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EDITORIAL COMMENT

The PROACT Study and Improving Prevention of ASCVD

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"It's tough to make predictions, particularly about the future"
—Yogi Berra, baseball great and homespun philosopher[1]

Yogi Berra was a Hall of Fame player for the New York Yankees, who became as well-known for his pithy and perceptive aphorisms as for his prowess as a catcher. But with due respect to Mr Berra, I believe this caution does not apply to the paper by Abou-Karam et al[2] in this issue of *JACC* that outlines the design and initial results of a trial that I believe will significantly advance prevention of cardiovascular disease. To be clear, the PROACT (Polygenic Risk Based Detection and Treatment of Subclinical Coronary Atherosclerosis) study is not completed, and these are only the initial, preliminary results, which immediately raises the question: why publish the preliminary results of a study? In general, my answer would be not to, but, after careful reflection, I think this study is a reasonable exception to a reasonable general rule. The design of the PROACT is sufficiently innovative and the initial observations sufficiently important that early publication is justified. For change to occur tomorrow, the current practice of prevention must be challenged today.

PROACT is not a test of the clinical value of screening with coronary computed tomography angiography (CCTA) to identify coronary artery disease (CAD) in otherwise well individuals. PROACT is intended to be a test of the value of polygenic risk score (PRS) to improve identification of those at risk of CAD. Different studies with different designs are required to establish the value of CCTA to screen for CAD. However, PROACT, in terms of study design, is a first in the cardiovascular research space. PROACT is modeled on the BARCODE1 (The Use of Genetic Profiling to Guide Prostate Cancer Targeted Screening) trial, which successfully applied a genome-first screening strategy for prostate cancer screening to >40,000 men.[3] From the Mass General Brigham hospital biobank of >140,000 subjects, PROACT identified 64,092 genotyped individuals, all with linked electronic health records. Of these, 2,495 (3.9%) were between 40 and 75 years, with high PRS, but a low pooled cohort equation 10-year risk score, with no history of atherosclerotic cardiovascular disease (ASCVD), and not on lipid-therapy. Of 1,314 invited individuals, 283 (21.5%) opted in and 204 (15.5%) have completed baseline imaging and are the basis of this report.

> *"CAD is frequently present in those who are 'healthy' and at low conventionally calculated ASCVD risk."*

The PROACT study randomizes participants without significant atherosclerotic disease on CCTA 1:1 to test whether being informed they have a high risk PRS will improve their health behavior. Participants with significant atherosclerotic disease on CCTA are randomized to 1 of 4 arms: 1 arm is treatment with placebo, and the other 3 involve differing medical treatments. Outcomes will be based on changes in CCTA in 1 year. The study design employed in PROACT produces rapid identification and recruitment of participants and this meaningfully reduces the time to conduct the study and, therefore, the cost of conducting the study. We will know more, faster, for less. The design of PROACT improves the feasibility of randomized controlled clinical trials. Other investigators need to be aware of these design advantages and this is the first reason, in my view. to publish this paper now.

The second reason is that publication at this point allows feedback to improve the study design. How

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much PRS adds to conventional risk tools to identify potential victims of ASCVD is not yet settled. Given that the major known causes of ASCVD are represented in both, there must be considerable overlap in predictive indices. This study selects a group with a low conventional risk score, but a high PRS. This design allows the selection tools to be used in an amplificative, complimentary mode to identify a group at low risk by the conventional approach, but at high risk based on the newer genomic approach—an attractive feature of the study. On the other hand, with the present design, there will be no evidence the high PRS score contributes any information at all. CCTA-evident coronary disease might be as prevalent, or almost as prevalent, in a low pooled cohort equation/low PRS subgroup. Accordingly, adding a control group of low pooled cohort equation/low PRS would, I believe, be a positive improvement in the PROACT protocol. In the CCTA-positive arm, I would also suggest the investigators test a low vs higher dose statin strategy rather than include a placebo group. My point is that publication at this stage of the process allows constructive feedback and the positive features of their study design give them the flexibility to respond to that feedback.

The third reason is that publication of PROACT should provoke a healthy debate about the future of cardiovascular prevention. The initial results of PROACT prove that significant CAD is frequently present in those who are "healthy" and at low conventionally calculated ASCVD risk. The advances in cardiovascular prevention have been impressive. But PROACT proves the job is not close to done. We need to improve how we prevent cardiovascular disease. This means that prevention will have to change. New technologies such as imaging, genomics and other omics, artificial intelligence are tools that we can apply to create change. But how will they be used? How should they be used? Predictions are difficult. Yogi taught me that. So, I have hopes, not predictions.

Here are my hopes. I hope that we will create preventive strategies that are just as evidence-based as those we use now but are more straightforward and less complex to apply in real-life clinical medicine. Presently ASCVD prevention is risk-based. Age and sex dominate 10-year ASCVD risk. Consequently, the 10-year risk model does not adequately identify those who will experience premature ASCVD events and allows disease that begins before age 60 to progress without hindrance until a clinical event occurs after 60.[4,5] I would argue that in addition to a risk model, we need to add a causal-benefit model of prevention.[6] The causal-benefit model integrates the benefit of therapy with the risk of a clinical event. The causal-benefit model identifies individuals at lower conventional risk but with evident causal factors who could benefit from medical prevention. More men, and especially more women and younger individuals, become eligible for medical intervention, earlier in the life history of atherosclerosis, before disease is well-established, at a period in the natural history of the disease, when appropriate medical intervention will almost certainly be most effective.[6] Another example: apolipoprotein B is a more accurate measure of the adequacy of lipid-lowering therapy than low-density lipoprotein cholesterol or non-high-density lipoprotein cholesterol are.[7,8] Measuring apolipoprotein B initially will make more individuals eligible for prevention.[9] Measuring just apolipoprotein B on follow-up would simultaneously improve and simplify care.

Improving the process of preventive care—changing what we do, and how we do it, and with whom we do it—is essential to improving the results of preventive care. I hope my hopes come true.

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