Coronary Artery Calcification A Janus-Faced Biomarker?

JACC: CARDIOVASCULAR IMAGING VOL. 11, NO. 9, 2018

PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Coronary Artery Calcification

A Janus-Faced Biomarker?*

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Coronary artery calcification (CAC) is highly prevalent in coronary heart disease and is associated with increased cardiovascular mortality and morbidity. CAC is strongly associated with atherosclerosis, and progression of CAC is a strong predictor of future adverse cardiac events (1). Calcification of atherosclerotic plaques mainly occurs as intimal calcification. This is different from medial calcification, also termed Mönckeberg sclerosis, which is thought to be less abundant in coronary artery disease (CAD) and is more frequently observed in the arteries of patients with renal disease and diabetes mellitus (2). CAC was long regarded as an end-stage product resulting from chronic inflammation with little clinical relevance to therapeutic intervention. This view changed dramatically during the last decade. CAC is now appreciated as a regulated process involving the active participation of vascular cells such as vascular smooth muscle cells (VSMCs) and macrophages. In fact, in many respects it resembles the tightly regulated ossification of bones (3). The unveiling of molecules and mechanisms of CAC not only provided a better understanding of its pathophysiology but also revealed potential targets for pharmacological modulation of the mineralization process.

These possibilities raise the intriguing and crucial question: are calcium deposits in atherosclerotic plaques friends or foes? In other words, do they contribute to plaque stability or do they increase plaque instability? This is still a matter of scientific and medical debate, and both sides have persuasive arguments supported by experimental and clinical data (4).

CAC can be measured clinically by noninvasive electron beam computed tomography (EBCT) and multidetector computed tomography (MDCT) and by invasive intravascular ultrasound (IVUS). These techniques register and quantify plaque volume and macrocalcifications (calcium deposits >200 μm), and they do not detect microcalcifications (calcium deposits <50 μm) and activity of the calcification process. EBCT and MDCT cannot discriminate between medial and intimal calcification. Macrocalcifications are detected as spotty and sheet calcifications; the spotty type is associated with plaque vulnerability. Microcalcifications have been observed in the fibrous cap of human atherosclerotic plaques, where they may cause biomechanical instability (5). Microcalcifications can also act detrimentally on plaque stability from a cell biology perspective. Investigators found that hydroxyapatite crystals (<8 μm) isolated from human atherosclerotic plaques significantly triggered VSMC apoptosis (6), which, in turn, accelerated calcification (7) and contributed to plaque destabilization (8). Microcalcifications in coronary atherosclerotic plaques are associated with increased inflammation and osteochondrogenic transdifferentiation of VSMCs (9), features indicating a vulnerable plaque phenotype. Progression of CAC as measured by EBCT, MDCT, and IVUS can predict adverse events. Because macrocalcification is accompanied and preceded by microcalcification (10), this makes sense from the standpoint that microcalcifications promote plaque instability by different mechanisms.

Paradoxically, several clinical studies reported that intensive lipid-lowering therapies reduced the risk of cardiovascular events, whereas progression of CAC was accelerated (11). A meta-analysis of 8 clinical studies revealed that intensive therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

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ISSN 1936-878X/$36.00 http://dx.doi.org/10.1016/j.jcmg.2017.04.009

inhibitors (statins) reduces plaque volume and increases CAC progression (12). These studies suggested that densely calcified plaques are more stable and less prone to rupture.

The mechanisms of statin-induced plaque stabilization in the presence of active calcification are still unknown and remain subjects for future investigations. An appealing hypothesis is that statin therapy accelerates calcification as well as conversion of microcalcifications into macrocalcifications, thereby reducing the life span of destabilizing microcalcifications in the plaque. Investigators postulated that statins may attenuate the vitamin K-based inhibition of vascular calcification by causing local vitamin K_2 deficiency in VSMCs (13).

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In this issue of *iJACC,* Andrews et al. (14) report that warfarin treatment of patients with CAD is associated with increased progression of CAC. The study is a post hoc patient-level analysis of 8 prospective randomized clinical trials using serial coronary IVUS studies of matched arterial segments in patients with CAD who were treated with warfarin (n = 171) or not (n = 4,129). Andrews et al. (14) used robust statistics to draw a solid conclusion on the association of warfarin use and CAC evolution from serially obtained data from the 8 different clinical trials. Interestingly, the association of warfarin use with accelerated CAC progression was independent of baseline CAC, atheroma volume, concomitant statin therapy, and renal function. The study is consistent with cross-sectional clinical studies reporting procalcific effects of warfarin on arteries (15).

The intriguing question arises again: is the observed increased progression of CAC in warfarin-treated patients good or bad? Warfarin is a vitamin K antagonist that targets both vitamin K-dependent coagulation factors and vitamin K-dependent extrahepatic proteins such as vascular smooth muscle cell-derived matrix Gla-protein (MGP). The crucial function of vascular MGP in suppressing calcification of arteries was shown in MGP knockout mice and in experimental animals with chemical knockdown by warfarin; in both groups, initiation and progression of vascular calcification resulted (16). Animal experiments also demonstrated that warfarin increases both medial calcification and intimal calcification of atherosclerotic plaques without affecting atheroma volume (17). The same animal study also showed that warfarin treatment shifts atherosclerotic plaques toward a vulnerable phenotype by producing intimal microcalcifications, increasing apoptosis, and promoting outward remodeling.

Similar mechanisms may be operative in coronary artery plaques of warfarin-treated patients, thus explaining the observed increased progression of CAC and the number of calcified coronary plaques (17). Andrews et al. (14) could not draw conclusions regarding plaque vulnerability because IVUS does not detect microcalcifications and metabolic processes underlying calcification such as apoptosis. Moreover, analysis protocols were not set up to measure outward remodeling. Hence, whether CAC progression during warfarin use is associated with increased plaque stability, as in the case of statin use, cannot be determined at this time.

Although both warfarin and statins likely increase CAC through vitamin K-dependent mechanisms, their effects on plaque stability may be not be similar and may not be reflected by CAC as recorded by IVUS. This notion is supported by the observations that statins reduced atheroma volume, whereas warfarin had no effect on atheroma volume. As pointed out by Andrews et al. (14), further clinical studies are needed to assess the effects of long-term warfarin use on clinical events in patients with coronary heart disease. Such studies will also probe the true value of CAC as a biomarker of adverse cardiac events.

Given that various features of CAC remain largely unseen by EBCT, MDCT, and IVUS, it can be anticipated that CAC may become a more informative and discriminative biomarker as soon as its features of medial and intimal localization and active microcalcifications can be visualized and metrically measured. Segregation of the aggregate CAC in this manner will require new noninvasive imaging protocols that can be used in clinical studies.

Determination of the true nature of CAC on a personalized basis by using noninvasive imaging techniques such as positron emission tomography or magnetic resonance imaging to identify metabolic processes underlying CAC will likely eliminate the apparent paradox arising from the association studies of statin and warfarin use and CAC. A clear view of the features of CAC will also guide the design of new therapeutic strategies aiming to modulate CAC progression and regression by targeting the molecular machinery of CAC.

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KEY WORDS atherosclerosis, calcium, intravascular ultrasound, warfarin