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EDITORS' PAGE

Address Cardiovascular Health in Middle Age

Time to Remove the Blindfold

Valentin Fuster, MD PhD, *Editor-in-Chief, Journal of the American College of Cardiology*
Borja Ibanez, MD, PhD, *Director of Clinical Research, National Center for Cardiovascular Research (CNIC)*

"A clever person solves a problem.
A wise person avoids it."
—Albert Einstein[1]

Atherosclerosis is the underlying mechanism of a vast majority of cardiovascular diseases (CVDs). The clinical manifestations of atherosclerosis (myocardial infarction, stroke, cognitive impairment, and sudden cardiac death, among others) are responsible for the majority of deaths worldwide[2] and atherosclerosis is one of the main contributors to the health care economic burden.[3] The prevalence and mortality derived from CVD in the world is increasing,[4] and if this trend continues, the capacity of health care systems to deal with the consequences of CVD will be tested.[5] There is a strong need to prevent the development of atherosclerosis and its transition to clinical manifestations when the former is already present.

Atherosclerosis begins early in life and progresses silently over decades.[6] In middle-aged adults, the prevalence of subclinical atherosclerosis is high,[7-9] which is alarming because the incidence of CVD events increases as the subclinical burden of atherosclerosis increases.[7,10,11] Despite this, the treatment of the disease today takes place mainly in the symptomatic stages, which entails high morbidity and mortality, in addition to unsustainable economic burden for health care systems.

Currently accepted risk stratification tools (Framingham, SCORE-2, and so on) are based on the presence of traditional risk factors, which are in turn associated with the incidence of clinical CVD.[12] However, although these tools are useful at the population level, they overtly fail at the level of the individual.[13] Traditional cardiovascular risk factors (CVRFs) are associated with future adverse events mainly through an intermediate mechanism, which is the development of subclinical atherosclerosis. However, to date, the risk predictive value of currently applied risk scales is not "modulated" by this intermediate step (subclinical atherosclerosis presence and extension) in daily practice. It is important to highlight that, although at the population level the impact of CVRFs on the development of atherosclerosis is robust, at the individual level there is great variability, such that there are some considered to be at low long-term CVD risk who have advanced atherosclerosis, and others considered high risk in the short term, according to currently used risk equations who have no degree of atherosclerosis.[14] Personalized complementary approaches are needed that improve the prediction of the scales and that can help to initiate interventions in a cost-effective manner.

Cholesterol (mainly low-density lipoprotein-cholesterol [LDL-C]) plays a central role in the development and progression of atherosclerosis.[15] It is the most prevalent CVRF[2] and has a synergistic effect on the rest of the CVRFs.[16,17] Recent solid evidence shows that long-term exposure to plasma cholesterol concentrations even considered "intermediate" or "borderline" according to current scales is associated with an incidence of CVD events.[18] In the CARDIA (Coronary Artery Risk Development in Young Adults) study, exposure to high levels of

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LDL-C between 18 and 30 years of age (measured as the area under the LDL-C curve) was associated with greater incidence of future CVD events (after the age of 40 years). Furthermore, the time course of accumulation was also observed to have prognostic consequences, such that the same area of cholesterol accumulated at a younger age resulted in a higher incidence of subsequent CVD events than if it was accumulated later in life.[19]

Cardiology societies define ideal cardiovascular health as total cholesterol levels <200 mg/dL (equivalent to approximately 120 mg/dL of LDL-C) in the absence of lipid-lowering drug treatment.[20] However, recent data from the PESA (Progression of Early Subclinical Atherosclerosis) study in asymptomatic (apparently healthy) middle-aged subjects show that the presence of subclinical atherosclerosis in individuals considered absent of CVRFs according to current metrics (including cholesterol) is alarmingly high (close to 50%).[21] Furthermore, in the subpopulation of the PESA considered to be free of CVRFs according to current equations, LDL-C values above 50 to 60 mg/mL are independently associated with the presence of atherosclerosis.[21] LDL-C levels at middle age (even those considered acceptable according to today's equations) thus have important prognostic effect on future development of atherosclerotic disease. For all of these reasons, very early control of LDL-C can have an unprecedented impact on CV prevention.[22] The association between subclinical atherosclerosis in apparently healthy middle-aged individuals and LDL-C risk factors considered acceptable according to current equations is a paradigmatic case, but similar associations have been shown for other risk factors: a linear association between glycated hemoglobin[23] and triglyceride[24] values within the range considered as acceptable according to current equations and atherosclerosis has also been shown in middle-aged individuals.

The current approach to CVRF control by clinical practice guidelines[12,25] is very age-dependent. This approach is based on the lower relative likelihood of short-term and mid-term incidence of CVD events in young vs old individuals. In fact, the recommendation for initiating risk factor control interventions is much more frequent in older than in younger individuals. Furthermore, recent primary prevention clinical practice guidelines do not even consider individuals younger than 40 years of age in their equations.[12,25] This age bias for tackling risk factors is against recent data showing that risk factor control at young ages has a stronger impact on event reduction: a meta-analysis showed that the relative risk reduction of CV mortality for each 40-mg/dL reduction in plasma LDL-C values is very high (56%) for middle-aged subjects (age 40-49 years), and progressively decreases at older ages until reaching "only" 15% at ages above 80 years.[17]

After accepting the new paradigm of a much more aggressive risk factor control in middle-aged individuals, the next question is whether health care systems can afford preventive strategies for the vast population presented in this commentary. The obvious answer is no. There is a need to identify tools that can discriminate subjects who would benefit from these early aggressive risk factor control. Identification of subclinical atherosclerosis by noninvasive imaging (including peripheral arteries vascular ultrasound) has been systematically demonstrated to improve the prediction of future events over classical risk factor–based equations.[7,10,11] However, to date there is no intervention trial based on its results. Quantification of coronary calcium score (CACS) has been so far the most widely noninvasive means for this matter. CACs has been implemented especially in the United States to guide clinical decision-making in primary prevention.[25] However, calcification of coronaries in middle-aged individuals is infrequent.[26] Conversely, the presence of plaques in femoral and carotid arteries in middle-aged individuals is more frequent.[14,27] For this reason, the tool better positioned for being used to better stratify risk in middle-aged individuals is vascular ultrasound of the peripheral arteries.[28,29]

In the end, whether the guidance of aggressive risk factor control based on atherosclerosis identification by peripheral artery vascular ultrasound will result in a cost-effective strategy is to be demonstrated. But now is the time to remove the blindfold and see what we have in front of us: data indicating the importance of much more aggressive risk factor control in younger and middle-aged individuals.

ADDRESS FOR CORRESPONDENCE: Dr Valentin Fuster, Editor-in-Chief, *Journal of the American College of Cardiology,* American College of Cardiology, 2400 N. Street NW, Washington, DC 20037, USA. E-mail: valentin.fuster@mountsinai.org.

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