

# Chronic Kidney Disease- Mineral and Bone Disorder (CKD-MBD): *A Focus on Vascular Calcification*

## The Burden of Calcification in Dialysis Patients<sup>1</sup>

**70** → The percent of patients with significant coronary artery and aortic calcification

**≈50** → The percent of patients with calcified valves

**50** → The percent of *incident* dialysis patients with significant coronary calcification

**50** → The percent of cardiovascular deaths that may be associated with abnormal tissue calcification in patients treated with dialysis<sup>2</sup>

### KEY POINT:

The presence and magnitude of arterial and valvular calcification are strongly associated with cardiovascular morbidity and mortality. Risk reduction may be achieved with a tailored, multifactorial approach to MBD: <sup>3,4</sup>

- Calcium or non-calcium-based phosphate binders
- Patient education
- CVD risk reduction measures
- Active vitamin D therapies
- Calcimimetic therapy
- Increased hemodialysis frequency, session time, dialyzer surface area and/or treatment type (eg, hemodiafiltration)

**PATIENTS RECEIVING DIALYSIS** bear a cardiovascular disease (CVD) mortality rate up to 20-fold of that of the general population, even after adjustment for age, gender, race, and presence of diabetes.<sup>5</sup> Disparity is also seen when children on dialysis are compared with their peers who do not have CKD, underscoring the need for aggressive CVD risk reduction in patients of all ages.<sup>6</sup> Further, CVD shows markedly increased prevalence in CKD stages 3-5, compared to patients without CKD, and predicts faster decline in glomerular filtration rate (GFR). Each sequential decrease in estimated GFR below 60 mL/min/1.73 m<sup>2</sup> raises the cardiovascular event and mortality rates, demonstrating a clear inverse relationship between CVD burden and preserved kidney function.<sup>7,8</sup>

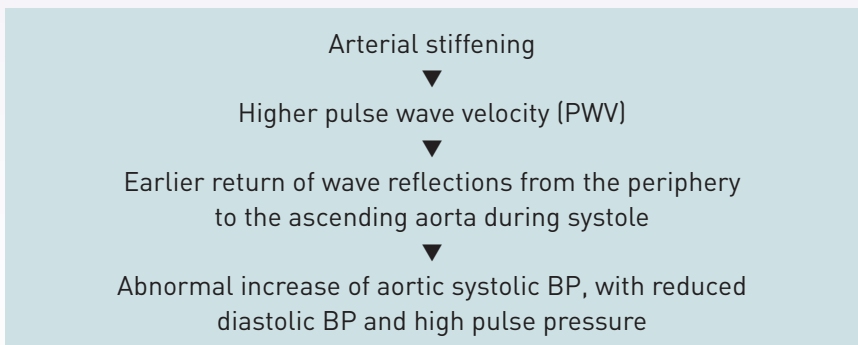
These morbidities are, in large part, due to calcification that modulates atherosclerosis and arteriosclerosis.<sup>9,10</sup>

### KEY POINT:

Traditional cardiac risk factors do not appear to entirely account for the elevated CVD morbidity seen in advanced CKD. Hyperphosphatemia, elevated Ca x P product, and hyperparathyroidism have been associated with CVD risk and mortality in advanced CKD. In addition, uremia is believed to confer non-traditional CVD risks (eg, a proinflammatory state and dysregulation of calcification inhibitors and inducers).<sup>10,11</sup>

The arterial locations of calcification are the neointima and the media.<sup>9,12</sup>

- Intimal calcification is advanced atherosclerosis, occurring in medium-to-large conduit arteries without smooth muscle cells. Plaques develop and arterial occlusion occurs.
- Medial calcification, known also as Mönckeberg's arteriosclerosis, is observed in both smaller and conduit arteries in elastin fibers around smooth muscle cells. It is typically less occlusive of the arterial lumen than intimal calcification.
  - Hemodynamic disturbances of increased wave reflections and high pulse pressure independently predict mortality in patients with ESRD.<sup>9</sup>



## AN EVOLVING PARADIGM OF VASCULAR CALCIFICATION (VC) IN CKD SUGGESTS MULTIPLE THERAPEUTIC TARGETS<sup>2,8,11,13</sup>

PAST PREMISE	CURRENT PREMISE	
<p>Extraskeletal calcification is mostly a passive process in which calcium-phosphorus (Ca-P) product exceeds Ca and P solubility</p> <p>▼</p> <p>Hydroxyapatite precipitation and deposition</p> <p>▼</p> <p>Vessels and soft tissues calcify</p> <p>▼</p> <p>Hyperphosphatemia as the key pathological focus</p>	<p>Elevated intracellular Ca and P triggers vascular smooth muscle cell (VSMC) apoptosis and phenotypic change of the VSMCs to osteoblast-like cells</p> <p>▼</p> <p>Mineralization of the vascular wall</p> <p>▼</p> <p>Clinically detectable vasculopathy</p> <p>▼</p>	<p>CKD adversely affects genetic pathways of VC inhibitor proteins (eg, Fetuin-A)</p> <p>▼</p> <p>Low serum levels of inhibitors</p> <p>▼</p> <p>Enhanced VC</p> <p>▼</p>
	<p>Focus on mediators of a complex, regulated osteogenic process, and functional impairment of VC inhibitors</p>	

**Current therapies** might have an impact beyond controlling parathyroid hormone (PTH), Ca and P. New therapy options might specifically target calcification mechanisms.

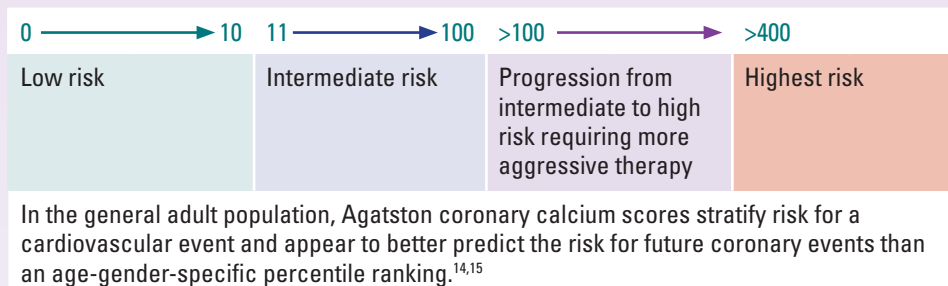
*In vitro* and *in vivo* studies are exploring potential anti-calcification therapies, using compounds with inhibitory properties (eg, vitamin K and pyrophosphate).

### KEY POINT:

Calcification in patients with end-stage renal disease (ESRD) was previously believed to occur as a result of passive mineral deposition processes. Differentiation of VSMCs into chondrocytes or osteoblast-like cells seems to be a key element in VC pathogenesis, meaning that calcification shares similarities with osteogenesis. Bone and mineralization regulatory factors are expressed in calcified vasculature. Therefore, potential anticalcification therapies must not adversely affect normal calcification, for example in bones and teeth.<sup>12</sup>

## CORONARY ARTERY CALCIFICATION SCORE (CACS)

The CACS is a quantitative assessment of calcified atherosclerosis, detectable by electron-beam or multislice computed tomography (CT). The score is calculated using a weighted value assigned to the highest density of calcification in a given coronary artery.



The severity of coronary artery calcification in patients on dialysis is underscored by studies demonstrating:

- A mean CACS of 4,290 in dialysis patients compared with a score of 406 in non-dialysis patients.<sup>16</sup>
- Normal angiography in patients with a mean CACS of 559, a score that would be indicative of significant coronary artery disease (CAD) in the non-CKD population.<sup>17</sup>
- Basal Agatston score predicts both incremental increase in the score after one year and subsequent mortality, with hypertension and diabetes being associated with progression of the basal Agatston score.<sup>18</sup>

CT-based measurements have the advantages of reproducibility, safety, and convenience. Potential obstacles are cost, availability, and radiation exposure. Indirect measurement techniques have shown limited clinical utility (eg, pulse pressure) or are predominantly a research tool (eg, pulse wave velocity).<sup>19</sup>

### KEY POINT:

Calcification is common, more severe, and follows an accelerated course in the CKD population, compared with healthy people.<sup>20</sup> CACS may be up to 5-fold higher in patients on maintenance hemodialysis than in age-matched non-CKD patients.<sup>16</sup> The following are some advantages of alternative screening techniques to CT (eg, electron beam technology, X-ray, echocardiogram, pulse pressure):<sup>21</sup>

- Demonstrated prognostic utility
- More readily available
- Less expensive
- Correlate well with CT measurements

## THE APPROACH TO ALL PATIENTS WITH CALCIFICATION SHOULD BE TO MINIMIZE CVD RISK FACTORS AND CONTROL BIOCHEMICAL PARAMETERS OF CKD-MBD<sup>20</sup>

### KDIGO suggests:<sup>20</sup>

Patients with CKD stages 3-5D with known vascular/valvular calcification should be considered at highest cardiovascular risk. [2A] It is reasonable to use this information to guide the management of CKD-MBD [not graded]. [Guideline 3.3.2]

Reasonable alternatives to computed tomography-based imaging are lateral abdominal radiographs to detect the presence or absence of vascular calcification, and an echocardiogram to detect the presence or absence of valvular calcification. [Guideline 3.3.1 (2C)]

### In patients with CKD stages 3-5D and hyperphosphatemia...

...with persistent or recurrent hypercalcemia



KDIGO recommends restricting the dose of calcium-based phosphate binders and/or the dose of calcitriol or vitamin D analog. [Guideline 4.1.5 (1B)]

...with arterial calcification and/or adynamic bone disease and/or persistently low serum PTH levels



KDIGO suggests restricting the dose of calcium-based phosphate binders. [Guideline 4.1.5 (2C)]

In patients receiving either hemodialysis (HD) or peritoneal dialysis (PD), the dialysate calcium concentration should be tailored to the individual patient's needs, if possible. In the longer term, calcium flux during HD is an important determinant of overall calcium balance. Bone health may be improved by reducing calcium flux during dialysis in patients with adynamic bone disease and extraskeletal calcification, and by inducing positive calcium flux during dialysis in patients with hypocalcemia. Prospective studies are needed to test these possibilities.

KDIGO suggests using a dialysate calcium concentration between 1.25 and 1.50 mmol/l (2.5 and 3.0 mEq/l). [Guideline 4.1.3 (2D)]

## THERAPIES TO CONTROL CALCIUM, PHOSPHORUS AND PTH IMBALANCE IN CKD-MBD HAVE BEEN INVESTIGATED FOR THEIR IMPACT ON CALCIFICATION AND CVD OUTCOMES

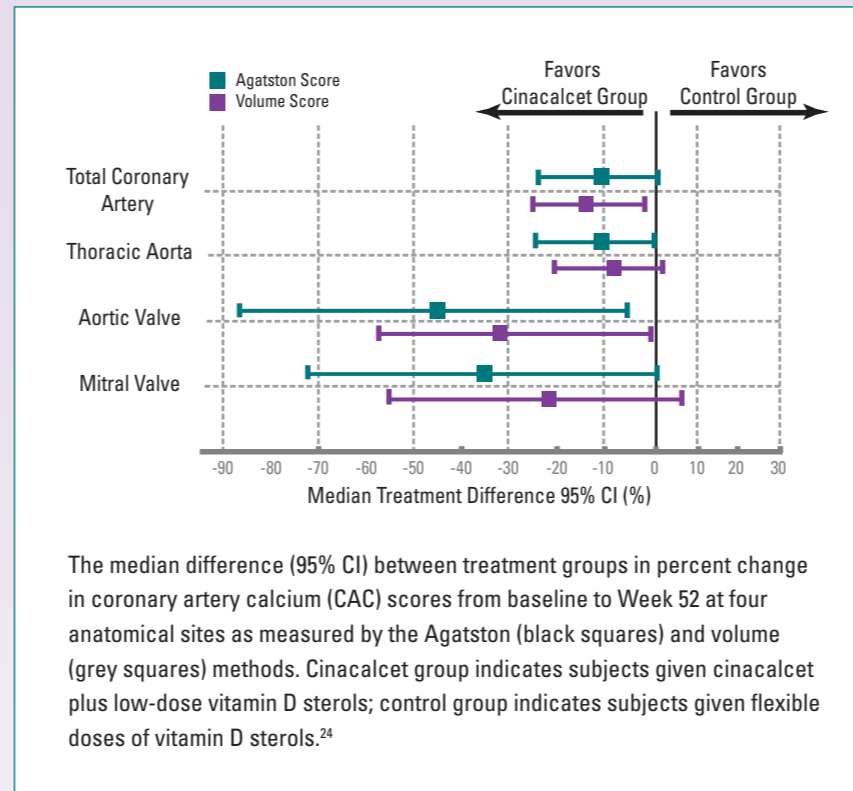
### Calcimimetics

The relationship of calcimimetics to extraskeletal calcification and cardiovascular outcomes has been investigated both in experimental and clinical studies. Calcimimetic agents are allosteric modulators of the calcium-sensing receptor (CaR) that increase the sensitivity of the CaR to extracellular calcium. They help control secondary hyperparathyroidism (SHPT) by attenuating PTH release, hyperphosphatemia, and hypercalcemia, and may exhibit a neutral or protective effect on extrasosseous calcification.<sup>20</sup>

Reports from animal models comparing the effect on calcification, SHPT, and survival in vitamin D-treated uremic rats have shown an advantage for each parameter when a calcimimetic was added to therapy. Animals treated with calcitriol alone<sup>22</sup> or paricalcitol alone<sup>23</sup> for SHPT developed aortic calcification which, when a calcimimetic was coadministered, regressed, while survival increased.

In a large observational study of patients receiving vitamin D therapy and either calcimimetic, or no calcimimetic, a significant survival benefit was reported in the former group after adjustment for numerous baseline demographic and laboratory characteristics.<sup>4</sup>

Recently, the ADVANCE study reported no significant differences in the primary outcomes (percentage change from baseline in Agatston coronary artery calcium score) between treatment groups (cinacalcet plus low-dose vitamin D sterols, versus flexible doses of vitamin D sterols alone) after 52 weeks of follow-up. Differences between treatment groups were seen for interval changes in coronary artery calcium (CAC) volume scores and for changes in Agatston and volume scores at the aortic valve. Moreover, smaller increases in calcification scores during follow-up were found consistently by both scoring methods at all anatomical sites evaluated.<sup>24</sup>



The ongoing EVOLVE trial will help determine whether cinacalcet can reduce cardiovascular morbidity and mortality in dialysis patients.<sup>25</sup>

### Phosphate Binders

Different phosphate binders may lower the patient's exogenous calcium load and modify VC progression; however, the superiority of one compound over another in terms of reducing mortality is less clear from recent trials. Although comparable in terms of lowering hyperphosphatemia, calcium-containing binders were reported in both incident<sup>26</sup> and prevalent<sup>27</sup> hemodialysis patients to result in more hypercalcemia and more rapid progression of coronary calcification, compared with sevelamer-HCl. However, in the CARE-2 trial comparing calcium acetate with sevelamer-HCl, patients experienced similar progression of CAC, even with the addition of atorvastatin to the regimen to lower LDL cholesterol.<sup>28</sup> The DCOR trial reported a trend toward lower mortality in hemodialysis patients older than 65 years of age who were treated with sevelamer versus calcium-containing binders; however, there was no survival benefit demonstrated in the overall study population.<sup>29</sup>

### Vitamin D

Calcitriol and vitamin D analogs are routinely used to control development and progression of SHPT.

Animal studies of atherosclerosis and uremia suggest that the observed effects on calcification of vitamin D analogs may be related to different effects on gene expression of bone-related markers in the aorta.<sup>30,31</sup> Experimental studies suggest a biphasic property whereby lower doses of calcitriol, for example, may have a lower calcific effect, whereas higher doses accelerate calcification.<sup>20,12</sup> Experimental data in general support the claim that there is reduced calcification with equivalent PTH lowering with different vitamin D analogs.<sup>20</sup>

### KEY POINT:

Therapies to effectively treat SHPT continue to be investigated in clinical and preclinical studies with a focus on calcification and CVD outcomes. An emerging theme is that combination therapy that includes calcimimetics with vitamin D analogs and phosphate binders may represent optimal therapy.

Grade for Strength of Recommendation <sup>20</sup>	Strength	Wording	Grade for Quality of Evidence <sup>20</sup>	Quality of Evidence
Level 1	Strong	“We recommend...should”	A	High
			B	Moderate
Level 2	Weak	“We suggest...might”	C	Low
			D	Very low

Note: Ungraded statements are used in areas where guidance was based on common sense and/or the question was not specific enough to undertake a systematic evidence review.<sup>20</sup>

On all panels of this resource, G stands for Guideline.<sup>20</sup>



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