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Does Vascular Calcification Accelerate Inflammation?

A Substudy of the dal-PLAQUE Trial

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ABSTRACT

BACKGROUND Atherosclerosis is an inflammatory condition with calcification apparent late in the disease process. The extent and progression of coronary calcification predict cardiovascular events. Relatively little is known about noncoronary vascular calcification.

OBJECTIVES This study investigated noncoronary vascular calcification and its influence on changes in vascular inflammation.

METHODS A total of 130 participants in the dal-PLAQUE (Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging) study underwent fluorodeoxyglucose positron emission tomography/computed tomography at entry and at 6 months. Calcification of the ascending aorta, arch, carotid, and coronary arteries was quantified. Cardiovascular risk factors were related to arterial calcification. The influences of baseline calcification and drug therapy (dalcetrapib vs. placebo) on progression of calcification were determined. Finally, baseline calcification was related to changes in vascular inflammation.

RESULTS Age >65 years old was consistently associated with higher baseline calcium scores. Arch calcification trended to progress more in those with calcification at baseline ($p = 0.055$). There were no significant differences between progression of vascular calcification with dalcetrapib compared to that with placebo. Average carotid target-to-background ratio indexes declined over 6 months if carotid calcium was absent (single hottest slice [$p = 0.037$], mean of maximum target-to-background ratio [$p = 0.010$], and mean most diseased segment [$p < 0.001$]), but did not significantly change if calcification was present at baseline.

CONCLUSIONS Across multiple arterial regions, higher age is consistently associated with higher calcium scores. The presence of vascular calcification at baseline is associated with progressive calcification; in the carotid arteries, calcification appears to influence vascular inflammation. Dalcetrapib therapy did not affect vascular calcification. (J Am Coll Cardiol 2016;67:69–78) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

[^{18}F]FDG = ^{18}F-labeled fluorodeoxyglucose

ANOVA = analysis of variance

AU = Agatston Units

BMI = body mass index

CHD = coronary heart disease

HDL = high-density lipoprotein

LDL = low-density lipoprotein

MDS = most diseased segment

PET/CT = positron emission tomography/computed tomography

SHS = single hottest slice

TBR = target-to-background ratio

Atherosclerosis is a chronic, systemic, multifocal inflammatory disorder, a response to the deposition of low-density lipoprotein (LDL) in the vascular wall. Although arterial calcification is thought to be an actively inhibited but passive process of mineralization (1), there is increasing evidence that it is an active and regulated process, analogous to bone formation. That supposition is supported by histological findings of ectopically formed bone, the presence of osteoblast- and osteoclast-like cells, and the secretion of several bone-related peptides within calcified atherosclerotic lesions. In preclinical models, inflammatory macrophage activity is seen to precede early osteogenesis (2).

Vascular calcification serves as a marker for the extent of atherosclerosis and is predictive of cardiovascular events and mortality (3,4). Calcification of the coronary arteries has been extensively investigated. In clinical practice, coronary calcium scoring is used to stratify patients' risk for coronary heart disease (CHD), providing better discrimination than classical risk factors alone (4).

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By comparison, relatively little is known about vascular calcification and its progression in other arterial regions. Contrary to the notion that calcification represents a stable end stage of the disease, dynamic microcalcification may increase the risk of plaque rupture and clinical events (5). Understanding this process is important because rapid progression of calcification, at least in coronary arteries, is associated with an increased risk of cardiovascular events. Current medical therapies, including statins, do not alter this progression (6,7).

In this study, we investigated the vascular calcification detected on serial positron emission tomography/computed tomography (PET/CT) imaging in the dal-PLAQUE (Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging) study, a phase 2 randomized clinical trial that investigated the effects of the cholesteryl ester transfer protein inhibitor dalcetrapib on vasculature.

Specifically, we hypothesized that: 1) the presence of classical cardiovascular risk factors would increase both baseline calcification and its progression in the ascending aorta, aortic arch, and carotid and coronary arteries over 6 months; and that 2) arteries with the highest baseline calcium levels would undergo the greatest additional calcification over the next 6 months.

METHODS

The current study was a post-hoc analysis of the dal-PLAQUE study. The study design, methods, and primary results have already been published (8,9). dal-PLAQUE was a phase 2b, double-blind, randomized, placebo-controlled study that investigated the effect of dalcetrapib on vessel wall inflammation, assessed by ^{18}F-labeled fluorodeoxyglucose ([^{18}F]FDG) PET/CT. Inclusion criteria included men and women 18 to 75 years of age with known CHD or who were at high risk thereof (with diabetes or a 10-year risk of CHD events >20% by Framingham risk scoring [10]) and whose triglyceride concentrations were ≤400 mg/dl, low-density lipoprotein cholesterol (LDL-C) concentrations were <100 mg/dl, or who were taking maximum tolerated doses of statins and had a target-to-background ratio (TBR) of 1.6 or higher in an index vessel (either right carotid, left carotid, or ascending aorta), as identified by [^{18}F]FDG uptake measured by PET/CT during the screening period.

PET/CT IMAGING. Details of [^{18}F]FDG-PET/CT imaging procedures, quantification of tracer uptake, and analyses have been published previously (8). [^{18}F]FDG-PET/CT imaging of the carotid arteries and ascending aorta was performed at baseline, as well as after 3 and 6 months of follow-up.

Arterial [^{18}F]FDG uptake was quantified by manually delineating a region of interest on coregistered transaxial PET/CT images. A circular region of interest was drawn to encompass the vessel wall on each contiguous axial segment. Next, the maximum arterial standardized uptake value was determined, defined as the decay-corrected tissue concentration of [^{18}F]FDG in kBq/ml, adjusted for the injected [^{18}F]FDG dose and body weight of the patient. We calculated TBR from the ratio of the standard uptake value of the artery compared with that of background

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