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EDITORIAL COMMENT

Primary Prevention of Atherosclerosis

Time to Take a Selfie?*

Vijay Nambi, MD, PhD,[a] Deepak L. Bhatt, MD, MPH[b]

"Normal" blood pressure, "normal" cholesterol, and "no" diabetes are terms that patients are happy to hear at the end of their clinical visit because they consider these terms to be markers of good cardiovascular health. However, what is normal (1,2)? Although guidelines may identify particular levels as "abnormal," dichotomizing continuous variables is always somewhat arbitrary. The expert panels that write guidelines or develop risk scores are clearly familiar with this conundrum, yet due to human fascination with goals and targets, they provide cutpoints. On occasions when they have not, there has been intense debate.

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In this issue of the *Journal*, Fernández-Friera et al. (3) report that approximately one-half of the 1,779 subjects with no conventional risk factors and on no medications enrolled in the PESA (Progression of Early Subclinical Atherosclerosis) study had subclinical atherosclerosis as detected by ultrasonography or coronary calcium imaging. In this cohort, ~50% were women, and the mean age was ~45 years. This analysis of PESA, by including a middle-aged population with no traditional risk factors and not on medications, allowed the investigators to get an unadulterated evaluation of the natural history of atherosclerosis. The authors found that the prevalence of subclinical atherosclerosis increased as low-density lipoprotein cholesterol (LDL-C) increased, but notably, even at an LDL-C concentration between 60 and 70 mg/dl, 11% of the subjects had subclinical atherosclerosis! Interestingly, the iliofemoral arteries had the highest prevalence of plaque, whereas the coronary calcium score identified the least plaque. The investigators also studied a subgroup (n = 740) with optimal risk factors by current standards (blood pressure: <120/80 mm Hg; fasting glucose: <100 mg/dl; hemoglobin A_{1c}: <5.7%; total cholesterol: <200 mg/dl). Plaque was detected in ~38% of these individuals.

This analysis from the PESA study is an important contribution in our efforts to understand primordial prevention (i.e., stopping the development of risk factors), as well as primary prevention of atherosclerotic cardiovascular disease (ASCVD). The study

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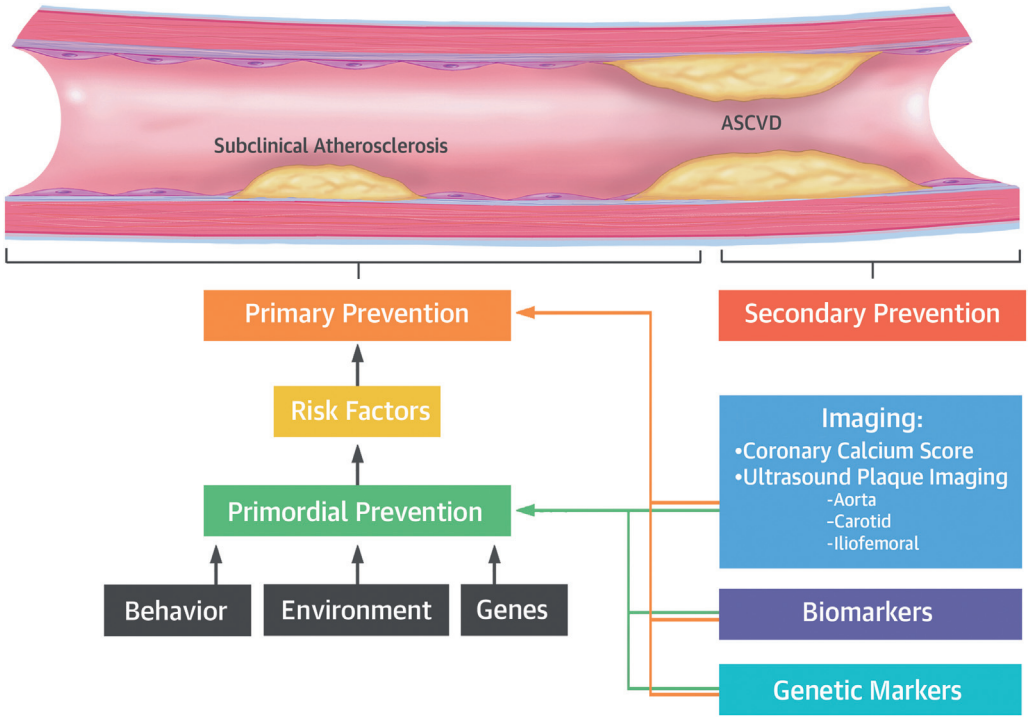
From the [a]Michael E. DeBakey Veterans Affairs Hospital, Baylor College of Medicine, Houston, Texas; and the [b]Heart and Vascular Center, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. Dr. Nambi has a provisional patent along with Baylor College of Medicine and Roche entitled "Use of biomarkers in prediction of heart failure"; has served as an event adjudicator for Siemens Diagnostics; and has served as a site principal investigator for Merck. Dr. Bhatt has served on the advisory boards of Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, and Regado Biosciences; has served on the board of directors of Boston VA Research Institute and the Society of Cardiovascular Patient Care; has served as chair of the American Heart Association Quality Oversight Committee, NCDR-ACTION Registry Steering Committee, and VA CART Research and Publications Committee; has served on data monitoring committees for Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, and Population Health Research Institute; has received honoraria from the American College of Cardiology (senior associate editor, *Clinical Trials and News*, ACC.org), Belvoir Publications (Editor-in-Chief, *Harvard Heart Letter*), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor-in-Chief, *Journal of Invasive Cardiology*), *Journal of the American College of Cardiology* (guest editor, associate editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (chief medical editor, *Cardiology Today's Intervention*), Society of Cardiovascular Patient Care (secretary/treasurer), and WebMD (CME steering committees); has served as deputy editor of *Clinical Cardiology*; has received research funding from Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi, and The Medicines Company; has received royalties from Elsevier (editor, *Cardiovascular Intervention: A Companion to Braunwald's Heart Disease*); has served as site co-investigator for Biotronik, Boston Scientific, and St. Jude Medical (now Abbott); has served as a trustee for the American College of Cardiology; and has performed unfunded research for FlowCo, Merck, PLx Pharma, and Takeda.

FIGURE 1 Prevention of ASCVD



A future framework for prevention of atherosclerotic cardiovascular disease (ASCVD), potentially incorporating imaging, biomarkers, and genetics.

showed that, even in a group that had reasonable primordial prevention, the prevalence of subclinical atherosclerosis was significant. The PESA study used a comprehensive, multi-bed, and clinically implementable noninvasive assessment of subclinical atherosclerosis that included computed tomography-based coronary calcium scoring and ultrasonography-based assessment of plaque in the infrarenal aorta and iliofemoral and carotid arteries. Thus, these data extend previous autopsy studies and invasive intravascular ultrasonography evaluations that had shown a high prevalence of atheroma at young ages (4) but accomplished this evaluation noninvasively, signifying a major conceptual advance.

Our definitions of "normal" or "optimal" for various risk factors have continued to evolve with science and are geared to predict the risk of ASCVD events and to provide goals for the management of ASCVD, not to predict the development of "subclinical" atherosclerosis. For example, the efficacy of statins in both primary and secondary prevention of ASCVD led to revising "optimal" values of cholesterol in both healthy and diseased patients (5). More recently, further intensive LDL-C-lowering (from ~70 mg/dl to ~50 mg/dl) when ezetimibe was added to statin therapy was shown to reduce incident ASCVD (6). Similarly, the addition of PCSK-9 inhibitors favorably altered atheroma on intravascular ultrasound imaging (7) and reduced ASCVD events while achieving an LDL-C of ~30 mg/dl (8). All these data have resulted in a discussion of how low the LDL-C target should be in the secondary prevention of ASCVD. In this context, the current analysis by Fernández-Friera et al. (3) is highly relevant and now raises the question of what the optimal cholesterol level may be in the primordial and primary prevention of ASCVD (1,2,9,10).

Furthermore, cholesterol is not the only conventional risk factor for which the optimal level is not clear. For example, the targets and goals for management of both blood pressure and blood glucose concentration have been the subject of much discussion. Identification of higher risk subgroups in whom the benefit-to-risk ratio may be favorable could be a strategy to consider. Hence, the incremental value of biomarkers such as troponin in gauging risk has been evaluated and demonstrated in primary and secondary prevention populations (11–14). Very recently, the

inflammatory axis has also been shown to influence atherosclerotic risk in a modifiable manner (15–17). "Lower" may indeed be better for cholesterol, blood pressure, glucose, and now inflammation as well. However, how low to go and how to get there for all these different axes of risk without provoking side effects may be the key challenge in personalizing therapies.

Perhaps, arterial imaging at an early stage could help guide such an algorithm (**Figure 1**). Potentially, combining information from noninvasive imaging with biomarkers and genetic markers would help further refine and personalize risk assessment prior to the establishment of atherosclerosis and/or ASCVD. Targeted intensive lifestyle efforts for primordial prevention and targeted pharmacotherapy (such as a polypill strategy) for selected primary prevention of ASCVD may be the answer. However, long-term randomized trials will be necessary, as will cost-effectiveness analyses. In the meantime, physicians should consider avoiding the term "normal," and instead, inform their patients of their current cholesterol, blood pressure, or blood glucose values and discuss what preventive efforts may be needed given their level of risk.

In summary, this elegant analysis from PESA (3) demonstrates that subclinical atherosclerosis is highly prevalent, even in individuals with "normal" values for conventional cardiovascular risk factors, bringing into question the definition of normal in primordial and primary prevention and, for that matter, the definition of primordial prevention itself. The management of ASCVD has conventionally focused on secondary prevention or short-term (~10-year) primary prevention. The findings from the current analysis underscore the need to start using advances in imaging, biomarkers, and genetics to re-examine the definition of "optimal" cardiovascular health. Given the significant lead time that atherosclerosis affords us, as a community, it may be time to take a "selfie" of not only our arteries but also our approaches to primordial and primary prevention of ASCVD.

ADDRESS FOR CORRESPONDENCE: Dr. Vijay Nambi, Michael E. DeBakey Veterans Affairs Hospital, Baylor College of Medicine, 2002 Holcombe Boulevard, Mail Code 111B, Houston, Texas 77030. E-mail: vnambi@bcm.edu.

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