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EDITORIAL COMMENT

Vitamins to Treat Heart Disease

Can Coronary Calcium Progression Show Us the Path Forward?*

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In this issue of *JACC: Advances*, the AVADEC trial (The Aortic Valve Decalcification Trial) is discussed, which is an investigator-initiated randomized, double-blinded, placebo-controlled multicenter trial with the primary aim to investigate progression of coronary artery calcium (CAC) in persons with aortic valve calcification under the influence of vitamin K2 and vitamin D for 24 months.[1] A total of 304 (male, mean age 71 years) were randomized to supplementation with vitamin K2 (720 μg/day) and vitamin D (25 μg/day) vs placebo in a multicenter double-blinded randomized controlled trial. Overall, there was no significant change in CAC progression, although a trend appeared favoring active treatment at 24 months (Δ203 vs Δ254 AU, $P = 0.089$). In a subset of patients with CAC score ≥400, CAC progression was lower with active treatment (Δ288 vs Δ380 AU, $P = 0.047$).

CAC can be used to detect atherosclerosis in the coronary arteries independent of traditional risk factors and also helps in cardiovascular risk stratification and predicts future cardiac events, including mortality.[2] CAC progression has been demonstrated to be associated with all-cause mortality and ASCVD events, independent of baseline CAC score, age, and risk factors. Several prior multicenter observational studies reported that the progression of CAC is directly associated with worse cardiovascular outcomes. A study by Budoff et al using Multi-Ethnic Study of Atherosclerosis dataset examined association between CAC progression and coronary heart disease outcomes with the interscan interval of 2.5 years. This study reported that the progression of CAC >100/year is associated with increased hard coronary heart disease outcomes with HR of 1.3 (95% CI: 1.1-1.5) at a median follow-up of 7.6 years.[3]

Another study of 4,609 consecutive asymptomatic individuals demonstrated that CAC progression was significantly associated with all-cause mortality regardless of baseline CAC score, time between scans, demographics, and other cardiovascular risk factors. The study reasoned that individuals with a baseline CAC ≥30 could benefit from assessment of CAC progression to add incremental information for prognostication and risk factor assessment for those individuals.[4]

Thus, the finding that vitamins K2 and D could slow CAC progression is concordant with prior studies and biologically plausible. Several prior studies of vitamin K2 have demonstrated slowing of atherosclerotic plaque, and this AVADEC study adds to the literature in that regard.

Biologically, there is evidence that vitamin K2 plays a role in protection against vascular calcification, theoretically by stimulating matrix Gla protein. Data on vitamin D is less well developed and unlikely to demonstrate benefit in cardiovascular outcome studies, based on 2 large prospective randomized trials of vitamin D3 totally >30,000 participants between them, both of which returned null results.[5]

Since CAC progression is a strong predictor of future cardiovascular disease event, and slowing CAC progression is associated with less coronary progression on computed tomography angiography studies, it makes an excellent surrogate marker. The finding that the subgroup of CAC >400 shows benefit is being used by the investigators to power a

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new study to evaluate the potential cardiovascular benefits of vitamin K.

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