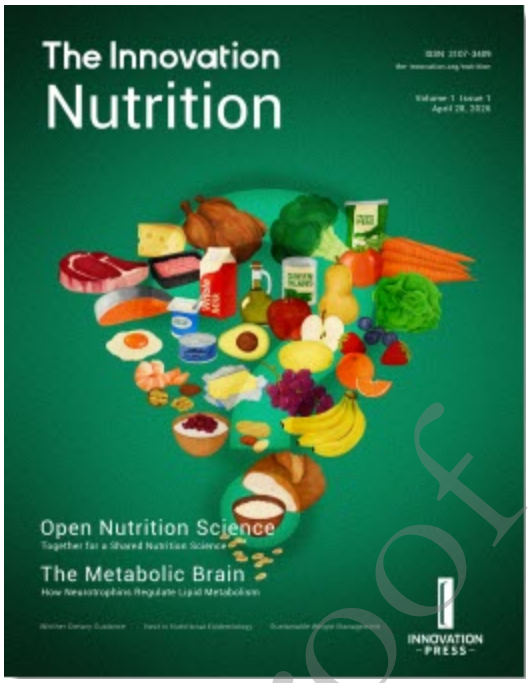

The Paradox of Coronary Artery Calcification and the "Endpoint" Myth of Nutritional Interventions: Academic Reflections from Menaquinone-7, Niacin, and Berberine

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Nutritional interventions slow coronary calcification, but do they improve clinical outcomes?

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I. INTRODUCTION：THE VITAK-CAC TRAIL IN CONTEXT

Vascular calcification ,once considered a passive degenerative sign of aging blood vessels, is now identified as an active, regulated biological process resembling ectopic osteogenesis rather than just necrotic precipitation.

This evolving understanding has fundamentally changed perceptions of coronary artery disease progression and plaque biology.

In the recently published VitaK-CAC trial,(JAMA Cardiology), Vossen and his colleagues[1] studied whether MK-7, a highly bioavailable vitamin K2, could slow coronary calcification progression in symptomatic CAD patients . A total of 180 symptomatic patients with baseline Agatston scores of 50 to 400 Agatston scores of 50 – 400 AU (mild-to-moderate calcification) were randomized to 360 μg MK-7 daily or placebo.

As the first randomized controlled trial studying MK-7 for coronary artery calcification progression specifically in symptomatic CAD, —rather than in end-stage kidney disease or diabetes cohorts characterized by advanced medial calcification—it reported statistically significant attenuation of coronary calcification in the MK-7 group versus placebo. Its rigorous design provides solid conceptual verification that MK-7 modulates vitamin K-dependent pathways related to vascular calcification. However, these results also raise important conceptual and clinical questions. Current research shows vascular calcification includes both early destabilizing calcification and late potentially stabilizing calcification, so it is still unclear whether slowing calcification progression means beneficial improvement of disease biology. Besides, the extent to which coronary artery calcification(CAC) scores changes translate into cardiovascular events remains unclear. These problems reflect broader challenges in interpreting surrogate endpoints and their relationship to clinically meaningful benefits. Collectively, this commentary holds that slowing coronary calcification is not equal

to beneficial plaque stabilization, and even statistically significant improvements in surrogate endpoints only put forward new hypotheses, which need to be confirmed by patient-centered hard outcome trials.

II. DEEP ANALYSIS OF VITAK-CAC DATA:MODEST ATTENUATION AND THE STAGNATION OF "FAST PROGRESSORS"

The primary results demonstrated that after 2 years , MK-7 significantly attenuated the CAC progression. The median unadjusted CAC score in the placebo group increased from baseline 145 AU to 173 AU at 1 year and 214 AU at 2 years, while the MK-7 group rose from 135 AU at baseline to 150 AU at 1 year and 184 AU at 2 years, yielding a significant difference-in-differences effect ($P = 0.02$). Multivariable generalized estimating equation models further showed MK-7 reduced the annual progression of CAC by an adjusted β coefficient of 19 AU ($P < 0.001$) and attenuated the 2-year coronary calcium mass progression by 2 mg (P=0.01). Biologically,plasma dp-ucMGP increase — a vitamin K status biomarker,— was significantly lower in the treatment group (difference 67 pmol/L, P<0.001), indicating MGP activation

Despite these apparently favorable results, several clinical and methodological caveats warrant consideration. First, the proportion of "fast progressors" did not differ significantly between groups (65% placebo vs 58% MK-7 at 2 years, P=0.38), so MK-7 failed to alter the progression trajectory of the highest-risk subgroup with accelerated mineralization. MK-7 failed to alter the trajectory of the subgroup with accelerated mineralization. Second, no significant difference in noncalcified plaque burden or stenosis severity suggested the intervention did not change the underlying atherosclerotic substrate.

Finally, CAC progression was significantly associated with the transition to partially calcified plaques （R^2 =0.17; P=0.04), but not with changes in advanced calcified plaques. This suggests coronary calcium accumulation mainly reflects incipient calcification rather than progression of established lesions. However, contemporary evidence indicates progression from early to advanced calcification may represent plaque healing and stabilization.

III. THE MECHANISTIC PARADOX:STAIN ANTAGONISM AND PLAQUE STABILITY

Within the arterial intima, carboxylated MGP acts as a potent local inhibitor of vascular mineralization. Activated MGP binds calcium-containing mineral crystals and bone morphogenetic proteins (BMP-2/4), suppressing osteogenic transdifferentiation of vascular smooth muscle cells and limiting ectopic calcification. Vitamin K2 serves as an essential

cofactor for gamma-glutamyl carboxylase, the enzyme catalyzing MGP activation. Consequently, MK-7 enhances MGP carboxylation, providing a biologically plausible mechanism for attenuating vascular calcification (Figure 1).

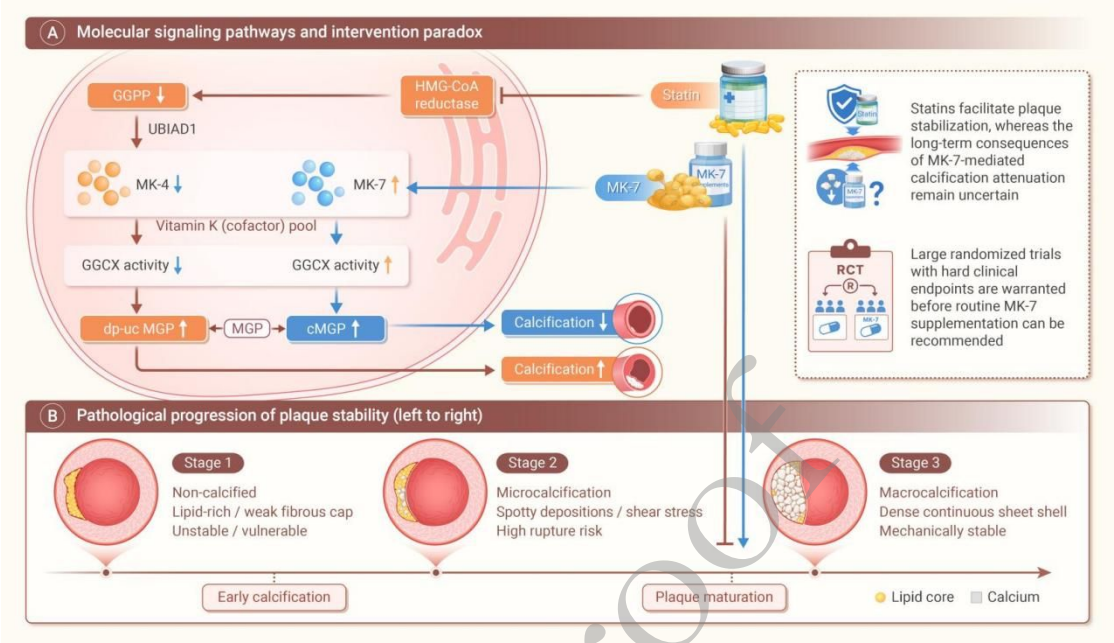

Figure 1. Mechanistic paradox of coronary artery calcification: opposing biological effects of statin-induced plaque maturation and MK-7-mediated calcification inhibition. Panel I illustrates the three-stage evolution of atherosclerotic plaques: Stage 1 (vulnerable noncalcified lesions), Stage 2 (rupture-prone plaques with incipient calcification), and Stage 3 (mechanically stable plaques with advanced calcification). Statins promote the transition to protective advanced calcification, while MK-7 slows calcification progression. Panel II contrasts their molecular pathways: statins reduce vascular GGPP and endogenous MK-4 synthesis, leading to accumulation of inactive dp-ucMGP; exogenous MK-7 bypasses statin interference, activates GGCX to produce functional carboxylated MGP and suppress vascular mineralization. A core paradox remains unresolved: whether MK-7 stalls plaques in high-risk Stage 2 and counteracts statin-induced plaque stabilization. (Glossary: geranylgeranyl pyrophosphate (GGPP);(UbiA prenyltransferase domain-containing protein 1 (UBIAD1); menaquinone-4 (MK-4); dephosphorylated-uncarboxylated matrix Gla protein (dp-ucMGP); menaquinone-7 (MK-7); gamma-glutamyl carboxylase (GGCX))

However, interpreting this mechanism becomes more complex with concurrent statin therapy. In the VitaK-CAC trial, 78% of patients in both groups were on statins. Statins reduce mevalonate and downstream isoprenoid intermediates, including GGPP.

Increased coronary calcification during statin therapy is not seen as treatment failure but a potential sign of plaque stabilization. High-resolution intravascular imaging studies show that

statins may drive the transition from lipid-rich noncalcified plaques, through partially calcified, to fully calcified lesions. This "healing mineralization" or "plaque maturation" is thought to enhance the mechanical stability of atherosclerotic lesions, reducing the risk of plaque rupture and subsequent acute coronary syndromes despite higher coronary calcium scores.

If statin-associated calcification reflects a reparative plaque maturation, enhancing MGP activity via MK-7 could theoretically alter this trajectory. Current evidence cannot distinguish between these competing biological models. Resolving this question requires studies integrating serial multimodality plaque imaging with hard clinical outcomes, rather than relying solely on CAC score changes.

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IV. THE THISTORICAL WARNING OF NIACIN:THE MISMATCH BETWEEN SURROGATE AND HARD ENDPOINTS

The history of niacin illustrates the limitations of surrogate markers in cardiovascular medicine. For decades, niacin was considered an ideal anti-atherosclerosis therapy based on conventional surrogate biomarkers. A cross-sectional analysis of 2238 middle-aged and elderly American adults found that dietary niacin intake was inversely correlated with abdominal aortic calcification (AAC). After adjusting, participants with the highest intake had significantly lower AAC scores and about 40% lower risk of severe AAC. Using serial intravascular ultrasound, Lee and colleagues [3] found that adding niacin to simvastatin in mild to moderate coronary stenosis led to plaque regression versus progression with simvastatin alone

Despite these positive surrogate markers results, subsequent large-scale outcome trials drew different conclusions. In both AIM-HIGH and HPS2-THRIVE trials, adding niacin to

intensive statin therapy did not reduce major adverse cardiovascular events but increased adverse reactions including new-onset diabetes. Excess niacin metabolism generates N1-methyl-4-pyridone-3-carboxamide, a terminal metabolite related to vascular inflammation and increased cardiovascular risk.[2] This example shows interventions improving surrogate endpoints may activate biological pathways that offsetting expected clinical benefits, favorable imaging biomarkers effects should not be equated with improved outcomes.

V. MIRROR REFLECTION OF NOVEL DIETARY SUPPLEMENT BERBERINE AND METHODOLOGICAL ETHICS

The same challenge is illustrated by berberine (BBR),BBR exerts anti-atherosclerotic effects via a gut microbiota-dependent mechanism: oral BBR converts to dihydroberberine (dhBBR), which inhibits microbial choline trimethylamine lyase, suppressing dietary choline's conversion to trimethylamine (TMA) and reducing trimethylamine-N-oxide (TMAO).This framework, described by Ma et al. (2022) [4], links gut modulation to cardiovascular risk pathways. In the clinical component, 21 atherosclerosis patients receiving oral BBR (0.5 g, bid) for 4 months had a 3.2% decrease in average carotid plaque score (P<0.05), a 2.2% reduction in plaque length, and plaque score decreases in 12/21 patients (57%). Fecal TMA and TMAO decreased by 38% and 29% (P<0.05), while plasma TMA and TMAO decreased by 37% (P<0.001) and 35% (P<0.05), respectively. A concurrent reference cohort of 12 patients on guideline-directed therapy showed similar plaque reduction (58% vs. 57%), but baseline imbalances and lack of randomization preclude comparative efficacy claims.

More fundamentally, this llustrates a recurring challenge in cardiovascular therapeutics. Although BBR successfully modulates the gut microbiota-dependent TMA-TMAO pathway and produces modest imaging biomaker improvements , no adequately powered long-term randomized clinical trials demonstrate MACE reductions. Biological plausibility and favorable surrogate biomarker changes, however compelling, should not be equated with proven clinical benefits. Surrogate endpoints are indispensable for understanding mechanisms and informing early-phase research, but cannot substitute for direct evidence that an intervention improves patient-important outcomes. This distinction is particularly important in nutritional medicine, where interventions are often adopted base on mechanistic or biomarker studies long before definitive cardiovascular outcome trials.

VI. CONCLUSION AND FUTURE TRIAL DESIGN

The VitaK-CAC trial adds to evidence that nutritional interventions affect pathways linked to vascular calcification. As a randomized proof-of-concept study, it shows MK-7 slows CAC progression, activates the vitamin K – MGP axis, and reduces coronary calcium accumulation in symptomatic CAD patients-an advance over previous data.However, the trial also

emphasizes that favorable biomarkers do not equal proven clinical benefit[5],requiring careful endpoint selection. CAC has prognostic value but reflects both pathological mineralization and protective plaque maturation, complicating interpretation.

For scientific and ethical reasons, interventions for widespread clinical use require patient-centric outcomes testing, reliance on unvalidated surrogate endpoints may overstate efficacy. Therefore, future MK-7 research should not stop at imaging biomarkers. Adequately powered cardiovascular outcome trials with plaque phenotyping, multimodality imaging and related biomarkers can clarify which groups can get derive clinical benefit, with patient-centered outcomes as primary endpoints.

Before relevant evidence emerges, slowing coronary calcification can only be seen as an encouraging biological finding, not definitive proof of clinical efficacy.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.