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Review Article

Vitamin D3 and vitamin K2 in vascular calcification: from mineral metabolism to matrix Gla protein activation and arterial diseases

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ABSTRACT

Vascular calcification is an actively regulated process influenced by mineral metabolism and endogenous inhibitors such as matrix Gla protein (MGP). MGP requires vitamin K-dependent γ-carboxylation for functional activity, whereas dephosphorylated-uncarboxylated MGP (dp-ucMGP) reflects impaired vitamin K-dependent activation. Vitamin D3 regulates calcium and phosphate homeostasis, while vitamin K2, particularly menaquinone-7 (MK-7), may enhance MGP activation. This narrative review summarizes mechanistic, observational, and randomized evidence examining the relationships among vitamin D3, vitamin K2, MGP activation, vascular calcification, and cardiovascular disease. Evidence from experimental studies, biomarker studies, imaging studies, and randomized clinical trials was considered to evaluate both biochemical and structural effects. Experimental studies indicate that excessive vitamin D exposure can promote arterial calcification, particularly when MGP activation is impaired, whereas human supplementation studies have not consistently demonstrated increased calcification. Randomized trials consistently demonstrate improved MGP carboxylation with vitamin K2, but structural outcomes have been heterogeneous. AVADEC and Trevasc-HDK showed biochemical improvement without significant overall reduction in structural calcification, while DANCODE and a 2026 MK-7 trial reported slower coronary calcium progression in selected populations. These findings support the biological relevance of the vitamin K–MGP pathway but do not establish that improvements in biomarkers or imaging outcomes translate into reductions in myocardial infarction, stroke, cardiovascular death, or all-cause mortality. Longer randomized trials integrating pathway biomarkers, standardized imaging, and patient-important clinical outcomes are required.

Keywords: Vitamin D3, Vitamin K2, Vascular calcification, Matrix Gla protein, dp-ucMGP, Coronary artery calcification

INTRODUCTION

Vascular calcification is characterized by deposition of calcium-containing mineral within the arterial wall and cardiovascular structures. It was historically viewed as a passive consequence of aging or elevated circulating minerals, but experimental and clinical evidence now supports a regulated process involving vascular smooth muscle cells (VSMCs), extracellular matrix, mineral-regulatory factors, osteogenic signalling, and endogenous inhibitors. Calcification occurs in distinct anatomical settings, including intimal calcification associated with atherosclerotic plaque and medial calcification, which can occur independently of conventional plaque formation. The burden is particularly high in chronic kidney disease (CKD) and hemodialysis, where disturbances of mineral metabolism coexist with impaired calcification-inhibitory mechanisms.[1-3]

Matrix Gla protein (MGP) is a central endogenous inhibitor of vascular mineralization. Its biological activity depends on vitamin K-dependent γ-carboxylation, so the

amount of MGP produced does not necessarily reflect the amount that is functionally active. Dephosphorylated-uncarboxylated MGP (dp-ucMGP) is an inactive circulating form that has been used as a functional marker of vitamin K-dependent MGP activation. Higher dp-ucMGP concentrations have been associated with progression of coronary and aortic calcification in the Multi-Ethnic Study of Atherosclerosis (MESA) and with incident cardiovascular disease and all-cause mortality in the Bruneck Study.[4,5] These observational findings support the biological relevance of MGP activation but cannot establish causality.

Vitamin D3 provides a complementary component of this pathway because it regulates calcium and phosphate homeostasis. Experimental high-dose vitamin D can accelerate arterial calcification, particularly when vitamin K-dependent MGP activation is impaired.[6] Human supplementation studies, however, have not demonstrated a consistent increase in vascular calcification at the doses studied.[7] This difference between experimental and clinical evidence is important when interpreting the vitamin D3–vitamin K2 relationship.

The clinical question is therefore not simply whether either vitamin is associated with calcification, but whether modification of mineral metabolism and MGP activation can alter established vascular disease. Earlier randomized studies consistently demonstrated biochemical improvement in MGP carboxylation but variable effects on structural calcification.[3,8,9] More recent trials, particularly DANCODE and the 2026 MK-7 trial, have renewed interest by reporting slower coronary calcium progression in selected populations.[10,11] This review integrates the mechanistic pathway, observational evidence, randomized trials, CKD-specific biology, and remaining uncertainties while avoiding the assumption that a biomarker response necessarily represents clinical benefit.

VASCULAR CALCIFICATION AS AN ACTIVE BIOLOGICAL PROCESS

Vascular calcification results from an imbalance between processes that promote mineral deposition and systems that restrain it. VSMCs can undergo phenotypic changes toward an osteogenic state, while extracellular matrix remodeling, matrix vesicles, apoptotic bodies, and osteogenic signalling can provide an environment favorable to mineral nucleation.[1,2] Bone-related signalling pathways, including bone morphogenetic protein (BMP) pathways, are involved, although vascular calcification should not be equated with normal bone formation.

Two broad patterns are clinically important. Intimal calcification commonly occurs within atherosclerotic lesions, whereas medial calcification affects the arterial media and is prominent in conditions such as CKD. The biological drivers differ between settings, but mineral balance, cellular phenotype, matrix composition, and endogenous inhibitors interact in both. This explains why a single intervention may have different effects according to baseline calcification burden, vascular territory, renal function, and duration of disease.

MGP is one of the best characterized endogenous inhibitors. It can interact with calcium-containing mineral and modulate BMP signalling, thereby limiting processes that favor vascular mineralization.[1,2] Vitamin K-dependent γ-carboxylation is essential for this activity. Consequently, impaired vitamin K availability or impaired vitamin K recycling can increase the proportion of inactive MGP. This provides the mechanistic foundation for studying vitamin K2 as a modulator of calcification biology.

The distinction between mineral availability and calcification inhibition is particularly relevant to vitamin D. Experimental models demonstrate that excessive vitamin D can increase arterial mineralization and that inhibition of vitamin K-dependent MGP activation with warfarin markedly enhances this effect.[6] The findings suggest an interaction between mineral-related stress and the integrity of endogenous anti-calcific pathways rather than a simple direct effect of vitamin D alone. In humans, however, the relationship is more complex and dose- and context-dependent.[7]

VITAMIN D3: MINERAL HOMEOSTASIS AND VASCULAR CALCIFICATION

Vitamin D3 regulates calcium and phosphate homeostasis and therefore influences the mineral environment in which vascular calcification occurs. Its relationship with calcification is context dependent. In experimental models, high-dose vitamin D induces arterial medial calcification, with the extent of calcification related to increases in serum calcium. When vitamin K-dependent γ-carboxylation is inhibited by warfarin, vitamin D-associated calcification is substantially enhanced.[6] These observations provide a mechanistic link between mineral loading and failure of MGP-mediated inhibition.

Human evidence is less supportive of a uniformly pro-calcific effect. In the Calgary Vitamin D Study, vitamin D-replete participants received 400, 4,000, or 10,000 IU/day of vitamin D3 for three years. The secondary analysis found no significant difference in development or progression of tibial artery calcification among the dose groups.[7] Thus, the experimental effects of excessive vitamin D cannot be directly extrapolated to routine supplementation in humans.

Vitamin D may also influence MGP expression, but expression and functional activation are distinct processes. An increase in MGP synthesis does not guarantee effective inhibition of calcification if vitamin K-dependent γ-carboxylation is inadequate. This distinction supports examination of vitamin D3 and vitamin K2 as complementary components of the mineral-regulatory network rather than as interchangeable interventions.

Overall, current evidence does not establish that vitamin D supplementation at clinically studied doses consistently accelerates or prevents vascular calcification. The strongest mechanistic concern relates to excessive mineral exposure in settings where endogenous calcification inhibitors are impaired, whereas clinical trials emphasize the importance of baseline mineral status, dose, population, and vascular context.[6,7]

VITAMIN K2 AND MATRIX GLA PROTEIN

Vitamin K is required for γ-carboxylation of glutamate residues in vitamin K-dependent proteins. Vitamin K1 (phylloquinone) and vitamin K2 (menaquinones) are the major forms; K2 includes compounds such as MK-4 and longer-chain menaquinones such as MK-7.[2,12,13,14] Interest in MK-7 has increased because of its extrahepatic availability and its capacity to influence the carboxylation of vitamin K-dependent proteins outside the liver.

MGP is synthesized by vascular tissues and undergoes post-translational modification before becoming functionally active. Vitamin K-dependent γ-carboxylation gives MGP calcium-binding capacity and contributes to inhibition of vascular mineralization. Inadequate activation results in accumulation of inactive forms, including dp-ucMGP.[1,2,12,15,16] Circulating dp-ucMGP therefore provides information about the functional status of this pathway rather than simply measuring total MGP.

Experimental work supports several anti-calcific actions of MGP, including interaction with mineral and modulation of BMP signalling.[1,2] The importance of the pathway is illustrated by experimental warfarin exposure, which inhibits vitamin K recycling and markedly enhances vitamin D-associated arterial calcification.[6] Observational studies extend these findings to humans: higher dp-ucMGP has been associated with progression of coronary and thoracic aortic calcification and with cardiovascular disease and mortality.[4,5]

Vitamin K2 supplementation generally improves the biochemical pathway. Trials in aortic valve disease and hemodialysis have demonstrated significant reductions in dp-ucMGP, indicating improved MGP carboxylation.[3,8] However, biochemical activation has not consistently translated into slower structural calcification. This distinction is central to interpreting the evidence: dp-ucMGP is a responsive biomarker, but it is not established as a surrogate endpoint proving that supplementation prevents cardiovascular events or reverses established calcification.[5,10,13]

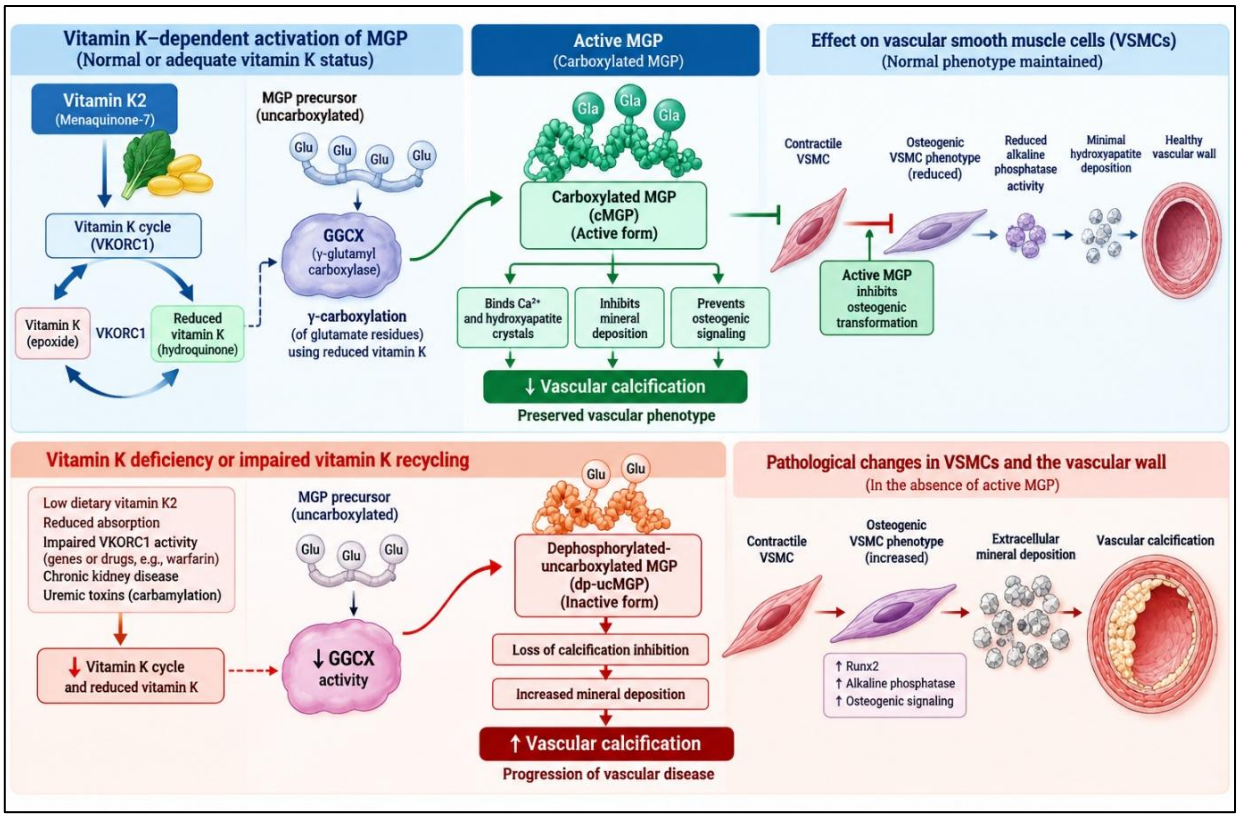


Figure 1: The vitamin K2–MGP axis in vascular calcification. The schematic illustrates vitamin K-dependent activation of MGP through the vitamin K cycle and GGCX-mediated γ-carboxylation, with impaired activation associated with loss of calcification inhibition. Source: Author-created figure; no external source used.

MGP, CARDIOVASCULAR RISK, AND THE BROADER VITAMIN K-DEPENDENT NETWORK

The association between inactive MGP and vascular disease has been demonstrated in population-based cohorts. In MESA, higher dp-ucMGP was associated with greater long-term progression of coronary artery and ascending and descending thoracic aortic calcification.[4] In the prospective Bruneck Study, higher dp-ucMGP was associated with incident cardiovascular disease and all-cause mortality.[5] These observations support the clinical relevance of MGP activation status, but they remain observational and therefore cannot establish that increasing MGP carboxylation will prevent cardiovascular events.

MGP is not the only vitamin K-dependent protein involved in mineral regulation. Gla-rich protein (GRP), also known as UCMA, contains a high density of γ-carboxyglutamate residues and has been detected in vascular and valvular calcification.[17] Experimental studies indicate that carboxylated GRP can inhibit vascular and valvular calcification, whereas undercarboxylated GRP has substantially less anti-calcific activity.[18] GRP may also interact with inflammatory and mineral-regulatory processes, but its clinical significance remains less established than that of dp-ucMGP.[17,18]

The expanding network of vitamin K-dependent proteins reinforces the concept that vascular calcification is regulated by several interacting pathways. MGP is currently the most clinically developed marker in this network, while GRP represents an emerging area of investigation. The presence of several vitamin K-dependent proteins also means that a single biomarker should not be interpreted as a complete representation of vascular calcification biology.

Table 1: Biological roles of vitamin D3, vitamin K2, and MGP in vascular calcification.

Component	Primary biological role	Key molecular pathway / mechanism	Role in vascular calcification
Vitamin D3	Regulates calcium and phosphate homeostasis	Modulates calcium and phosphate metabolism	Influences the mineral environment in which vascular calcification occurs; excessive exposure can promote calcification in experimental settings
Vitamin K2	Supports activation of vitamin K-dependent proteins	Vitamin K cycle → reduced vitamin K → GGCX-mediated γ-carboxylation	Promotes functional activation of MGP and other extrahepatic vitamin K-dependent proteins, supporting endogenous anti-calcification mechanisms
GGCX	Catalyzes γ-carboxylation of vitamin K-dependent proteins	Uses reduced vitamin K to convert glutamate residues to γ-carboxyglutamate (Gla)	Required for conversion of newly synthesized MGP into its functional form
Matrix Gla protein (MGP)	Endogenous inhibitor of vascular mineralization	Vitamin K-dependent γ-carboxylation; interaction with mineral and BMP signalling	Inhibits inappropriate vascular mineral deposition and modulates osteogenic signalling
Carboxylated MGP	Functional form of MGP	Vitamin K-dependent γ-carboxylation of glutamate residues	Active anti-calcific form that contributes to inhibition of vascular mineralization
dp-ucMGP	Inactive/undercarboxylated MGP species	Reflects inadequate vitamin K-dependent MGP activation	Higher concentrations are associated with vascular calcification and cardiovascular outcomes in observational studies
GRP (Gla-rich protein)	Emerging vitamin K-dependent calcification-regulatory protein	Extensive γ-carboxylation provides calcium-binding capacity	May contribute to inhibition of vascular and valvular calcification; role remains less established than MGP

VITAMIN K2 IN CHRONIC KIDNEY DISEASE AND UREMIA

CKD provides a particularly relevant setting for the vitamin K-MGP pathway because vascular calcification is common and mineral metabolism is substantially disturbed. Patients receiving hemodialysis may have increased dp-ucMGP, consistent with impaired vitamin K-dependent MGP activation.[3,9,19] Randomized studies demonstrate that vitamin K2 can reduce dp-ucMGP in dialysis populations, but reductions in this biomarker have

not consistently produced significant reductions in coronary, aortic-valve, or another vascular calcification.[3]

Mechanistic work suggests that uremia may affect the vitamin K pathway beyond simple dietary deficiency. Experimental studies demonstrated impaired vitamin K recycling in uremia, resulting in increased proportions of uncarboxylated vitamin K-dependent proteins.[19] More recent experimental work identified post-translational carbamylation of γ-glutamyl carboxylase (GGCX), an enzyme required for MGP γ-carboxylation. Carbamylation reduced GGCX activity, while vitamin K2 prevented the reduction in experimental models.[20] These findings provide a molecular explanation for impaired MGP activation in uremia, although the extent to which GGCX carbamylation contributes to human vascular calcification remains uncertain.

Genetic determinants of vitamin K metabolism, including VKORC1 and GGCX pathways, are biologically plausible modifiers of vitamin K-dependent protein activation, but the evidence available in this review does not establish specific genetic variants as clinical explanations for differences in vascular calcification risk. CKD therefore remains an important setting for further research, particularly trials that combine mechanistic biomarkers with standardized imaging and cardiovascular outcomes.

BONE–VASCULAR CROSSTALK AND THE VITAMIN D3–VITAMIN K2 AXIS

Bone and vascular tissues share mineral-regulatory pathways, but vascular calcification is not simply misplaced bone formation. Under pathological conditions, vascular cells can activate signalling programs resembling skeletal mineralization, while extracellular mineral balance and endogenous inhibitors determine whether calcium-phosphate is deposited appropriately or ectopically.[1,2]

Vitamin D3 and vitamin K2 act at complementary points in this system. Vitamin D3 regulates calcium and phosphate availability, whereas vitamin K2 supports activation of MGP and other vitamin K-dependent proteins. Vitamin D may influence MGP expression, but functional MGP activity still requires vitamin K-dependent γ-carboxylation.[1,2,7,16] The combination therefore has a biologically plausible rationale: one component influences the mineral environment and the other supports endogenous inhibition of mineral deposition.

Experimental evidence provides the clearest demonstration of interaction. High-dose vitamin D produces more pronounced arterial calcification when vitamin K-dependent MGP activation is inhibited.[6] Clinical evidence is more nuanced. In AVADEC, MK-7 plus vitamin D reduced dp-ucMGP but did not significantly reduce progression of aortic-valve, aortic, or coronary calcification in the primary analysis.[8] Thus, pathway activation was demonstrated without a corresponding overall structural benefit. The DANCODE trial later reported a lower increase in coronary artery calcium with combined vitamin K2 and vitamin D3 in patients with severe baseline calcification.[10]

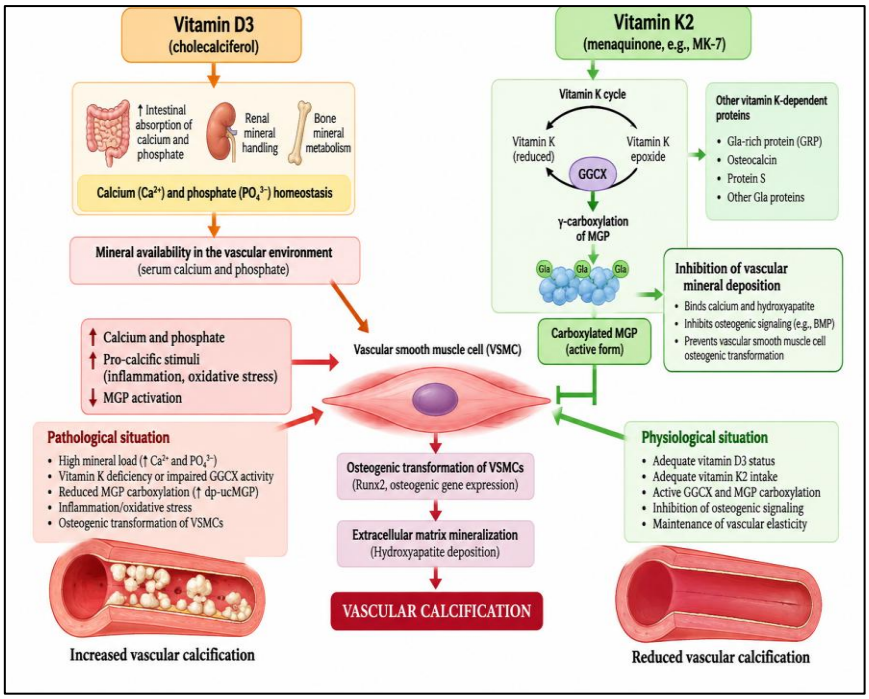


Figure 2: Integrated vitamin D3–vitamin K2–MGP pathway in vascular calcification. The figure integrates vitamin D3-mediated regulation of calcium and phosphate availability with vitamin K2-dependent MGP activation and downstream vascular calcification biology. Source: Author-created figure; no external source used.

These findings support the concept of complementary biological effects while demonstrating that the relationship between pathway activation and structural disease is not linear. Baseline calcification burden, disease duration, vascular territory, intervention duration, vitamin K formulation, and the imaging endpoint may all influence observed effects.

CLINICAL EVIDENCE: FROM BIOMARKERS TO CALCIFICATION OUTCOMES

Randomized trials provide the strongest evidence for determining whether biochemical improvement translates into structural benefit. The overall pattern is consistent in one respect: vitamin K2 improves MGP carboxylation, generally reflected by lower dp-ucMGP. The structural outcome has been less consistent.

In AVADEC, older men at cardiovascular risk with aortic valve calcification received MK-7 720 µg/day plus vitamin D3 25 µg/day or placebo for 24 months.[8] Supplementation significantly reduced dp-ucMGP but did not significantly reduce progression of aortic valve calcification or aortic and coronary calcification. A subsequent analysis of coronary artery calcification found no significant overall difference in CAC progression, although participants with higher baseline CAC appeared to have a lower progression rate with supplementation.[21] Because the overall analysis was neutral, this subgroup observation remains hypothesis-generating rather than definitive evidence of benefit.

A substudy of AVADEC evaluated epicardial adipose tissue (EAT), pericoronary adipose tissue (PCAT), and systemic inflammatory markers. Despite improved MGP activation, vitamin K2 plus vitamin D3 did not produce significant between-group differences in EAT volume, EAT attenuation, or PCAT attenuation. Most systemic inflammatory markers also did not differ significantly, although osteopontin increased modestly in the intervention group.[22] These results further demonstrate that a biochemical response in the MGP pathway does not necessarily produce parallel changes across other cardiovascular phenotypes.

In hemodialysis, the Trevasc-HDK trial similarly demonstrated reduced dp-ucMGP with vitamin K2 without a significant reduction in vascular calcification progression.[3] A pediatric hemodialysis study reported favorable changes in calcification-related biomarkers with vitamin K2 and native vitamin D, but the population and study duration limit extrapolation to broader clinical outcomes.[9]

The INTRICATE trial reflects a newer approach to evaluating calcification biology. It was designed to investigate combined vitamin K2 and vitamin D3 using sodium [18F] fluoride PET/MRI in patients with carotid artery disease.[23] Such imaging may detect metabolically active microcalcification in addition to established structural calcification, potentially providing an intermediate outcome between biochemical biomarkers and late anatomic disease.

DANCODE represents an important recent development. In 400 participants with severe coronary artery calcification, combined vitamin K2 and vitamin D3 was compared with placebo for 24 months. The intervention group had a smaller increase in coronary artery calcium, indicating attenuation of progression rather than reversal of established calcification.[10] This result differs from earlier neutral structural outcomes and raises the possibility that baseline disease burden may modify treatment response.

Table 2: Major randomized evidence on vitamin K2 and vitamin D3 calcification.

Study	Population	Intervention	Biochemical finding	Structural outcome
AVADEC[8]	Older men with cardiovascular risk/aortic valve calcification	MK-7 + D3, 24 months	↓ dp-ucMGP	No significant overall reduction in aortic-valve/aortic/CAC progression
Trevasc-HDK[3]	Hemodialysis	Vitamin K2	↓ dp-ucMGP	No significant reduction in vascular calcification progression
INTRICATE[23]	Carotid artery disease	K2 + D3	Pathway-focused trial	18F-NaF PET/MRI assessment of calcification activity
DANCODE[10]	Severe coronary calcification	K2 + D3, 24 months	Pathway intervention	Lower increase in CAC; progression attenuated, not reversed
2026 MK-7 trial[11]	Symptomatic CAD with moderate CAC	MK-7, 2 years	—	Slower CAC progression

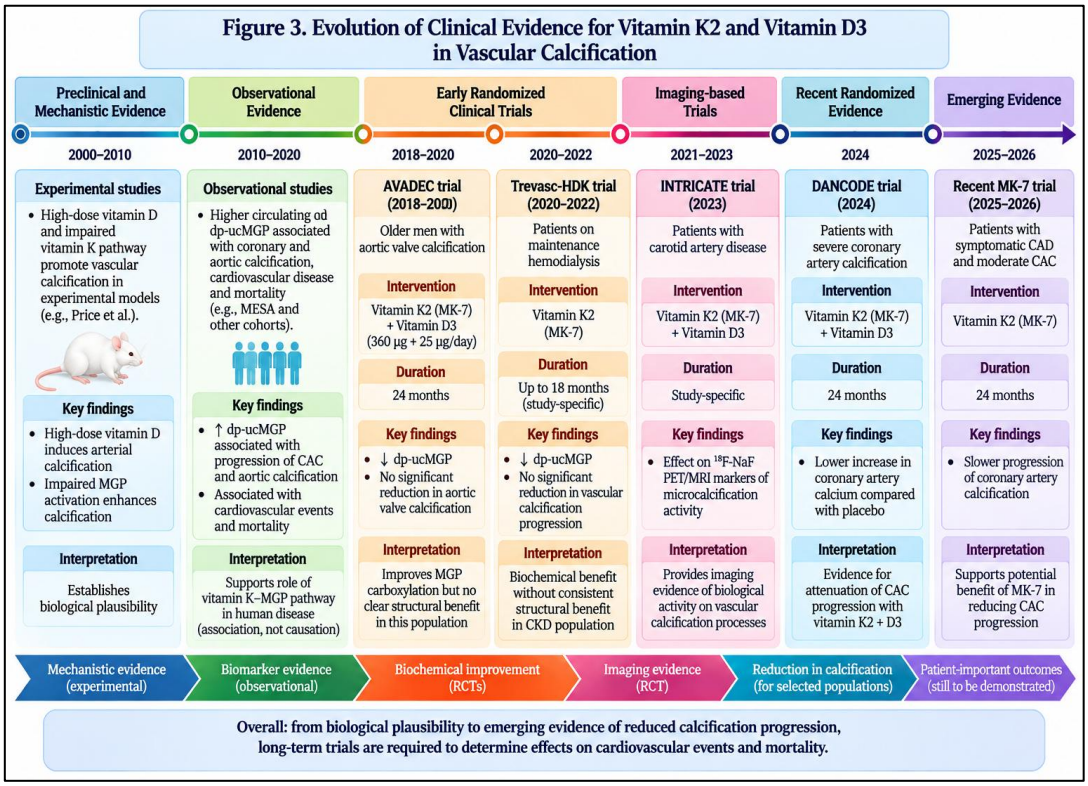


Figure 3: Evolution of clinical evidence for vitamin K2 and vitamin D3 in vascular calcification. The timeline summarizes mechanistic, observational, and randomized evidence, including AVADEC, Trevasc-HDK, INTRICATE, DANCODE, and the 2026 MK-7 trial. Source: Author-created figure; no external source used.

A 2026 randomized clinical trial evaluated two years of MK-7 supplementation in patients with symptomatic coronary artery disease and moderate baseline CAC and reported slower CAC progression.[11] Together with DANCODE, this provides emerging randomized evidence that vitamin K2-containing interventions may influence the trajectory of coronary calcification in selected patients. Nevertheless, these trials do not establish that slowing CAC progression prevents myocardial infarction, stroke, cardiovascular death, or all-cause mortality. They also do not demonstrate regression of established calcification.

Taken together, the clinical evidence is best described as a progression from a well-established biochemical effect toward increasingly suggestive structural findings. The most reproducible endpoint is improved MGP carboxylation; the magnitude and consistency of structural benefit remain under investigation.

INTERPRETING THE BIOMARKER–OUTCOME GAP

The apparent gap between biochemical and imaging outcomes is biologically plausible. MGP activation is only one component of a larger calcification network, and established mineral deposits may be difficult to modify over short periods. Calcification also reflects cumulative renal dysfunction, inflammation, plaque burden, mineral imbalance, and vascular remodeling.[1,2,3,19,20]

Direct comparison of trials is limited by differences in baseline calcification, renal function, vascular territory, vitamin K formulation and dose, vitamin D co-administration, treatment duration, and imaging method. CAC, valvular calcium, dialysis-associated vascular calcification, and 18F-sodium fluoride PET are related but distinct outcomes.[3,8,10,11,23]

The evidence is therefore hierarchical: vitamin K2 modifies the vitamin K-MGP pathway; higher inactive MGP is associated with vascular disease in observational cohorts; randomized trials have produced mixed structural findings, although recent coronary trials suggest slower CAC progression in selected populations; and evidence for reduction of patient-important cardiovascular events remains insufficient.[3,4,5,8,10,11,21]

SAFETY AND CLINICAL CONSIDERATIONS

Vitamin D supplementation should be interpreted in relation to dose and mineral status. Experimental high-dose exposure can promote arterial calcification, whereas human randomized data at studied doses have not demonstrated a consistent increase in peripheral arterial

calcification.[6,7] Excessive supplementation should therefore not be inferred to be beneficial simply because vitamin D participates in mineral homeostasis.

Vitamin K2 has generally been investigated as a nutritional or supplemental intervention, but clinical context matters. Vitamin K-dependent pathways are directly relevant to anticoagulation with vitamin K antagonists, and supplementation should not be considered independently of anticoagulant management. Patients with CKD may have particularly complex mineral and vascular biology, so results from general populations cannot automatically be extrapolated to dialysis patients.

The current evidence does not justify describing vitamin K2 or combined vitamin K2–vitamin D3 supplementation as an established therapy for prevention or reversal of cardiovascular calcification. Individualized decisions should consider indication, baseline vitamin status, renal function, concomitant medications, and the evidence supporting the specific population and formulation under consideration.

LIMITATIONS OF CURRENT EVIDENCE AND KNOWLEDGE GAPS

Important limitations include the observational nature of dp-ucMGP associations, substantial heterogeneity among randomized trials, and the fact that most studies were powered for biomarker or imaging outcomes rather than cardiovascular events.

dp-ucMGP is responsive to vitamin K2, but its validity as a surrogate for clinical benefit remains unproven. Similarly, CAC progression is an important imaging phenotype but is not equivalent to cardiovascular morbidity or mortality.

Table 3: Current evidence and remaining knowledge gaps in vitamin K2-MGP-vascular calcification research.

Domain	What is currently established	What remains uncertain / knowledge gap
Vitamin K2 and MGP activation	Vitamin K2 supplementation consistently improves vitamin K-dependent MGP carboxylation, particularly by reducing circulating dp-ucMGP.	Whether improved MGP carboxylation consistently produces clinically meaningful reduction in vascular calcification remains uncertain.
dp-ucMGP	Higher dp-ucMGP concentrations are associated with vascular calcification and cardiovascular outcomes; levels decrease with vitamin K supplementation.	Its optimal clinical role—as a risk biomarker, marker of vitamin K status, or treatment target—has not been established.
Structural vascular calcification	Recent randomized evidence suggests that vitamin K2 ± vitamin D3 may attenuate calcification progression in selected populations, including severe CAC. [10,11]	Whether vitamin K2 can prevent, reverse, or substantially modify established calcification remains uncertain.
Coronary artery calcification (CAC)	DANCODE and a recent MK-7 randomized trial reported slower CAC progression in selected populations. [10,11]	It remains uncertain whether slowing CAC progression translates into fewer myocardial infarctions, cardiovascular deaths, or other major cardiovascular events.
Vitamin K2 formulation and dose	Studies have evaluated different vitamin K forms, including MK-4 and MK-7, with biological effects on MGP activation.	The optimal formulation, dose, treatment duration, and dosing regimen have not been established.
Target population	Effects may differ according to baseline calcification burden, disease stage, kidney function, and underlying mineral metabolism.	It remains unclear whether patients with substantial or rapidly progressive calcification derive greater benefit than those with minimal calcification.
CKD and hemodialysis	Vitamin K2 can improve MGP activation in CKD/hemodialysis populations, including reduction of dp-ucMGP. [3,19]	Randomized evidence has not consistently demonstrated reduced vascular calcification progression; the optimal CKD population and treatment strategy remain unclear.
Vitamin D3–Vitamin K2 interaction	Vitamin D3 regulates calcium/phosphate homeostasis, while vitamin K2 supports activation of MGP, providing a biologically complementary pathway.	The extent to which combined D3–K2 supplementation produces additional structural or clinical benefit requires further investigation.

Continued.

Domain	What is currently established	What remains uncertain / knowledge gap
MGP–GGCX–vitamin K cycle	MGP activation depends on vitamin K-dependent γ-carboxylation through GGCX.	The effects of GGCX activity, vitamin K recycling, and uremia-associated protein modification on clinical calcification require further clarification.
Other vitamin K-dependent proteins	MGP is an important calcification inhibitor, while proteins such as Gla-rich protein (GRP) may also participate in mineral regulation.	The contribution of GRP and other vitamin K-dependent proteins to human vascular calcification remains incompletely defined.
Imaging outcomes	CT-based CAC and other imaging techniques provide objective measures of structural calcification; advanced imaging can assess calcification activity.	Standardization of imaging methods and determination of which imaging endpoints best predict clinical outcomes are needed.
Patient-important outcomes	Current evidence mainly demonstrates biochemical and imaging effects.	Whether modification of the vitamin K–MGP pathway reduces cardiovascular events, hospitalization, heart failure, or mortality remains unproven.
Long-term effects	Existing trials generally provide relatively short- to intermediate-term evidence.	Long-term randomized studies are required to establish sustained effects, safety, and cardiovascular benefit.

Dose, formulation, duration, baseline calcification, renal function, and patient selection remain unresolved. DANCODE and the 2026 MK-7 trial suggest that treatment effects may differ in patients with established coronary calcification, but these population-specific findings require confirmation.[10,11]

Future trials should integrate vitamin K-dependent biomarkers with standardized CT or PET-based imaging and clinically meaningful outcomes, with prespecified subgroup analyses and adequate follow-up.

INTEGRATED INTERPRETATION OF THE EVIDENCE

The populations studied are biologically distinct, ranging from older men with aortic valve disease and dialysis patients to people with carotid disease or severe coronary calcification. CKD adds abnormalities in phosphate handling, inflammation, uremic toxins, and vitamin K recycling. Stratification by baseline calcification, renal function, and vitamin K status may therefore be more informative than a single treatment estimate.

Treatment duration is also unresolved. Vascular calcification accumulates over years, whereas most trials followed participants for about two years. Future studies should distinguish prevention of new calcification from slowing progression of established disease.

CAC is a useful measure of coronary calcium burden, but changes in CAC do not necessarily translate proportionally into clinical events. Metabolic imaging may identify active microcalcification before large changes in total calcium are detectable; combined CT and PET approaches may therefore be informative.

Standardized vitamin K formulations, dosing, vitamin D exposure, imaging protocols, and reporting of baseline calcification and renal status would improve comparability across trials.

CONCLUSION

Vascular calcification is an active biological process involving mineral metabolism, VSMC remodeling, extracellular matrix changes, and endogenous inhibitors. MGP is a central vitamin K-dependent defense mechanism, while vitamin D3 regulates the mineral environment in which calcification develops.

Vitamin K supplementation consistently improves MGP carboxylation and lowers dp-ucMGP, but earlier randomized studies did not consistently demonstrate slower structural calcification. DANCODE and a 2026 MK-7 trial suggest that coronary calcification progression may be attenuated in selected patients with established coronary disease, without demonstrating regression or prevention of cardiovascular events.[10,11]

Overall, the evidence supports biological relevance of the vitamin D3-vitamin K2-MGP axis but remains insufficient to establish a cardiovascular preventive therapy. Long-term randomized trials combining pathway biomarkers, standardized imaging, and patient-important outcomes are needed.

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REFERENCES

1. Proudfoot D, Shanahan CM. Molecular mechanisms mediating vascular calcification: role of matrix Gla protein. Nephrology (Carlton). 2006;11(5):455-61.
2. Bjørklund G, Svanberg E, Dadar M, Card DJ, Chirumbolo S, Harrington DJ, et al. The role of matrix Gla protein (MGP) in vascular calcification. Curr Med Chem. 2020;27(10):1647-60.
3. Haroon S, Davenport A, Ling LH, Tai BC, Teo LL, Schurgers L, et al. Randomized controlled clinical trial of the effect of treatment with vitamin K2 on vascular calcification in hemodialysis patients (Trevasc-HDK). Kidney Int Rep. 2023;8(9):1741-51.
4. Berlot AA, Fu X, Shea MK, Tracy R, Budoff M, Kim RS, et al. Matrix Gla protein and the long-term incidence and progression of coronary artery and aortic calcification in the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2024;392:117505.
5. Willeit K, Santer P, Tschiderer L, Pechlaner R, Vermeer C, Willeit J, et al. Association of desphospho-uncarboxylated matrix Gla protein with incident cardiovascular disease and all-cause mortality: results from the prospective Bruneck Study. Atherosclerosis. 2022;353:20-7.
6. Price PA, Faus SA, Williamson MK. Warfarin-induced artery calcification is accelerated by growth and vitamin D. Arterioscler Thromb Vasc Biol. 2000;20(2):317-27.
7. Billington EO, Burt LA, Plett R, Rose MS, Boyd SK, Hanley DA. Effect of high-dose vitamin D supplementation on peripheral arterial calcification: secondary analysis of a randomized controlled trial. Osteoporos Int. 2020;31(11):2141-50.
8. Diederichsen ACP, Lindholt JS, Möller S, Øvrehus KA, Auscher S, Lambrechtsen J, et al. Vitamin K2 and D in patients with aortic valve calcification: a randomized double-blinded clinical trial. Circulation. 2022;145(18):1387-97.
9. El Borolossy R, El-Farsy MS. The impact of vitamin K2 and native vitamin D supplementation on vascular calcification in pediatric patients on regular hemodialysis: a randomized controlled trial. Eur J Clin Nutr. 2022;76(6):848-54.
10. Hasific S, Øvrehus KA, Mejldal A, Hosbond S, Lambrechtsen J, Kumarathurai P, et al. Vitamin K2 and D3 supplementation in patients with severe coronary artery calcification: the DANCODE trial. Circulation. 2026;154(17):1974.
11. Vossen LM, de Leeuw PW, Schurgers LJ, Heuts S, Adriaans BP, de Haan C, et al. Two years of menaquinone-7 supplementation and coronary artery calcification: a randomized clinical trial. JAMA Cardiol. 2026;11(8):719-26.
12. El Asmar MS, Naoum JJ, Arbid EJ. Vitamin K-dependent proteins and the role of vitamin K2 in the modulation of vascular calcification: a review. Oman Med J. 2014;29(3):172-7.
13. Vlasschaert C, Goss CJ, Pilkey NG, McKeown S, Holden RM. Vitamin K supplementation for the prevention of cardiovascular disease: where is the evidence? A systematic review of controlled trials. Nutrients. 2020;12(10):2909.
14. Schurgers LJ, Dissel PE, Spronk HM, Soute BA, Dhore CR, Cleutjens JP, et al. Role of vitamin K and vitamin K-dependent proteins in vascular calcification. Z Kardiol. 2001;90 Suppl 3:57-63.
15. Barrett H, O'Keeffe M, Kavanagh E, Walsh M, O'Connor EM. Is matrix Gla protein associated with vascular calcification? A systematic review. Nutrients. 2018;10(4):415.
16. Schurgers LJ, Cranenburg EC, Vermeer C. Matrix Gla-protein: the calcification inhibitor in need of vitamin K. Thromb Haemost. 2008;100(4):593-603.
17. Viegas CS, Cavaco S, Neves PL, Ferreira A, João A, Williamson MK, et al. Gla-rich protein is a novel vitamin K-dependent protein present in serum that accumulates at sites of pathological calcifications. Am J Pathol. 2009;175(6):2288-98.
18. Viegas CS, Rafael MS, Enriquez JL, Teixeira A, Vitorino R, Luís IM, et al. Gla-rich protein acts as a calcification inhibitor in the human cardiovascular system. Arterioscler Thromb Vasc Biol. 2015;35(2):399-408.
19. Kaesler N, Magdeleyns E, Herfs M, Schettgen T, Brandenburg V, Fliser D, et al. Impaired vitamin K recycling in uremia is rescued by vitamin K supplementation. Kidney Int. 2014;86(2):286-93.
20. Kaesler N, Kaushik S, Frisch J, Ziegler S, Grommes J, Gombert A, et al. Vitamin K preserves gamma-glutamyl carboxylase activity against carbamylations in uremia: implications for vascular calcification and adjunct therapies. Acta Physiol (Oxf). 2025;241(5):e70040.
21. Hasific S, Øvrehus KA, Lindholt JS, Mejldal A, Dey D, Dahl JS, et al. Effects of vitamin K2 and D supplementation on coronary artery disease in men: a RCT. JACC Adv. 2023;2(9):100643.
22. Hasific S, Ravn EJ, Rasmussen LM, Mejldal A, Dey D, Frandsen NE, et al. Effects of vitamin K2 and D3 supplementation on epicardial adipose tissue and systemic inflammation: a substudy of the AVADEC trial. Atherosclerosis. 2025;410:120540.
23. Florea A, Kooi ME, Mess W, Schurgers LJ, Bucerius J, Mottaghy FM. Effects of combined vitamin K2 and vitamin D3 supplementation on Na[18F]F PET/MRI in patients with carotid artery disease: the INTRICATE rationale and trial design. Nutrients. 2021;13(3):994.

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