EDITORIAL

Coronary Artery Calcium Progression—A Useful Outcome in Clinical Trials?

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In this issue of *JAMA Cardiology*, Vossen et al[1] report the results of a randomized clinical trial investigating whether supplementation with the vitamin K homologue menaquinone-7 (MK-7) at a daily dose of 360 µg would delay progression of coronary artery calcification. Among 180 patients with baseline coronary artery calcium (CAC) scores of 50 to 400 Agatston units (AU), they observed a small but statistically significant slowing of CAC progression, measured as either AU or calcium mass score.

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This Editorial spans from the biology of coronary artery calcification, from which CAC scores are measured, to factors that contribute to its progression, placed into context of prior observational and randomized studies. It concludes with our recommendations on how readers should interpret the clinical significance of the article's findings and with our recommended future directions for clinical investigation.

Biology of Coronary Calcification and Its Implications

The biology of atherosclerosis and its progression have been well described.[2,3] Coronary artery calcium is indicative of a moderately advanced atheroma, with the total amount of coronary calcium closely correlated with the total volume of coronary atherosclerosis. Coronary artery calcification is known to propagate during episodes of subclinical plaque disruption in a process driven by localized inflammation resembling healing. The progression of calcification is known to be related to all traditional atherosclerotic cardiovascular disease risk factors, their interaction, and some biomarkers, such as C-reactive protein level.[2]

Literature exists on phenotypes of calcifications and their association with plaque stability, although uncertainty remains.[4] Briefly, spotty or early calcifications, reflected by lower calcium density, are associated with plaque instability and seem to have predictive value for future acute coronary syndromes. Heavy calcifications, associated with higher calcium density and older mature plaques, are associated with chronic coronary syndromes and long-term all-cause mortality.[4]

It has been speculated that locally, advanced calcium progression contributes to clinical plaque stability, as acute coronary syndromes are associated with relatively lower degrees or lack of calcification in culprit lesions.[2] However, calcification is merely 1 component of the underlying plaque, and clinical CAC scores are summed values representing the totality of all plaques of varying ages across the coronary tree. As such, the progression of CAC cannot be interpreted simply as a sole reflection of action within a single plaque, which helps explain why overall CAC progression remains a strong predictor of future cardiovascular events.

Therapeutic Trials of CAC Progression

Prior studies, including the SALTIRE (Scottish Aortic Stenosis and Lipid Lowering Therapy, Impact on Regression) Study,[5] St Francis Heart Study,[6] and EBEAT Study,[7] among others,[8,9] have investigated the effect of lipid-lowering therapy on CAC. These trials found that statins do not delay or regress CAC scores but rather may modestly increase them.[5,6,8-10] This is likely due to plaque delipidation, which results in a reduction of low-attenuating components of plaque compared with high-density calcium as well as resolution of inflammation and healing. The trials have contributed to the notion that existing calcifications, which can be thought of as the fossilized remains of prior atherogenesis, cannot be reversed. The clinical implications of this are recognized in the 2018 and 2026 American College of Cardiology and American Heart Association dyslipidemia guidelines,[11,12] as once lipid-lowering therapy is optimized, "repeat CAC testing is not indicated because statin therapy often increases CAC scores, even though they may stabilize or reduce plaque volume by decreasing cholesterol and inflammation while improving clinical outcomes."[12] However, the degree to which this applies to therapies that directly act on calcification as opposed to statins, which target the underlying drivers of atherogenesis, remains unclear.

Biology of MK-7 and the VitaK-CAC Trial

The biological role of MK-7 as a cofactor for matrix Gla protein, which acts as a powerful inhibitor of vascular calcification, has historically intrigued researchers and has motivated studies probing its impact on coronary artery calcification and coronary heart disease.[13] However, prior studies have generally been limited to investigating dietary consumption of menaquinone, as opposed to controlled supplementation, and outcome measures were predominantly cross-sectional.[14,15] The Vitamin K-Coronary Artery Calcification (VitaK-CAC) trial[1] therefore fills a gap in the current literature by addressing the role of a specific supplemental MK-7 dose in reducing the extent of CAC progression in a controlled trial.

In the 2-center VitaK-CAC trial conducted over 10 years in the Netherlands, investigators enrolled 180 patients (approximate mean age, 60 years; 42% female; 78% receiving statins; mean baseline low-density cholesterol level, 77 mg/dL [to convert to millimoles per liter, multiply by 0.0259]) with chronic coronary atherosclerosis, characterized by median CAC scores of approximately 140 AU, aiming to test the hypothesis that the vitamin K_2 homologue MK-7 attenuates progres-

sion of CAC compared with placebo.[1] Participants were randomized to receive either 360 µg of MK-7 or a placebo daily for 2 years, with follow-up CAC scans at 1 and 2 years after baseline. The study revealed a statistically significant reduction in CAC progression of approximately 20 AU while receiving MK-7 over 2 years of follow-up (with progression by 49 AU in the MK-7 group vs 69 AU in the placebo group). Sensitivity analyses using alternative statistical models of CAC progression, including the Hokanson methods and an analysis of calcium mass scores, yielded congruent results.

Interpretations and Future Recommendations

As was the case in statin trials, interpretation of CAC progression requires caution. Importantly, Dalmeijer et al[16] reported that although daily 360-µg MK-7 supplementation decreased desphospho-uncarboxylated matrix Gla protein levels in a dose-dependent fashion, other cardiovascular disease risk factors were unchanged (eg, lipid profiles, blood pressure). This helps to isolate its impact on calcification propagation vs underlying drivers like lipoprotein retention or vascular inflammation. In a secondary analysis coupled with computed tomography (CT) angiography data, the effect of MK-7 on calcification appeared to be most evident in early to moderately developed plaques, reducing incident calcification of previously noncalcified plaque, rather than CAC progression in advanced plaque or on de novo atherogenesis. MK-7 has been suggested to structurally shift macrocalcifications, detectable by CT, to microcalcifications,[17] subtle changes that are not detectable at the plaque level with routine CAC-protocol noncontrast cardiac CT.

Given what is known about plaque-level calcium density, it is difficult to surmise what the impact on future cardiovascular events might be. This discussion brings us back to beginning of this Editorial, reflecting on the value of CAC progression in clinical trials. Would MK-7 reduce acute coronary syndromes by slowing early propagation of coronary calcification, reducing the mechanical instability thought to be associated with early calcifications? Would MK-7 increase risk by interfering with later plaque stabilization, reversing the favorable process we associate with statin treatment? Or would there be no effect at all since calcification is largely a byproduct along the continuum of plaque development?

Regardless, the results remain intriguing because sometimes calcification is indeed the primary clinical problem. In rare diseases of impaired calcium metabolism, affected children can have catastrophic consequences of systemic vascular calcification. In interventional cardiology, marked calcification poses distinct therapeutic challenges. In aortic stenosis, calcification is largely what leads to hemodynamic compromise, although earlier studies of MK-7 in calcific aortic valve disease were less favorable.

Clearly, much more data are required before one can advocate for broad use of MK-7 for any indication. The small VitaK-CAC trial[1] with slow enrollment and only 80% adherence failed to show differences in stenosis or number of affected vessels. Most importantly, it cannot inform the question of whether a reduction in CAC progression translates into a reduced number of cardiovascular events that reaches clinical significance.

It is therefore our opinion that future trials are justified to build on the VitaK-CAC study with larger sample sizes, longer follow-up, innovative CT imaging (eg, artificial intelligence–based calcium-omics), and complementary imaging modalities (eg, fluorine 18–labeled sodium fluoride positron emission tomography imaging) that can capture microcalcifications to better quantify any potential clinical benefits of MK-7.

ARTICLE INFORMATION

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