in patients with stage 3b or 4 CKD, treatment with lanthanum over 96 weeks did not affect arterial stiffness or aortic calcification compared with placebo [211]. If CKD-MBD (chronic kidney disease-mineral and bone disorders) guidelines recommend lowering elevated phosphate levels towards the normal range in patients with CKD stages 3A to 5D, the optimal target level of serum phosphate remains uncertain. In 2021, the randomized trial EPISODE showed for the first time that strict phosphate control towards the normal range (3.9–4.55 mg/dl) by non-calcium-based phosphate binders delayed the progression of coronary arterial calcification in patients on dialysis [212]. Taken together, these data suggest that lowering phosphate by non-calcium-based phosphate binders may be an interesting strategy to prevent VC. Further studies are needed to evaluate whether phosphate-lowering therapies are effective in slowing VC and to determine the optimal target serum phosphate level to achieve efficiency.

Targeting IL-6

In patients with CAS, plasma levels of inflammatory cytokines such as IL-8, IL-6, TNF, and IL-1β are associated with an increased risk of mortality and hospitalization for heart failure with IL-6 being the best predictor [77]. Genome-wide association study meta-analysis identified the IL-6 locus as significantly associated with CAS [213]. Expression of IL-6 is elevated in CAVD samples and correlates with the remodelling process [214, 215]. Mendelian randomization approach showed that genetically proxied tocilizumab was associated with a reduced risk of CAS [216]. This observation reinforces the idea that targeting IL-6 might be a promising strategy. This seems particularly true in CKD patients, for whom plasma IL-6 independently associated with mortality [217] and with the presence of VC [75]. In preclinical studies, neutralizing IL-6 reduces indoxyl-sulfate-induced human VICs osteogenic transition and calcification [58]. This observation is of particular interest since monoclonal antibodies directed against IL-6, ziltivekimab [176, 177], and clazakizumab [178], are currently in clinical investigation in patients with stage 3–5 CKD and elevated hsCRP [176, 177]. Subcutaneous administration of these anti-IL-6 efficiently reduced median hsCRP levels as well as biomarkers associated with cardiovascular events as compared to placebo group. Studies should soon provide formal evidence of whether or not reducing circulating IL-6 levels leads to reduce major adverse cardiovascular events [177]. If the clinical outcomes are positive, further studies will have to determine whether targeting IL-6 slows VC progression. The fact that clazakizumab reduced secretory phospholipase A2, and lipoprotein a (lp(a)) concentrations relative to placebo is particularly promising. In CKD, AV calcifications and inflammation inversely correlate with bone mineralization [218] in an interdependent bone-vascular axis. Since IL-6 promotes osteoclast formation, the possibility that neutralizing IL-6 may influence the bone mineral density should not be neglected.

Vitamin K supplementation

In the VitaVask trial, vitamin K1 supplementation (5 mg, three times a week for 18 months) failed to slow the progression of calcification in the AV and MV in HD patients, whereas aortic calcification progress was significantly retarded [187]. In the VALKYRIE study, supplementation of HD patients with atrial fibrillation with rivaroxaban (10 mg daily) plus vitamin K2 [menaquinone 7 (MK-7), 2000 µg three times a week] for 18 months improved vitamin K status but did not change the VC score as compared to a supplementation with rivaroxaban or vitamin K antagonists [188]. These data are consistent with those obtained in the AVADEC study, which showed that 2 years of supplementation with MK-7 (720 µg/day) and vitamin D (25 µg/day) did not affect the progression of CAS in elderly men with normal renal function [219]. Interestingly, Kaesler *et al.* showed that HDL particles isolated from long-term HD patients exhibit an almost absent MK-7 incorporation *in vitro* compared to those from control subjects [220]. When HDL particles were spiked with MK-7, only those isolated from healthy controls showed significantly reduced uncarboxylated matrix-gla protein levels in VSMCs. This crucial change in MK-7 pharmacology may partly explain why, in contrast to what has been observed in the general population [221], MK-7 in CKD patients, had not shown a clear benefit in preventing VC in VALKYRIE, or cardiovascular calcification in the KURNATOWSKA [222], K4KIDNEYS [223], OIKONOMAKI [224], and RENAKVIT [225] studies.

Lipid-lowering therapies

Despite an association with hypercholesterolaemia, randomized clinical trials failed to demonstrate the efficacy of statins, even in combination with ezetimibe, in delaying CAS progression [226–228]. Whether the off-target effects of statins, which are known to promote cardiovascular calcification [229] and increase circulating lp(a) [230], are responsible for their lack of efficacy remains unclear. Contrary to statins, the absolute reduction in cardiovascular events on proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors is numerically greater in patients with advanced CKD [231]. Whether PCSK9 inhibitors efficiently prevent VC in this population remains to be investigated. If lowering lp(a) appears to be a promising strategy to prevent CAS [232], most CKD patients were excluded from the randomized controlled trials evaluating the efficacy of pelacarsen [a hepatocyte-directed antisense oligonucleotide targeting the lp(a) gene mRNA] in lowering lp(a) levels [233], and 'significant renal disease' is an exclusion criterion in ongoing phase 3 trials evaluating the cardiovascular outcomes of novel treatments designed to specifically lower lp(a) [234], suggesting that it will be several years before we know whether lp(a) levels contribute to VC in CKD [235].

Dialysis modalities

Improvement in dialysis could also be considered to be a means to prevent VC. Although it is always difficult to make comparisons between different populations, some data may suggest an advantage of PD over HD in the incidence of CAS. Indeed, studies estimate the prevalence of VC to be ~32% in patients who have been on PD for at least 31 months [46, 236], while it ranges from 34% to 85% in patients on HD for a similar duration [237–239]. A recent study of 30 PD and 34 HD patients showed a significantly higher prevalence of VC in HD compared to PD patients (70.6% vs. 29.4%), further supporting the benefit of PD [240]. In fact, PD provides a more physiologic approach to volume removal, greater preservation of residual renal function, and is associated with improved CKD-MBD. This approach may therefore have theoretical advantages over HD to reduce the incidence of VC [241]. The absence of fistula may also account for this protective effect [242]. Indeed, the presence of an arteriovenous fistula has important haemodynamic consequences because it creates a high-flow, low-resistance environment that decreases total systemic vascular resistance while increasing venous return to the heart, thereby increasing cardiac output [243]. It is known that temporary compression of the arteriovenous fistula induces a significant decrease in transvalvular flow rate [142]. Besides, revision of the fistula to reduce blood flow decreased V_{max} and improved dyspnoea to NYHA class II [244]. In addition, given that changes in shear stress promote valvular endothelial dysfunction [21], as well as monocyte inflammation, adhesion, and lipoprotein uptake through activation of the mechanosensitive ion channel Piezo-1 [245], it is plausible that the arteriovenous fistula directly influences the process of VC.

Besides, it should be noted that patients with no residual renal function or with severe diabetes, who are the most prone to develop VC, are also more likely to be referred to HD rather than PD, which may partly explain this reduced incidence. In this context, it is interesting to note that a recent Chinese multicentre prospective cohort study of 1489 patients aged 18 to 74 years undergoing HD or PD (21.6%) showed no difference in progression of VC after 4 years of follow-up [207]. In light of these conflicting results, further studies seem necessary to reach a firm conclusion regarding the potential benefit of PD over HD on the risk of VC [246].

Optimizing HD modalities in patients at risk of developing cardiovascular calcification could be an interesting alternative for reducing the prevalence of VC. On-line hemodiafiltration, high cut-off (HCO), and medium cut-off (MCO) dialysers provide an improved clearance of uremic retention solutes with middle-to-high molecular weight compared with conventional high-flux dialysis [247], and could theoretically help to prevent VC. In line with this hypothesis, HCO and MCO dialysers reduce systemic inflammation [180, 183, 184], decrease monocytes expression of inflammatory cytokines [179, 180] and are less prone to induce vascular cell calcification *in vitro* [181, 182] compared to standard high-flux dialysers. In addition, the composition of dialysis buffers appears to be particularly important. In 2019, Villa-Bellosta *et al.* exposed rat aortic rings to blood samples collected before and after HD from patients on acetate- ($n = 35$) or citrate- ($n = 25$) acidified bicarbonate dialysis. Using this system, they showed that citrate protects against calcium accumulation [185], which suggested that citrate-acidified bicarbonate dialysis may be an alternative approach to reduce ectopic calcification in HD patients. In 2018, Lorenz *et al.* showed that citrate-acidified acetate-free bicarbonate HD sustainably improved serum calcification propensity as assessed by T50 values in 78 prevalent European HD patients [186]. To date, the impact of dialysis buffers on VC has never been studied.

CONCLUSION

VC is common and, like vascular calcification, is associated with worse outcomes in patients with CKD. Although the genesis of VC involves several mechanisms similar to those that induce vascular calcification, it may also have specific and independent mechanisms. Although the behaviour of VICs has long been compared to that of VSMCs due to their anatomical proximity, it has recently been reported that valve cells exhibit more complex and unique behaviours than vascular cells. Indeed, human VSMCs exposed to an os-

teogenic environment expressed higher levels of osteogenic markers and exhibited greater matrix remodelling than human VICs from the same patient [248]. These data suggest the existence of cell-mediated differences between vascular and VC processes, which may account for some opposite calcification responses of human VICs compared to VSMCs. Understanding these mechanisms may lead to the development of specific therapeutic strategies to prevent and/or reverse VC. Whether modulation of VC can influence mortality and morbidity in patients with CKD remains to be demonstrated. To date, the paucity of data does not allow us to make robust evidence-based recommendations regarding the best way to monitor and protect heart valves in CKD patients (best monitoring tool, frequency of monitoring, promising preventive, and/or curative treatment). Further research is needed to address these issues.

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AUTHORS' CONTRIBUTIONS

L.H., Z.M., and S.S. designed the literature review. L.H. wrote the section on the mechanisms and consequences of VC. L.H., N.I., and S.S. collected information on preclinical and clinical associations. A.C. and Z.M. wrote the section on clinical management of VC. L.H. and A.C. wrote the section on the prevention of VC. L.H. and N.I. designed the tables and figures. All authors critically revised the manuscript.

DATA AVAILABILITY STATEMENT

No new data were generated or analysed in support of this research.

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