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EDITORIAL COMMENT

Using Trial Eligibility to Personalize Statin Therapy Appears No More Accurate Than a Coin Flip in Determining High-Risk Status*

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Is it possible that around one-half of middle-aged adults estimated to be at high enough atherosclerotic cardiovascular disease (ASCVD) risk to warrant statin therapy using conventional risk equations or clinical trial results actually have very low "real-world" risk as predicted by a zero coronary artery calcium (CAC) score? Are we exposing such individuals to long-term pharmacologic therapy to prevent the consequences of a disease that they are unlikely to get? Such an illogical scenario could be thought of as akin to giving metformin to all adults over age 40 regardless of their glycemic status.

Middle-aged and older adults with a CAC score of zero have excellent survival with 10-year cardiovascular event rates of approximately 1% (1), and zero CAC is present in 40% to 50% of those with conventional indications for statin therapy (based either on primary prevention trials or risk equation thresholds) (2,3). Thus, the use of conventional trial or risk-based allocation of statin therapy could be thought of as equivalent to the coin toss at the beginning of overtime in Super Bowl LI to decide which team would have possession of the ball and control of their own fate. In essence, there is an approximately 50:50 chance that any middle-aged adult with a statin indication has zero CAC.

In this issue of *iJACC*, Mortensen et al. (4) extend our understanding of CAC prevalence and absence among those with randomized controlled trial-based indications for statin therapy. They used data from the MESA (Multi-Ethnic Study of Atherosclerosis) study, which followed 5,600 participants not receiving statin therapy at baseline for 10 years. On the basis of the enrollment criteria for 7 randomized controlled trials (RCTs) of statin therapy in primary prevention, nearly three-quarters of MESA participants were eligible for statin therapy, according to a trials-based approach. This percentage increased to 91% when only those individuals >55 years of age were considered.

Similar to other publications from MESA (2,4) and analogous to the football game coin toss by the head referee, nearly one-half of individuals in this RCT-eligible population had no CAC. Absence of CAC was associated with a very low rate of ASCVD events. (3.9 per 1,000 person-years). Another common method is to use an estimated risk-based approach. However, conventional risk estimators like the 2013 pooled cohort equation are dominated by chronological age rather than physiological or biological age. Consequently, with the lowering of potential statin eligibility to an ASCVD risk estimate of 7.5% from the prior threshold of at least a 10-year CHD risk >10% in the Adult Treatment Panel III guidelines, an additional 13 million Americans have an indication for a clinician-patient risk discussion to help decide whether to initiate statin therapy (5).

Clinicians may believe they are appropriately allocating statins on the basis of either their patient's absolute risk of ASCVD or known indications for statin therapy based on primary prevention trial inclusion criteria; however, Mortensen et al. (4) demonstrate that approximately one-half of these individuals have zero CAC and are at very low risk

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for ASCVD over the next decade (3). If more clinicians considered selective use of CAC imaging in those with "intermediate" ASCVD risk estimates and/or indications for statin based on prior trial criteria, then we may be able to better target individuals most likely to benefit from pharmacological therapy with a statin (and possibly aspirin) in primary prevention.

Information about CAC could help especially those patients with indications of long-term statin use in primary prevention who are hesitant to commence chronic pharmacotherapy. For example, some clinicians have greatly expanded their statin prescriptions based on the HOPE-3 (Heart Outcomes Prevention Evaluation-3) trial, which tested the effect of rosuvastatin 10 mg in men ≥55 and women ≥60 years of age (if 2 categorical risk factors) or ≥65 (if 1 risk factor) (6). The authors reported a 24% relative risk reduction in the first coprimary endpoint, but the absolute risk in the placebo group over a median follow-up of 5.6 years was 4.8% for the first coprimary outcome with an absolute risk reduction of just 1.1% (6). The 5-year number needed to treat (NNT) was very high at approximately 100. Most patients, as well as clinicians and health care economists, would not be impressed by such a high NNT estimate as well as the lack of benefit with respect to the risk of cardiovascular death.

The results of the excellent paper by Mortensen et al. (4) inform the selection of individuals least and most likely to benefit from statin therapy. The number needed to screen (NNS) to identify 1 subject with either a CAC = 0 or CAC >100 was <2. Compared with a CAC score of 0, CAC scores >100 were associated with an adjusted hazard ratio of 5.2 for ASCVD (4).

In addition, if one assumes 30% relative risk reduction with statin therapy, the NNT for 10 years (NNT_{10}) to prevent an ASCVD event is unfavorably high at 87 for those with no CAC versus 19 for those with CAC >100. Furthermore, if one assumes a 40% relative risk reduction, which is closer to what was observed in the JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, the NNT_{10} for men and women together was as low as 14 for ASCVD events in those with CAC >100 (4).

This analysis has some potential limitations to consider. First, the NNT calculations for 5- or 10-year benefit, although similar to that for the 5-year maximum duration of statin trials, may underestimate the benefit of statin therapy over a longer period. Over time, as more events accrue, a larger absolute risk reduction and lower NNT for statins will emerge (presumably regardless of baseline CAC status). The typical clinical trial duration of 3 to 5 years for statin therapy is much shorter than the anticipated treatment period of decades for many patients.

Using CAC to routinely allocate statin therapy needs to be tempered by issues of cost, low-level radiation exposure, and inadvertent, incidental findings that may require follow-up. Of note, the cost of a CAC score is generally $100 or less. Advocates of widespread high-sensitivity C-reactive protein (hsCRP) testing to determine statin eligibility maintain that this is the most evidence-based therapy and that there are no incidental lung findings for clinicians to have to deal with; however, they often neglect to point out that JUPITER did not test the efficacy of statin therapy in those with an hsCRP concentration of <2 mg/dl. Furthermore, the HOPE-3 (Heart Outcomes Prevention Evaluation-3) study found that there was no utility at all in using hsCRP to determine statin efficacy (6).

In summary, Mortensen et al. (4) should be congratulated for demonstrating that selective use of a CAC scan can truly identify those individuals who are at very low risk and those who are at significantly higher long-term risk, something that no other risk assessment strategies available to us appear able to do. Just as Patriots' Coach Bill Belichick often defers receiving the kickoff to the second half after winning the coin toss at the beginning of a game, we as physicians can defer the use of pharmacotherapy (i.e., statin use) based on a CAC result.

Armed with the information of a CAC scan and a patient-physician discussion about cardiovascular risk, we can better follow Coach Belichick's familiar mantra to "do our job" by providing our patients with important prognostic information about the "power of zero" to decide the appropriate strategy for primary prevention of ASCVD (1–4). Whether this is appropriate use of medical therapy or other risk factor modifications, Mortensen et al. (4) have again taught us that clinicians can be more judicious in allocating statin use in order to maximize net benefit.

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