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Review

Title: Current and potential therapeutic strategies for the management of vascular calcification in patients with chronic kidney disease including those on dialysis

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Key words

Vascular calcification, chronic kidney disease, end-stage kidney disease, cardiovascular mortality

Abbreviations:

ALP alkaline phosphatase
CKD chronic kidney disease
CPP calciprotein particles
CRP C-reactive protein
CVD cardiovascular disease
ESKD end-stage kidney disease
MGP matrix Gla protein

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PTH parathyroid hormone

RCT randomized controlled trial

SHPT secondary hyperparathyroidism

VC vascular calcification

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Abstract

Patients with chronic kidney disease (CKD) have accelerated vascular stiffening contributing significantly to excess cardiovascular morbidity and mortality. Much of the arterial stiffening is thought to involve vascular calcification (VC), but the pathogenesis of this phenomenon is complex, resulting from a disruption of the balance between promoters and inhibitors of calcification in a uremic milieu, along with derangements in calcium and phosphate metabolic pathways. Management of traditional cardiovascular risk factors to reduce VC may be influential but has not been shown to significantly improve mortality. Control of mineral metabolism may potentially reduce the burden of VC, although using conventional approaches of restricting dietary phosphate, administering phosphate binders, and use of active vitamin D and calcimimetics, remains controversial because recommended biochemical targets are hard to achieve and clinical relevance hard to define. Increasing time on dialysis is perhaps another therapy with potential effectiveness in this area. Despite current treatments, cardiovascular morbidity and mortality remain high in this group. Novel therapies for addressing VC include magnesium and vitamin K supplementation, which are currently being investigated in large randomized control trials. Other therapeutic targets include crystallization inhibitors, ligand trap for activin receptors and BMP-7. This review summarizes current treatment strategies and therapeutic targets for the future management of VC in patients with CKD.

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Introduction

Vascular calcification (VC) is highly prevalent in patients with chronic kidney disease (CKD) and advancing age but can also be seen in other groups including those with diabetes mellitus and chronic inflammatory conditions.
Observational studies report VC present in up to 25% of patients with CKD stage 3 and over 50% in patients on dialysis [1]. Once present, VC progresses rapidly, irrespective of age [2,3]. Two types of VC are identified in patients with

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CKD [4]. Intimal calcification is associated with atherosclerotic plaques and its presence increases the risk of plaque erosion and rupture. Additionally, medial calcification in large elastic arteries and arterioles results in increased arterial stiffness and cardiac afterload [5-7]. These subtypes are not mutually exclusive and often co-exist. In large epidemiological studies VC is associated with increased cardiovascular mortality [8] and morbidity [9] as well as reduced bone mineral density (BMD) and increased fracture risk [10]. However, the precise mechanisms that link radiological or histological findings of VC and enhanced mortality remain speculative.

The pathophysiology of VC is likely to be a result of multiple interlinked mechanisms, some of which include phenotypic changes in cells, cell death, elastic degradation, calcinosis and passive deposition of calcium, in addition to changes in calcification inhibitors and possibly promotors [11]. The initial triggers for calcification remain unknown but likely depend upon the type of calcification (intimal versus medial) and the location of the vessel, since VC proceeds at different rates in different areas. In patients with CKD, and especially end-stage kidney disease (ESKD), a significant contribution to VC is likely to result from a reduction in calcification inhibitors in association with deranged calcium and phosphate metabolism.

Numerous experimental studies show how vascular smooth muscle cells (VSMCs) can transform to an osteoblast-like phenotype [12], with the ability to produce collagenous extracellular matrix on to which mineral is deposited [13,14]. This differentiation of VSMCs is characterized by expression of genes that are normally restricted to bone, such as bone morphogenetic protein 2 (BMP-2), osterix, runt-related transcription factor 2 (RUNX2) and alkaline phosphatase (ALP) [15], although whether VC is the cause or effect of this upregulation remains contentious[16]. Expression of these osteoblastic genes is accompanied by

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downregulation of VSMC lineage markers, such as transgelin and calponin [17]. Patients with CKD also develop a pro-inflammatory milieu, with increased C-reactive protein [CRP] and interleukin-6 [IL-6], and this may contribute to endothelial dysfunction and to the development of enhanced soft tissue calcification.

A key systemic inhibitor of VC is the circulating phosphoglycoprotein fetuin-A. This protein inhibits VC by binding to nascent nanoparticles of calcium and phosphate in the circulation, preventing mineral accretion. These particles are known as calciprotein particles (CPP) and may provide an important pathway for mineral transport and clearance. Chronic dysregulation of mineral metabolism, such as in CKD, results in accumulation and transformation of these particles from amorphous fetuin-calcium-phosphate (CPP1) to larger, more crystalline, particles (CPP2). Whilst cellular uptake of CPP1 causes little in the way of cellular responses, uptake of CPP2 results in phenotypic change [18] and inflammatory cytokine release in some cells [19]. In observational studies, increased serum CPP [20] and specifically CPP2 are associated with increased VC and mortality in patients with CKD [21].

At a tissue level, important VC inhibitors include endogenous pyrophosphate and carboxylated matrix Gla protein (MGP). Pyrophosphate binds to mineralization surfaces to prevent crystal growth, and extracellular levels are tightly regulated by tissue nonspecific alkaline phosphatase (TNAP). TNAP is vital for healthy skeletal development, and a fine balance exists in order to maintain calcification within specific tissue confines. MGP is another key protein expressed by chondrocytes and VSMC. It requires vitamin K as an essential cofactor for enzymatic carboxylation and function. MGP inhibits calcification by binding to and inactivating pro-mineralization BMP2 [22,23], as well as having a direct effect on hydroxyapatite formation[24]. As more is

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discovered about VC, it is likely that there are interlinked mechanisms and multiple pathways between various calcification inhibitors, which work together to prevent this pathological process in healthy adults. Figure 1 highlights identified inhibitors and inducers of VC.

Patients with CKD have increased cardiovascular mortality and morbidity due to the presence of both traditional (e.g. hypertension and diabetes) and non-traditional cardiovascular risk factors (e.g. albuminuria and deranged calcium phosphate metabolism) [25,26]. Many therapeutic interventions applicable to the general population to reduce cardiovascular disease burden, have had limited success when applied to the CKD population. Further research is underway to better understand the underlying pathophysiology. This review will summarize the current therapeutic strategies used for prevention and management of VC in patients with CKD. We will also discuss novel targets and future directions for the management of VC.

Current therapeutic strategies to reduce VC

General cardiovascular risk reduction

Compared to the general population, patients with CKD have a higher prevalence of many traditional cardiovascular risk factors, including hypertension, diabetes and hypertriglyceridemia [27]. Reduction of traditional cardiovascular risk factors may play a management role in this patient population, but the complex interplay and direction of causality between renal impairment and cardiovascular disease remains enigmatic [28]. Few studies have looked specifically at risk factor modification in patients with CKD, and most evidence is derived from *post hoc* analyses or meta-analyses.

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Nevertheless, blood pressure management plays a significant role in attempting to retard the progression of CKD stages 2-5 and complications in CKD stage 5D. The international Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend targeting a blood pressure of ≤ 140mmHg systolic and ≤ 90mmHg diastolic for patients without albuminuria and ≤ 130mmHg systolic and ≤ 80mmHg diastolic for patients with albuminuria [29] in CKD. Blood pressure targets become more difficult to recommend once patients commence dialysis, although two meta-analyses [30,31] reported benefits of antihypertensive therapy compared to placebo for cardiovascular protection in hemodialysis patients. There is no evidence that antihypertensive therapy affects VC but may reduce myocardial fibrosis and left ventricular hypertrophy.

Lipid profiles in patients with CKD vary significantly from the general population, typically with higher levels of triglycerides and low high-density lipoprotein (HDL). Low HDL may contribute to complex inflammatory and oxidative stress pathways and may exacerbate uremic endothelial dysfunction [32]. Use of cholesterol-lowering statin therapy in patients with CKD, as in the general population, has been found to reduce cardiovascular mortality, with a recent meta-analysis reporting that statins result in a reduced risk - relative risk (RR) 0.72 (95% confidence interval [CI]; 0.66-0.79) for major cardiovascular events [33]. However, the benefit of statins on dialysis is less clear, with lipid lowering inconsistently improving cardiovascular outcomes. Only one of three randomized controlled trials (RCTs) showed a statistically significant effect in dialysis patients (SHARP [34] using statin plus ezetemibe), whilst two others failed to find an effect (AURORA [35] and the 4D [36] trials). No RCT evidence supports the use of fibrates in patients with CKD. There are reasonable data linking some other traditional cardiovascular risk factors, like diabetic control

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and smoking, to suggest that intervention may be of value in dialysis patients and guidelines are as for the general population.

Improving abnormalities of mineral metabolism

Phosphate-lowering therapy:

Observational studies have shown significant and independent associations between elevated serum phosphate levels and all-cause mortality and cardiovascular disease in people with normal kidney function and in patients with CKD. This relationship has been consistently reported across the spectrum of CKD from mild renal impairment to patients with ESKD on dialysis [37,38]. Despite these associations, mechanisms and the direction of causality by which elevated serum phosphate are associated with vascular disease and death remain unclear. They may involve endothelial dysfunction, enhanced extra-osseous calcium apatite deposition or energy pathway disruption.

Management of hyperphosphatemia in CKD has involved dietary phosphate restriction, the use of phosphate binders and dialysis. Prescription of phosphate binders has become routine in dialysis patients, although it is becoming increasingly controversial, and there remain conflicting views on their role and serum phosphate targets. An early RCT, the Treat-to-Goal study, reported greater aortic and coronary artery VC progression in 200 prevalent dialysis patients receiving calcium-based phosphate binders compared with sevelamer [39]. At study completion, the median absolute calcium score in the coronary arteries (p=0.03) and aorta (p=0.01) increased significantly in calcium-treated compared to sevelamer-treated subjects. The median change in calcium score was higher with calcium-based binders compared with sevelamer in coronary arteries (25% vs. 6%, p=0.02) and the aorta (28% vs. 5%, p=0.02). The results

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were congruent in the Renagel in New Dialysis (RIND) study of sevelamer vs calcium-based binders in 129 incident hemodialysis patients over 18 months with pre-existing coronary artery calcification (CAC) [40,41]. This study reported a lower mortality in the non-calcium arm compared to the calcium-based binder arm.

Sevelamer may also have effects beyond phosphate binding, such as increasing fetuin-A levels ($p<0.001$) and improving flow mediated dilation (FMD) ($p<0.001$) [42]. In the Calcium Acetate Renagel Evaluation-2 (CARE-2) study [43] of 203 prevalent hemodialysis patients, there was no difference in CAC after one year of follow up between the two study arms involving atorvastatin plus either sevelamer or calcium acetate (mean increase 35% in the calcium acetate group vs 39% in the sevelamer group; 95% CI, 0.851-1.161).

A number of systematic reviews have been performed and one study of 77 trials (12,562 participants) compared phosphate binding agents in adults with CKD and concluded that there was insufficient evidence that any drug class lowered mortality or cardiovascular events compared to placebo [44]. However, compared to calcium, sevelamer did appear to reduce all-cause mortality (odds ratio [OR], 0.39; 95% CI 0.21-0.74). A similar meta-analysis of 71 RCTs assessing phosphate binder use in dialysis patients failed to find a statistically significant difference in cardiovascular mortality between the calcium and non-calcium based binders (RR 2.54, 95% CI 0.67-9.62) [45]. An earlier meta-analysis of phosphate binders in patients with CKD concluded that non-calcium based binders were associated with a 22% reduction in all-cause mortality based on 18 studies of over 700 patients (risk ratio 0.78, 95% CI 0.61-0.98) [46].

In the pre-dialysis CKD population however, there is less evidence for the role of phosphate binders. A recent RCT by Block *et al* compared phosphate binders

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(sevelamer, lanthanum and calcium-based) with placebo in patients with CKD stages 3-4 over 9 months and reported minimal decline in serum phosphate within the active treatment groups and, in fact, increases in CAC for the combined phosphate binder groups [47]. Although the greatest increase in VC was seen in patients on the calcium-based binders, these results question the efficacy and safety of phosphate binders in this population with normal serum phosphate levels.

Although studies relating to this issue are conflicting and the case for phosphate binders *per se* has not yet been proven, the most consistent finding, limiting exogenous calcium, has been recommended in the current KDIGO Chronic Kidney Disease Mineral and Bone Disorder (CKD-MBD) guidelines. [48]. Currently a number of studies are being conducted to assess the impact of phosphate binders in CKD, including the IMpact of Phosphate Reduction On Vascular End-points in Chronic Kidney Disease (IMPROVE-CKD) trial, assessing vascular compliance and VC in patients with CKD stage 3b and 4 with lanthanum carbonate versus placebo. This trial will, it is hoped, be informative in addressing whether early phosphate binder use will confer any vascular protection in pre-dialysis CKD patients.

Calcimimetics:

Calcimimetics act to allosterically modulate the calcium sensing receptor (CaR). The CaR is a G-protein coupled receptor expressed in a variety of tissues including the parathyroid gland and VSMC. In the vasculature, it may exert a physiological role by controlling arterial function and contributes to development of VC. As renal function declines, there is down regulation of the CaR. In animal models, cinacalcet markedly attenuates vascular remodeling and calcification [49-52] and proposed mechanisms include abrogating endothelial to

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mesenchymal cell transition [49], reduced expression of osteoblastic genes [50], activation of the CaR in endothelial and VSMCs [51], and upregulation of MGP expression [53-55].

Calcimimetics are used for the treatment of secondary hyperparathyroidism (SHPT) in patients with ESKD, with two available preparations: oral cinacalcet and a new intravenous formulation, etelcalcitide. Cinacalcet has been associated with reduced progression of abdominal aortic calcification over a 12-month period [56]. In a *post hoc* analysis, Cunningham *et al* [57] combined data on clinical outcomes from four RCTs and showed that treatment with cinacalcet resulted in a significant reduction in the risk of cardiovascular hospitalization (hazard ratio [HR] 0.61, 95% CI 0.43-0.86). The effect of calcimimetics on VC was seen in the ADVANCE study (A Randomized Study to Evaluate the Effects of Cinacalcet Plus Low Dose Vitamin D on Vascular Calcification in Subjects with CKD) [58]. In this study, 360 hemodialysis patients with SHPT were treated with either cinacalcet plus low dose vitamin D, or flexible doses of vitamin D alone. A stratified median treatment difference in aortic valve calcification was seen in the cinacalcet group (-44.7%; 95% CI -85.8%- -6.1%, p=0.01), along with a trend to lower CAC scores in the cinacalcet plus vitamin D group (median increase of 24%) compared to the vitamin D group (median increase of 31%, p=0.073). A major limitation was the short 12-month duration of this study, which was unlikely to be sufficient for the detection of substantial changes in VC.

Despite the possible benefits on VC, cardiovascular benefits of calcimimetics were inconclusive in the Effect of Cinacalcet on Cardiovascular disease in Patients Undergoing Dialysis (EVOLVE) trial [59], which to date remains the largest RCT conducted in a dialysis population (3883 participants). This trial failed to show a difference in primary composite end point (death, myocardial

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infarction, hospitalization for unstable angina, heart failure or peripheral vascular event) in the cinacalcet compared to placebo group (HR 0.93, 95% CI 0.85-1.02, p=0.11). Results of this trial however should be interpreted with caution because of numerous limitations including a relatively low expected event rate in the age group studied and high study treatment cross over (significant drop-in and drop-out rate) due to commercially available cinacalcet. Although the primary analysis of the EVOLVE trial was negative, *post hoc* analyses demonstrated reduced incidence of calcific uremic arteriolopathy (CUA) (unadjusted HR, 0.31; 95% CI, 0.13-0.79; p=0.014) [60], a trend towards reduced fracture rate (adjusted HR 0.83 (95%CI, 0.72-0.98) [61] and decreased risk of death and cardiovascular events, although the latter benefit only in patients over the age of 65 years (adjusted HR 0.7, 95% CI 0.6-0.81) [62].

Surgical management of SHPT has, however, failed to demonstrate a protective effect on VC. A recent prospective observational study of 19 hemodialysis patients with severe SHPT reported that parathyroidectomies resulted in increased CAC (p=0.02) and were associated with a shift from high to low bone turnover disease on bone biopsy over a 12-month period (90% of patients evolved to either very low or low bone turnover) [63]. The presence of low bone turnover disease has previously been associated with a substantially increased risk of VC [64].

Vitamin D:

In observational studies of patients with CKD [65,66] and the general population[67], 25-hydroxy vitamin D (25[OH]D) deficiency has been associated with VC, arterial stiffness and cardiovascular mortality. Cardiovascular benefits of nutritional vitamin D supplementation may result from altered vascular oxidative stress, smooth muscle function or improvement in left ventricular

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mass index [68]. Treatment of VSMCs with vitamin D receptor analogs has been associated with inhibition of osteogenic processes [69] as well as anti-inflammatory effects [70,71] and increasing endothelial cell nitric oxide production [72]. In animal models, physiological doses of vitamin D supplementation have shown protective effects against VC [73], but excessive 25(OH)D or active vitamin D can result in VC [74].

In patients with CKD and those on dialysis, the efficacy of both nutritional vitamin D and active vitamin D treatment on vascular health has been investigated; however, beneficial effects are uncertain. Presently there is inconsistent evidence and conflicting literature regarding the form and dose of vitamin D supplementation. Of three recent RCTs [75-77] examining the role of both nutritional and active vitamin D supplementation on markers of vascular stiffness in non-dialysis CKD patients, only two [75,76] reported improvement in surrogate markers of vascular stiffness (pulse wave velocity [PWV]) with nutritional vitamin D supplementation but not active vitamin D. The KDIGO CKD-MBD guidelines recommend nutritional vitamin D for treatment of 25(OH)D deficiency but not routine use of calcitriol or vitamin D receptor analogs in pre-dialysis patients, given the risk of hypercalcemia and likely associated pro-calcific effects, unless prescribed cautiously for severe and progressive SHPT [48].

Bisphosphonates

Bisphosphonates are synthetic analogues of pyrophosphate and inhibit osteoclast-mediated resorption as well as calcium-phosphate crystal deposition in bone. They have been used for treatment of osteoporosis over the past two decades but they may also play a role in inhibiting arterial calcification and in macrophage suppression in atheromatous lesions. Reports dating back to 1970's

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in human [78] and animal [79] studies have shown that the early developed bisphosphonates, such as etidronate, inhibit ectopic calcification. Since then, animal models have suggested that these drugs may inhibit VC [80,81] without significant changes to other known cardiovascular risk factors like lipids [82].

However, human trials of bisphosphonates for the treatment of VC are sparse. In the general population, the largest study involved 474 elderly osteoporotic women treated for three years with ibandronate; it showed no effect on aortic calcification [83]. Smaller studies in patients with type 2 diabetes and osteopenia did show a reduction in carotid intima-media thickness with 12 months of etidronate versus placebo ($p<0.005$) [84]. In the only RCT in the pre-dialysis CKD population, 18 months of weekly alendronate failed to demonstrate a difference in progression of CT-measured aortic VC (adjusted difference, -24.2 Hounsfield units, 95% CI, -77-28.6, $p=0.4$) [85]. Three small Japanese trials assessed the use of low dose bisphosphonates on VC in hemodialysis patients. Etidronate administration for 12 months reduced [86] or inhibited [87] CAC progression, but was associated with an increased risk of osteomalacia [88]. In current clinical practice these medications are reserved for osteoporosis in patients with CKD stages 1-3 [48], and potentially contraindicated for more advanced CKD due to possible risk of exacerbating adynamic bone disease, osteomalacia and SHPT.

Improving dialysis adequacy and renal transplantation

There is evidence to suggest more frequent and extended hours hemodialysis improves vascular physiology [89] compared with conventional thrice weekly hemodialysis. This may be a result of better blood pressure control (with a reduction in antihypertensive medication requirement) [90] and/or better management of SHPT and a reduction in serum phosphate levels which in most cases includes reduced prescription of phosphate binders and a more liberal diet

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[91]. Extended hours and/or more frequent dialysis also augments uremic toxin clearance, which, in animal models, reduces endothelial injury and death [92].

In two prospective observational studies, conversion from conventional hemodialysis (CHD) to nocturnal hemodialysis (NHD) (6-9 hours per night for 3.5-4 sessions per week) for a 12-month period resulted in a non-significant 9% decrease in CAC scores (p=0.1) [93] and improvement or stabilization in VC and ectopic calcification in 22 out of 26 patients on home dialysis as seen in hand and foot X-rays. There was also a reduction in serum phosphate and parathyroid hormone (PTH) [94]. In a case study supporting the benefit of improving dialysis adequacy, conversion from CHD to NHD led to symptom and improvement and increased blood flow in the lower limb vessels of a patient with refractory claudication [95].

The role of renal transplantation in improving VC remains controversial. There are conflicting data on VC progression as evaluated by coronary artery imaging post transplantation, with studies showing reversal of calcification [96], no change in CAC [97], and also progression of disease [98] depending on the population studied. Challenges in assessing post-transplant VC progression include the heterogeneity of transplant recipients (including age and dialysis vintage at time of transplant) which can contribute significantly to VC development and progression, as well as exclusion of patients with significant iliac artery calcification from transplantation. Post-transplant related diabetes and complications of immunosuppressive therapy also can have an impact on VC.

Future potential management for VC in clinical evaluation

Magnesium

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Magnesium plays an important role in vascular health [99], with normal magnesium homeostasis in VSMC maintained via TRPM7 cation channels. Magnesium prevents post-transcriptional changes in VSMC differentiation and apoptosis [100,101] and upregulates VC inhibitors (MGP and osteopontin) [102], whilst counteracting expression of osteogenic transcription factors (BMP-2, RUNX2, Msh homeobox 2, and SRY- box 9), bone proteins and genes associated with matrix mineralization (osteocalcin and TNAP) [103]. In animal models of VC, dietary supplementation with magnesium results in marked reduction in VC and mortality, improved mineral metabolism, including lowering of PTH, as well as improvement in renal function [104].

In the general population, higher dietary magnesium intake is associated with reduced all-cause mortality, stroke, heart failure and diabetes mellitus [105]. Serum magnesium concentration < 0.8mmol/L has been associated with a 36% increased risk of death from coronary artery disease [106,107] and two meta-analyses report serum magnesium is inversely associated with cardiovascular risk in both healthy controls and hemodialysis cohorts [108,109]. Similar findings were seen in a study of 80 patients on peritoneal dialysis [110], with higher serum magnesium associated with less abdominal aortic calcification (R^2=0.06, unstandardized coefficient[B]= -7.81, p=0.03). Magnesium has also been reported to delay CPP maturation and transition from primary to secondary CPP in hemodialysis patients [111] by slowing calcification propensity.

Currently, robust data on magnesium supplementation in the CKD population is lacking. Tzanakis *et al* [112] reported the largest RCT to date studying the effect of magnesium on VC. It compared the effect of the phosphate binder calcium acetate with and without magnesium carbonate on arterial calcification (evaluated by plain X-ray) in 72 hemodialysis patients and demonstrated

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improved VC in the magnesium arm (p=0.04). On multivariate logistic regression analysis, serum magnesium was an independent predictor of slower progression of arterial calcification. There is an RCT underway (without the confounding use of calcium) assessing the effect of 30 mmol magnesium/day vs placebo on VC in patients with CKD stages 3-4 over a 12-month period [113]. Table 1 summarizes interventional and observation clinical trials assessing magnesium supplementation in VC.

Vitamin K

Vitamin K is an essential cofactor in the enzymatic carboxylation of glutamate, and exists in two biologically active forms, vitamin K1 (phylloquinone, found in green leafy vegetables) and vitamin K2 (menaquinone, found in dairy products). Vitamin K is necessary for carboxylation and thus activation of clotting factors as well as several proteins involved in bone matrix formation (osteocalcin [OC]), inhibition of soft tissue mineralization (MGP) and prevention of VSMC apoptosis (growth arrest specific 6 protein [GAS6]). In animal studies, vitamin K2 supplementation reduces VC, via enhancement of MGP carboxylation [114] and MGP mRNA expression [115] in tissues.

Deficiency of active vitamin K in the general population has been associated with increased aortic stiffness as measured by PWV [116], as well as VC [117] and increased all-cause mortality [118] in hemodialysis patients. Greater rates of vitamin K deficiency or activation are consistently identified in dialysis populations with dietary questionnaires identifying reduced daily intake of phylloquinone and or menaquinone; in some cohort studies deficiency is present in up to 30% of patients [119,120]. One possible cause for this may be the use of phosphate binders. *In vitro* studies suggest that and many commonly used phosphate binders (including lanthanum and calcium carbonate) can sequester

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vitamin K in the gut preventing its absorption. Only sucroferric-oxyhydroxide and sevelamer carbonate do not appear to bind much vitamin K [121].

Vitamin K supplementation has been trialed in patients with CKD including those on hemodialysis. CKD patients given 90mcg/day of vitamin K2 supplementation, combined with 10mcg of nutritional vitamin D, for 270 days had significantly lower carotid intimal thickness compared to those with vitamin D supplementation alone (p=0.005) [122]. In patients on hemodialysis, short duration of vitamin K2 supplementation (4-6 weeks) at a dose of 360mcg/day reduces markers of vitamin K deficiency [uncarboxylated MGP [123], uncarboxylated OC and protein induced by vitamin K absence (PIVKA-II) levels], whilst also being safe and well tolerated [124]. Currently there is a large multicenter RCT recruiting incident hemodialysis patients (Inhibiting the progression of arterial calcification with vitamin K in HemoDialysis patients [iPACK-HD]) comparing 10mg vitamin K1 treatment thrice weekly versus placebo, with the primary endpoint as change in CAC over one year of therapy [125]. Another clinical trial is also underway evaluating the effect of vitamin K1 compared to placebo on CUA (ClinicalTrials.gov identifier NCT02278692)[126].

Mineralocorticoid receptor antagonists (MRA)

Following the discovery of mineralocorticoid excess in Klotho deficient mice with accelerated VC, research interest has increased in the role of hyperaldosteronism triggering osteoinductive changes in the vasculature. In both human and animal studies, hyperaldosteronism is associated with vascular stiffness, damage and accelerated atherosclerosis [127-129]. VSMCs have intracellular mineralocorticoid receptors (MRs) [130] as well as aldosterone synthase, an enzyme involved in the synthesis of mineralocorticoids, which is upregulated in a high phosphate environment [131]. Stimulation of the MR by

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circulating aldosterone from the adrenal glands or locally produced aldosterone [132] triggers osteoblast signaling pathways [133-135] by upregulating the type 3 sodium dependent phosphate transporter PIT1, and upregulating expression of osteoblastic transcription factors in VSMCs and expression of TNAP, leading to reduction of local pyrophosphate. Aldosterone also has other cellular effects including upregulating BMP2 [133] and TNFα [129], perhaps further contributing to VC.

In vitro, mineralocorticoid receptor antagonists (MRAs) ameliorate phosphate-induced osteogenic transformation [131] in human aortic VSMCs. A recent systematic review [136] incorporating nine trials of 829 patients with ESKD found MRAs were associated with a 66% RR reduction in cardiovascular mortality compared with controls (RR 0.34; 95% CI 0.15-0.75). However, there was an associated 3-fold increase in the risk of hyperkalemia. Due to the small size and heterogeneity of the studies collected, the data were not robust enough to determine the true benefit of MRAs in patients with ESKD; two larger RCTs are underway currently to further delineate the benefit of MRAs in patients on dialysis. SpinD (ClinicalTrials.gov identifier NCT02285920)[137] is a 125-patient pilot trial assessing the comparative safety and tolerability of three different doses of spironolactone versus placebo and ALCHEMIST (ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial, (ClinicalTrials.gov identifier NCT01848639)[138] is an 825-patient European trial assessing cardiovascular mortality in dialysis patients with spironolactone therapy.

Sodium Thiosulphate

Sodium thiosulphate, primarily used for the treatment of cyanide poisoning, has become an adjunctive treatment for CUA. It is said to participate in a cation

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exchange reaction with calcium in insoluble tissue deposits, leading to more soluble calcium thiosulphate. However, this mechanism is unlikely since it does not explain why sodium thiosulphate does not appear to chelate circulating calcium; any benefit may simply be due to its induction of a metabolic acidosis. Sodium thiosulphate was initially trialed for recurrent nephrocalcinosis in the 1980's with some reports of success [139,140]. In CUA, sodium thiosulphate is thought to have antioxidant properties with generation of glutathione and prevention of reactive oxygen species thereby reversing endothelial dysfunction [140]. However, long term use of sodium thiosulphate is hampered by the development of metabolic acidosis [141] as a major side effect.

Two trials to date have evaluated sodium thiosulphate in the treatment of VC. Matthews *et al* [142] assessed the effect of sodium thiosulphate on CAC (Agaston score > 50) in 22 hemodialysis patients over a five-month period. At trial conclusion there was no mean annualized rate of change in VC in the cohort although individual analysis showed calcification progression in 14 out of 22 subjects. The main reported adverse effect was nausea and vomiting although these symptoms were managed by reduction in dose of medication. In the second study, 87 stable patients on hemodialysis with CAC scores of ≥ 300 received intravenous sodium thiosulphate, 12.5mg twice weekly post dialysis, for four months [143]. Despite a statistically significant reduction in VC progression, treatment was associated with a decline in hip BMD and a high side effect profile likely as a result of worsening metabolic acidosis. A clinical trial currently recruiting will evaluate the effects of IV Sodium Thiosulphate compared to placebo in patients with CUA (ClinicalTrials.gov identifier NCT03150240)[144]

A summary of completed interventional clinical trials looking at novel agents for VC is presented in Table 2.

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Novel targets for other potential future therapies of VC

Crystallization inhibitors

Crystallization inhibitors are a new class of drug that may prove to be beneficial in the treatment of VC. They work by obstructing or preventing crystal development, much like pyrophosphate or bisphosphonates, by binding to the crystal nucleus or the apatite crystal face to disturb its development without any cellular signaling capacity. Currently under development is SN472, an intravenous formulation of myoinositol hexaphosphate, a small, highly water-soluble molecule. In animal models, this drug has been effective in reducing VC [145,146]. The use of SNF472 on progression of VC in hemodialysis patients is currently being evaluated in a phase 2 clinical trial (ClinicalTrials.gov identifier NCT02966028)[147].

Ligand trap for the activin type IIA receptor (ActRIIa) and bone morphogenetic protein 7 (BMP 7)

Activin and BMP7 protein are part of the TGF β superfamily. Both of these proteins can bind to ActRIIa receptors on the cell surface leading to regulation of gene transcription [148]. Activin-A is normally expressed in bone, however if it binds to ActRIIa receptors in VSMCs it can inhibit BMP7 signaling which results in transdifferentiation of the VSMC into an osteoblastic phenotype. Activin-A upregulation can occur in CKD and is thought to contribute to increased bone remodeling.

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In vivo trials of ligand trap for ActRIIa in an animal model of atherosclerosis reported downregulation of ActRIIa signaling with a resultant decrease in atherosclerotic calcification as well as decreased expression of osteoblastic proteins and increased levels of smooth muscle cell specific proteins [149]. Other beneficial effects of this drug included increased levels of klotho, reduced renal fibrosis [149], and improvement in bone changes associated with CKD [150]. Animal and *in vitro* human studies of BMP7 therapy have also been promising in attenuating VC [151,152]. Figure 2 summarizes the mechanism of action of new therapeutics for VC.

Conclusion

VC is a complex pathological process that occurs as part of ageing but can be accelerated in many pathological conditions including CKD, inflammatory disorders and diabetes. In patients with CKD some of the mechanisms to account for this phenomenon include disruption to calcium and phosphate metabolic pathways, together with an imbalance of promoters and inhibitors of calcification which can tip the balance towards a pro-calcific milieu. Once VC is established it is unlikely to be reversed and management should be based on slowing its progression. By the time VC is evident radiologically, opportunities to intervene in its pathogenesis may have been missed. Therefore, there needs to be a focus on identification of early markers of micro-calcification as well as research on the cohort of patients with ESKD without radiological evidence of calcification. These patients may have intrinsic protection and or genetic resistance to this pathology that we could harness therapeutically.

Current treatment is challenging but perhaps should be aimed at addressing multiple physiological targets; addressing traditional vascular risk factors may

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play a role but it is likely we need to further understand and address mineral stress pathways. Large clinical trials are currently underway looking at the potential benefits of vitamin K and magnesium supplementation and these hold promise for future management. Novel treatment targets on the horizon include crystallization inhibitors, ligand trap for ActRIIa and BMP7 protein. Ongoing and future clinical trials assessing VC reduction in the CKD population are desperately needed to improve cardiovascular and mortality outcomes in these high-risk patients.

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Figure Legends

Figure 1. Identified inhibitors and inducers of vascular calcification.

Figure 2. Mechanism of action of new therapeutics for vascular calcification.

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Tables

Table 1. Clinical studies assessing the association between or effect of magnesium on vascular calcification or atherosclerotic vascular disease in patients with chronic kidney disease

Study	**Study type**	**Population**	**Treatment**	**Duration**	**Primary outcome**	**Results**
Mortazavi *et al* [153]	RCT	HD (n=54)	440mg Mg oxide thrice weekly versus placebo	6 months	cIMT	Decrease in cIMT in Mg group (from 0.84±0.13mm to 0.76±0.13mm, p=0.001)
Tzanakis *et al* (107)	RCT	HD (n=72)	Mg carbonate + Ca acetate versus Ca	12 months	SVCS	Improvement in small proportion of Mg group (n=4), no

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			acetate alone			improvement in Ca group (n=0). Remainder of population either stable or worsening VC (n=ns)
Turgot *et al* [154]	RCT	HD (n=47)	Mg citrate (610mg) alternate daily vs Ca acetate	2 months	cIMT	Improvement in cIMT in Mg group (left cIMT p=0.001, right cIMT p=0.002)
Spiegel *et al* [155]	RCT	HD (n=7)	Mg carbonate +Ca carbonate as phosphate binder	18 months	CAC	No median percent change in CAC at completion (p=0.07)
Molnar *et al* [110]	Cross-sectional	PD (n=80)	N/A	N/A	Lateral lumbar X-rays	Higher serum Mg (>0.8mmol/L) associated with lower AAC score

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						(R^2= 0.006, unstandardized coefficient [B]=-7.81, p=0.003)
Ishimura *et al*[156]	Cross-sectional	Non-diabetic HD (n=390)	N/A	N/A	Hand X-ray	Serum mg significantly lower in patients with VC than those without (p<0.05)
Matias *et al* [157]	Prospective	Hemofiltration (n=206)	N/A	48 months	Plain X-ray	Significantly lower serum mg in patients with SVCS>/=3 (p=0.008)
Zaher *et al* [158]	Cross-sectional	Children on HD (n=25)	N/A	N/A	cMIT	Higher cIMT in aorta and carotids in HD group than controls (p=0.034 and p=0.001 respectively)

Abbreviations: RCT, randomised controlled trial; HD, hemodialysis; PD, peritoneal dialysis; cIMT, carotid intimal medial thickness; Ca, calcium; Mg,

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magnesium; CKD, chronic kidney disease; CAC, coronary artery calcification, SVCS, simple vascular calcification score; AE, adverse events

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Table 2. Clinical studies assessing novel interventions for vascular calcification in patients with chronic kidney disease

Study	**Study type**	**Population**	**Treatment**	**Duration**	**Primary outcome**	**Results**
Vukusich *et al* [159]	RCT	HD (n=53)	50 mg spironolactone thrice weekly post dialysis vs placebo	2 years	cIMT	Reduced progression of cIMT in spironolactone group arm (R CCA<0.03, L CCA <0.0001)
Adirekkiat *et al* [143]	Prospective	HD (n=87)	Sodium thiosulfate twice weekly post dialysis	4 months	CAC	Reduced progression of CAC in treatment group (p=0.03). High rate of AE

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Matthews *et al* [142]	Prospective	HD (n=22)	Sodium thiosulfate post dialysis	5 months	CAC	No progression in mean annualized rate of change of VC in entire cohort.
Kurnatowska *et al* (117)	RCT	CKD (n=42)	90mcg K1+10mcg Vit D vs 10mcg Vit D	9 months	CAC, cIMT	Less cIMT increase in combined group (p=0.005). Similar increase in CAC in both groups (p=0.7)

Abbreviations: RCT, randomised controlled trial; HD, hemodialysis; PD, peritoneal dialysis; cIMT, carotid intimal medial thickness; Ca, calcium; Mg, magnesium; CKD, chronic kidney disease; CAC, coronary artery calcification, SVCS, simple vascular calcification score; AE, adverse events

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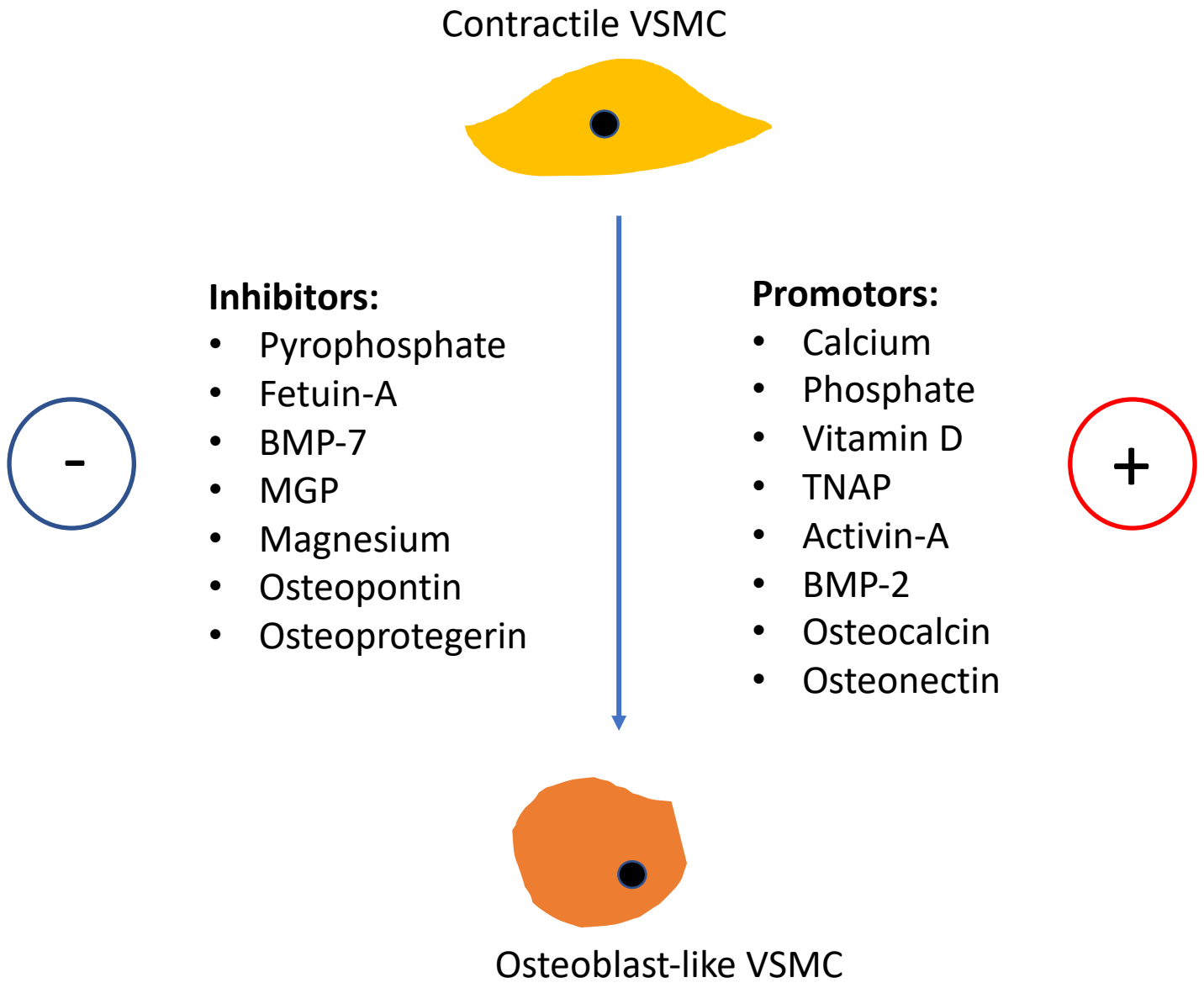
Figure 1: Hypothesized Inhibitors and inducers of VC



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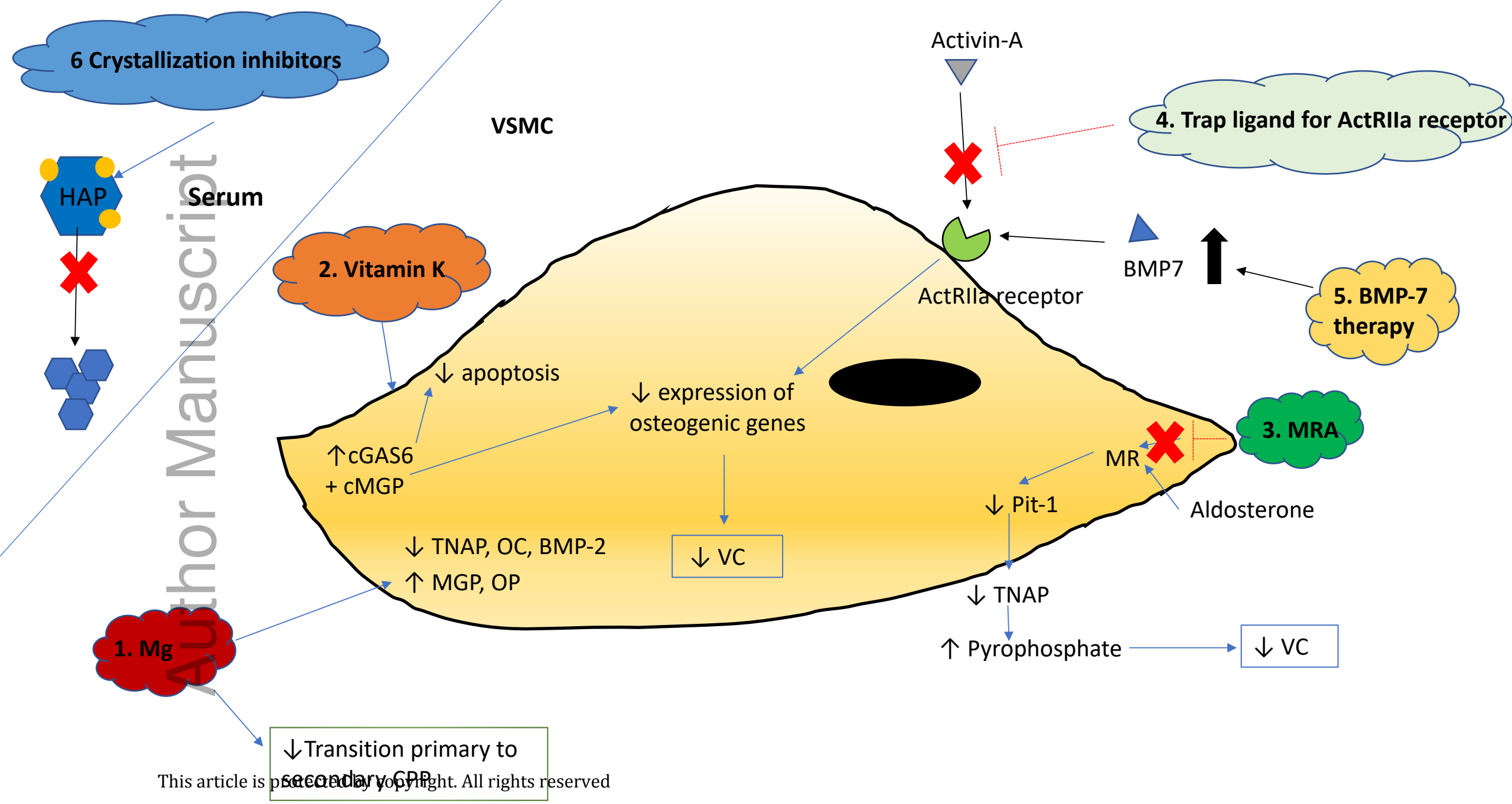

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Figure 2: New therapeutic targets for VC

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