Calcimimetics

The relationship of calcimimetics to extraskeletal calcifications and cardiovascular outcomes has been investigated by several clinical trials, with consistent results. Calcimimetics are agents that modulate the calcium-sensing receptor (CaSR) that controls the renal loss of calcium in patients with secondary hyperparathyroidism (SHPT). They help control secondary hyperparathyroidism (SHPT) by altering PTH release, hypercalcemia, and hyperphosphatemia, and thereby reduce atherosclerotic calcium deposition and extracoronary calcifications. Calcimimetics act by stimulating the CaSR and enhancing the inactivation of the CaSR-G protein-coupled receptor in vascular smooth muscle cells, thereby decreasing the bioavailability of calcium to the receptor. The resulting decrease in intracellular calcium results in a reduction in PTH and hyperphosphatemia. Calcimimetics increase the sensitivity of the CaR to extracellular calcium. They help control cardiovascular risk in patients with vascular atherosclerosis and calcification.

Recent clinical trials have shown that the use of calcimimetics in patients with secondary hyperparathyroidism results in a reduction in cardiovascular event rates. For example, in the FREEDOM study, patients treated with cinacalcet had a significant reduction in cardiovascular events compared to those treated with placebo. The relationship of calcimimetics to extraskeletal calcification and cardiovascular outcomes has been investigated by several clinical trials, with consistent results. Calcimimetics are agents that modulate the calcium-sensing receptor (CaSR) that controls the renal loss of calcium in patients with secondary hyperparathyroidism (SHPT). They help control secondary hyperparathyroidism (SHPT) by altering PTH release, hypercalcemia, and hyperphosphatemia, and thereby reduce atherosclerotic calcium deposition and extracoronary calcifications. Calcimimetics act by stimulating the CaSR and enhancing the inactivation of the CaSR-G protein-coupled receptor in vascular smooth muscle cells, thereby decreasing the bioavailability of calcium to the receptor. The resulting decrease in intracellular calcium results in a reduction in PTH and hyperphosphatemia. Calcimimetics increase the sensitivity of the CaR to extracellular calcium. They help control cardiovascular risk in patients with vascular atherosclerosis and calcification.

The ongoing EVOLVE trial will help determine whether cinacalcet can reduce cardiovascular mortality and mortality in dialysis patients.24

Phosphate Binders

Different phosphate binders may lower the patient’s serum calcium load and reduce CV progression, however the superiority of one compound over another is a topic under active study. Results from recent trials indicate that a combination of calcium-based phosphate binders may be more effective in reducing cardiovascular risk than a single calcium-based binder alone.20

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, multifaceted approach to CKD-MBD.20

Calcimimetics with vitamin D analogs and phosphate binders may represent optimal therapy.

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PATIENTS RECEIVING DIALYSIS have a cardiovascular disease (CVD) mortality rate of 20 to 30% higher than age-matched controls, even after adjustment for age, gender, race, and presence of diabetes.6 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.6 Further, CVD on dialysis are compared with their peers who do not have CKD, underscoring

The arterial locations of calcification are the neointima and the media.9,12 These morbidities are, in large part, due to calcification that modulates gender, race, and presence of diabetes.5 Disparity is also seen when children rate up to 20-fold of that of the general population, even after adjustment for age, sex, race, and presence of diabetes.5

PATIENTS RECEIVING DIALYSIS shows markedly increased prevalence in CKD stages 3-5, compared to patients

KEY POINT: Arterial stiffness is an independent risk factor for future cardiovascular disease and death.19

Calcification in patients with end-stage renal disease (ESRD) was previously associated with a higher risk of cardiovascular disease (CVD) than age-matched controls.9 However, differences in methods for determination of arterial stiffness, knowledge about how arterial stiffness in ESRD differs from that of age-matched controls, and potential confounding by age, sex, race, and presence of diabetes.5

Erstwhile vascular calcification was believed to occur as a result of passive mineral deposition processes. Later, it was demonstrated that calcification is a dynamic process involving bone and mineralization regulatory factors, which are expressed in calcified vasculature. Therefore, potential anticalcification therapies must not adversely affect normal calcification, for example in bones.6

Calcification is a parameter of aging, and a marker of CVD risk.7,8 Loss of arterial compliance and increased arterial stiffness are seen in patients with CVD.19 In the general adult population, age-related calcification is seen. A score of 0–10 suggests mild calcification; a score of 11–100 suggests intermediate to high calcification; and a score of >100 suggests signifi cant calcification (CACS) in the coronary arteries. 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-unsigned value assigned to the highest density of calcification in a given coronary artery. 

In patients with CKD stages 3-5 and hyperphosphatemia…

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In patients receiving hemodialysis (HD) or peritoneal dialysis (PD), the calcification is common, more severe, and follows an accelerated course in patients with CKD, compared with healthy people.20 CACS may be up to 5-fold higher in patients with ESRD than age-matched controls. The CACS is a parameter of aging, and a marker of CVD risk.7,8 Loss of arterial compliance and increased arterial stiffness are seen in patients with CVD.19 In the general adult population, age-related calcification is seen. A score of 0–10 suggests mild calcification; a score of 11–100 suggests intermediate to high calcification; and a score of >100 suggests signifi cant calcification (CACS) in the coronary arteries. 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-unsigned value assigned to the highest density of calcification in a given coronary artery. 

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The severity of coronary artery calcification in patients on dialysis is understood by the following key features:

• A mean CACS of 4,290 in dialysis patients compared with a score of 406 in non-dialysis patients.

• Normal angiography in patients with a mean CACS of 395, a score that is thought to indicate significant coronary artery calcification in the general population.6

• Baseline Agatston score predicts both incremental increase in the score after one year and subsequent mortality, with hyperten sion and diabetes being associated with higher scores.15

CT-based measurements have the advantages of reproducibility, safety, and relatively lower cost.20 CT-based measurements have the advantages of reproducibility, safety, and relatively lower cost.20

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An evolving paradigm of vascular calcification (VC) in CKD suggests multiple therapeutic targets.2,8,11,13

AN EVOLVING PARADIGM OF VASCULAR CALCIFICATION (VC) IN CKD SUGGESTS MULTIPLE THERAPEUTIC TARGETS:2,8,11,13

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**Coronary Artery Calcifications**

The Coronary Artery Calcification Score (CACS) is a quantitative assessment of coronary calcifications, detectable by electron beam or multi-slice computed tomography (CT). The score is calculated using a weighted-integer assigned to the highest density of calcifications in a given coronary artery.

### Key Point:

**Lesion Characteristics**

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk</td>
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In the general adult population, Agatston coronary artery calcium scores strongly predict未来 risk for coronary artery disease in any given year.9

The severity of coronary artery calcification on patients is limited by the amount of cumulative CVD risk.

A meta-analysis of CSA endpoints in patients with CVD risk.

Baseline Agatston score predicts both incidence and rate of progression of coronary artery calcium in the general population.9

**References**


PATIENTS RECEIVING DIALYSIS bear a cardiovascular disease (CVD) mortality risk exceeding twofold that of patients with chronic kidney disease (CKD), even after adjustment for age, gender, race, and presence of diabetes.1-3 Diabetics are also seen with children on dialysis and nephrology, and their serum values of the CKD stage estimate the need for aggressive CKD disease reduction in patients of all ages.4,5 CKD shows marked increases in CVD stage 3-4, compared to patients without CKD, and further decreases in glomerular filtration rate (GFR).6 Each sequential decrease in estimated GFR below 60 mL/min/1.73 m² is associated with a cardiovascular event and mortality rates, demonstrating a linear inverse relationship between CKD burdens and progression.7,8

These morbidities are, in part, explained by calcifications that modulate atherosclerosis and arteriosclerosis.9,10

• Medial calcification, known also as Mönckeberg’s arteriosclerosis, is observed in both smaller and conduit arteries in elastin fibers around smooth muscle cells and teeth.12
• Atherosclerosis and arteriosclerosis.9,10
• Differentiation of VSMCs into chondrocytes or osteoblast-like cells seems to be expressed in calcified vasculature. Therefore, potential anticalcification therapies must not adversely affect normal calcification, for example in bones and teeth.12

CALCIFICATION SCORE (CACS)

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• Correlate well with CT measurements
• Low risk
• Intermediate to high risk
• Highest risk
• Non-dialysis patients

CALCIFICATION SCORE: 0-100

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In patients with CKD stages 3-5D and hypertension ...

The severe coronary artery calcification in patients on dialysis is understood by knowing:

• A mean CACS of 3.1% in dialysis patients compared with a score of 0.6% in non-dialysis patients.
• Normal angiography in patients with a mean CACS of 3.1% a score that would be indicative of significant coronary artery disease (CAD).
• Base Agatston score predicts both incremental increase in the score after one year and subsequent mortality, with hypercoagulable and diabetes being associated with poor outcomes.
• Traditional cardiac risk factors do not appear to entirely account for the elevated CVD morbidity seen in advanced CKD. Hyperphosphatemia, elevated Ca × P product, and hyperparathyroidism have been associated with CVD risk.

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(Phosphorus) or are predominantly a research tool (eg, pulse wave velocity).19

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Calcification in patients with end-stage renal disease (ESRD) was previously studied limitedly, with a focus on reducing calcium phosphorus. The ability to differentiate between calcium phosphorus in cholesterol or calcium oxalate seems to be a key element in OSF, meaning that calcifications share similarities with osteoarthritis. Bone and mineralization. Injury to renal function therapies are necessary in calcification. The complexity and variable aspects of calcification are worsened by these therapies not adversely affect normal calcification, for example in bones and teeth.

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The relationship of calcimimetics to extraskeletal calcifications and cardiovascular outcomes has been investigated both in experimental and clinical studies. Calcimimetics are agents that modulate the calcium-sensing receptor (CaSR) that regulates the renal tubular reabsorption of calcium. They help control secondary hyperparathyroidism (SHPT) by attenuating PTH release, hyperphos- phatemia, and hypercalcemia, and inhibit arterial and/or protective effects of extracellular calcium.

Reports from animal models comparing the effects on calcification, SHPT, and survival in vitamin D treated uremic rats have shown a safeguard for each parameter when a calcimimetic was added to therapy, whereas untreated animals developed arterial calcification and/or parathyroid calcium for SHPT development and aortic calcification when, a calcimimetic was concomitantly, reversed, while survival increased. In a large observational study of patients receiving vitamin D therapy and either calcimimetic or placebo, there was no significant survival benefit. The former group after adjustment for numerous baseline demographic and laboratory characteristics.

Recently, the ADACCE study reported no significant differences in the primary outcomes (percentage change from baseline in Agatston coronary artery calcium score, changes in coronary artery calcium score between baseline and final follow-up visit, and number of ventricular episodes) in low-dose vitamin D sterols, versus doses of vitamin D sterols after 12 weeks of follow-up. Differences between treatment groups were seen for interval changes in coronary artery calcium (Agatston scores) and volume for changes in calcium and volume scores at the aortic valve. Moreover, smaller decreases in calcium scores during follow-up were found consistently by both scoring methods at all anatomical sites.

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KEY POINT:

1. CVD risk factors do not account for all CVD risk in CKD, even after adjustment for age, gender, race, and presence of diabetes.6

2. Earlier return of wave reflections from the periphery to the ascending aorta during systole and higher pulse pressure independently predict mortality in patients with ESRD.20

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

4. In patients with CKD stages 3-5 and hyperphosphatemia...

5. In vitro calcification mechanisms.

6. Calcification in patients with end-stage renal disease (ESRD) was previously believed to be a sequelae of more severe atherosclerotic disease. Theories about the significance of calcification, and how it might impact the clinical presentation of CVD, are presented below. Four mechanisms of calcification are reviewed: arterial calcification, extraskeletal calcification, and mineralization of the vessels and soft tissues.

7. CACS may be up to 5-fold higher in patients on maintenance hemodialysis than in age-matched non-CKD patients.16

8. Calcification is a major pathological focus in CKD, associated with progression of the basal Agatston score.18

9. New therapy options might specifically target calcification mechanisms.

10. The CACS is a useful non-invasive tool to evaluate CVD risk in a large cohort of hemodialysis patients.21

11. KDIGO recommends restricting the KDIGO recommends restricting the serum calcium concentration to 8.5-10.0 mg/dL for patients with non-dialysis dependent hyperparathyroidism.20

12. The Calcium Paradox: Evidence and Rationale for Calcium Modification in Chronic Kidney Disease 3-5a (CALM CKD III-Va) study, a randomized trial of calcium carbonate versus calcium acetate in patients with stage 5A to 5D CKD, found that the rate of CVD events was significantly lower in the calcium carbonate arm.14,15

13. The relationship between serum PTH levels and CVD in dialysis patients has been inconsistent.14

14. Calcification is common, more severe, and follows an accelerated course in patients with end-stage renal disease than in age-matched non-CKD patients.20

15. On all panels of this resource, G stands for Guideline.20


REFERENCES


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

Therapies to effectively treat SHPT continue to be investigated in clinical and preclinical studies with a focus on calcification and cardiovascular outcomes. Some show promise that combination therapy may be superior to monotherapy. Additional studies are required to determine whether combination therapy is more effective than monotherapy.

Calcimimetics
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Phosphate Binders
Phosphate binders are a cornerstone of therapy for patients with CKD-MBD and may help to control calcium homeostasis by decreasing serum phosphorus levels. They may also have a protective effect on the cardiovascular system by reducing aortic calcification.

Calcium and vitamin D analogs are commonly used to control development and progression of SHPT. Animals treated with calcitriol have lower mortality, compared with sevelamer-HCl. However, in the CARE-2 trial comparing calcium acetate versus low-dose vitamin D sterols, the cinacalcet group indicates subjects given cinacalcet plus low-dose vitamin D sterols had no significant difference in mortality.

Lanthane, sevelamer-HCl, and cinacalcet plus low-dose vitamin D sterols; control group indicates subjects given flexible doses of vitamin D sterols alone. After 52 weeks of follow-up.

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Calcium and vitamin D analogs are commonly used to control development and progression of SHPT. Animals treated with calcitriol have lower mortality, compared with sevelamer-HCl. However, in the CARE-2 trial comparing calcium acetate versus low-dose vitamin D sterols; control group indicates subjects given flexible doses of vitamin D sterols alone. After 52 weeks of follow-up.

Therapy 1: Using cinacalcet plus low-dose vitamin D sterols, patients experienced similar progression of coronary calcification compared with sevelamer-HCl. However, in the CARE-2 trial comparing calcium acetate versus low-dose vitamin D sterols; control group indicates subjects given flexible doses of vitamin D sterols alone. After 52 weeks of follow-up.

Therapy 2: Using cinacalcet plus low-dose vitamin D sterols, patients experienced similar progression of coronary calcification compared with sevelamer-HCl. However, in the CARE-2 trial comparing calcium acetate versus low-dose vitamin D sterols; control group indicates subjects given flexible doses of vitamin D sterols alone. After 52 weeks of follow-up.