

EDITORIAL COMMENT

# Arterial Inflammation

## The Heat Before the Storm\*

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Although nearly one-half of U.S. adults have cardiovascular disease, most do not recognize that the development of atherosclerosis often starts decades before the development of any clinical manifestations. Unfortunately, this prolonged “incubation phase” has not translated into successful efforts for arresting cardiovascular events. Indeed, prevention has lagged behind the substantial advances in the diagnosis and treatment of established atherosclerosis. The increased prevalence of obesity and diabetes among young adults unfortunately portends a future increase in the burden of cardiovascular events (1). To prevent such events, recent guidelines (2) emphasize the importance of a heart-healthy lifestyle in young individuals. Yet these directives rarely sanction lipid-lowering therapies

earlier than age 40. Current risk algorithms classify the vast majority of young individuals who experience a myocardial infarction as “low risk” before their event, despite most of them having at least 1 established risk factor (1).

Further emphasizing the importance of primordial prevention, several prior studies have shown that the development of cardiovascular risk factors early in life associates with a higher risk of having incident atherosclerosis (3). For example, in the Bogalusa Heart Study, having higher body mass index and low-density lipoprotein cholesterol levels at 4 to 17 years of age correlated with increased risk for being at the >75th percentile for carotid intima medial thickness in young adulthood (4). Other data suggest that atherosclerosis can occur frequently in individuals

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

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and Population Health Research Institute; has received honoraria from the American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org, and vice-chair, ACC Accreditation Committee), Baim Institute for Clinical Research (formerly Harvard Clinical Research Institute; RE-DUAL PCI clinical trial steering committee funded by Boehringer Ingelheim), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), HMP Global (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor; associate editor), Population Health Research Institute (for the COMPASS operations committee, publications committee, steering committee, and USA national coleader, funded by Bayer), Slack Publications (chief medical editor, *Cardiology Today’s Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (CME steering committees); has other relationships with *Clinical Cardiology* (deputy editor), NCDR-ACTION Registry Steering Committee (chair), and VA CART Research and Publications Committee (chair); has received research funding from Abbott, Amarin, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Idorsia, Ironwood, Ischemix, Lilly, Medtronic, PhaseBio, Pfizer, Regeneron, Roche, Sanofi, Synaptic, and The Medicines Company; has received royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald’s Heart Disease*); has been a site coinvestigator for Biotronik, Boston Scientific, St. Jude Medical (now Abbott), and Svelte; has been a trustee for the American College of Cardiology; and has performed unfunded research for FlowCo, Fractyl, Merck, Novo Nordisk, PLx Pharma, and Takeda.

who lack established cardiovascular risk factors (5,6). These findings could result from our limited understanding of what is the “optimal” level of various risk factors to prevent atherosclerosis (7). Conversely, these findings may reflect the presence of many unmeasured (or unknown) risk factors for the development of atherosclerosis. As a result of our inability to identify accurately patients who have an increased (or decreased) risk of atherosclerotic cardiovascular events, cardiovascular imaging has emerged as an important clinical and research tool for identifying (2) and guiding the treatment of (8) subclinical atherosclerosis.

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In this issue of the *Journal*, Fernández-Friera et al. (9) extend their prior findings from the PESA (Progression of Early Subclinical Atherosclerosis) study by evaluating the presence of vascular inflammation among 946 individuals who previously had atherosclerosis detected by coronary artery calcium testing or arterial ultrasound. Specifically, they performed a comprehensive hybrid <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) positron emission tomography/magnetic resonance imaging (MRI) study that aimed to detect plaque involving the aorta and carotid, iliac, and femoral arteries, as well as assess the presence of inflammation, as determined by <sup>18</sup>F-FDG uptake. A total of 755 individuals (80%) completed the detailed, and technically demanding, imaging protocol.

It is notable that this was a young population (average age 50 years, most of whom [84%] were men). Of these patients, 90% had plaque detected by MRI, an expected finding given that the enrollment criteria required prior evidence of plaque, albeit with different imaging modalities. Unexpectedly, nearly one-half of the study participants (n = 364) had evidence of arterial inflammation, most commonly in the femoral territory, and only 11% of plaque identified by MRI had FDG uptake. In fact, most FDG avidity occurred in plaque-free arterial segments, suggesting that active arterial inflammation precedes the development of atherosclerosis. Individuals with arterial inflammation had a higher overall plaque burden, underscoring the importance of inflammation in atherogenesis.

#### **COULD ARTERIAL INFLAMMATION BE THE COMMON PATHWAY BY WHICH MANY DIFFERENT INSULTS PROMOTE ATHEROSCLEROSIS?**

Inflammation is a well-known contributor to development of atherosclerosis (10). The current study by Fernández-Friera et al. (9) advances this concept by

showing that the arteries of many young adults already display evidence of inflammation. Although this study suggests that inflammation actually precedes the development of plaque, the definitive proof of this principle will require follow-up imaging of the PESA cohort. Arterial uptake of FDG may arise from smooth muscle metabolism, hypoxemia, or the presence of inflammatory cells within the atherosclerotic plaque. Not all of these areas of FDG uptake will subsequently evolve into plaque. It also remains to be seen whether plaques that have FDG uptake (although rare in this study) are the ones that are most likely to progress over time or rupture.

The findings of CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcome Study) reinforced the role of inflammation in promoting cardiovascular disease (3). This trial showed that people who have previously sustained a myocardial infarction and who have an elevated high-sensitivity C-reactive protein of 2 mg/l, have a significant reduction in the rate of recurrent cardiovascular events when administered a monoclonal antibody that neutralizes the proinflammatory cytokine interleukin-1 $\beta$  (11). This result spurred the quest for developing and studying other and more accessible agents that can lower the risk of cardiovascular events by treating inflammation (12).

Various risk factors and lifestyle factors can promote inflammation, including obesity, tobacco use (13,14), environmental pollution, and a poor diet. Thus, many of these risk factors might contribute to the development of atherosclerosis by promoting inflammation, and in turn, for some individuals, lifestyle changes may reduce inflammation. For instance, tobacco cessation, weight reduction (15), and adhering to a plant-based diet (16,17) all lower inflammation.

#### **DOES ARTERIAL INFLAMMATION PRECEDE THE DEVELOPMENT OF ATHEROSCLEROTIC PLAQUES?**

Future studies will be needed to understand better the temporal relationship between the development of vascular FDG uptake and subsequent plaque and to identify whether reduction in inflammation by either anti-inflammatory therapy or lifestyle interventions can prevent incident atherosclerosis. In addition, the expense of MRI and FDG imaging precludes the feasibility of the routine use of these modalities in screening unselected populations. Thus, we need future studies to determine the best methods to detect plaque or inflammation and whether the detection of such findings would enhance risk prediction or alter patient

management in a way that would improve patient outcomes.

Coronary artery calcium testing offers an inexpensive method to detect plaque, now supported by guidelines (2). Perhaps detection of iliofemoral plaque may identify earlier manifestations of atherosclerosis and can be detected in young individuals before the development of coronary calcifications (18). Imaging pericoronary fat on routine coronary computed tomography angiography might enable the identification of coronary inflammation in the future (19). We need further studies to determine whether in addition to imaging tests, blood biomarkers of inflammation or the use of genetic risk scores may provide a similar level of risk assessment among young individuals.

Meanwhile, the investigators should be congratulated for performing such a detailed and comprehensive evaluation of atherosclerosis, using novel imaging techniques that combine MRI and FDG positron emission tomography (9). Their study disclosed a high prevalence of arterial inflammation in asymptomatic individuals and reminds us of the urgent need for greater efforts to prevent, or at least reduce, both atherosclerosis and its possible predecessor: arterial inflammation.

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**KEY WORDS** <sup>18</sup>F-FDG PET/MRI, arterial inflammation, plaque inflammation, prevention, subclinical atherosclerosis