EDITORIAL COMMENT

Coronary Artery Calcium Scores of Zero and Establishing the Concept of Negative Risk Factors*

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The term "risk factor" was first coined in 1961 in a seminal article by Kannel et al. (1) from the Framingham Heart Study. Since then, risk factors for atherosclerotic cardiovascular disease (ASCVD) have largely been used to identify high-risk patients who might benefit from preventive pharmacotherapy. This emphasis on use of risk factors for upgrading risk made sense in an era when the bar to justify pharmacological intervention in primary prevention was high. For example, in the early Adult Treatment Panel guidelines, presence of multiple risk factors was required for an otherwise healthy patient to reach a risk category in which potentially lifelong medical therapy would be recommended (2).

In contemporary medicine, the bar for preventive therapy has justifiably fallen, reaching a point where many patients will qualify based on their age alone (3). In this context, a new role for risk factors has gained momentum. The negative risk factor is one that might meaningfully downgrade risk and help identify truly low-risk patients—individuals who may choose to safely concentrate on lifestyle therapies while deferring initiation of preventive medication. The fundamental difference in approach cannot be understated (**Figure 1**). Although the traditional interpretation of risk factor is inextricably tied to more testing and more treatment, the negative risk factor may be used to justify conservative treatment and less follow-up testing.

Unfortunately, traditional risk factors, serum biomarkers, and even genetic risk scores appear poorly suited to serve as negative risk factors. For example, if a person does not have diabetes, has a high-sensitivity C-reactive protein (hs-CRP) <2 mg/dl, or has a low polygenic ASCVD risk score, low-risk status cannot be affirmed; this individual cannot be reassured based on these findings alone. These individual findings lack sufficient sensitivity for ASCVD to meaningfully downgrade risk estimates.

Driven by the observation that few ASCVD events occur in the absence of substantial atherosclerosis, recent research has focused on atherosclerosis imaging tests as powerful negative risk factors. The imaging hypothesis of risk prediction states that imaging studies, which are unique in their superior sensitivity for detecting clinically important ASCVD, are ideally suited for downwardly modifying post-test risk estimates (4). For example, a coronary artery calcium score of zero (CAC = 0) has been shown to be the most powerful negative risk factor among predominantly middle-aged adults from the MESA (Multi-Ethnic Study of Atherosclerosis) trial (5).
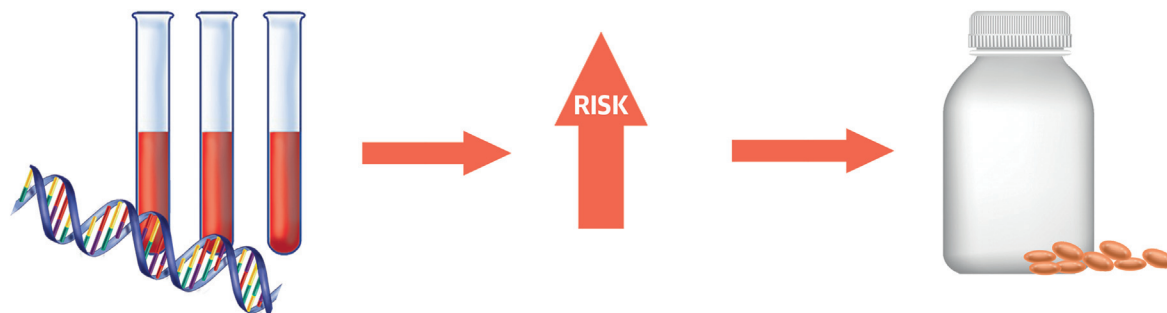
The new emphasis on negative risk factors requires investigators to develop innovative new statistical tools for their evaluation. Although the C-statistic or area under the curve (AUC) remain excellent statistical strategies for assessing overall risk discrimination, they give little sense of the ability for a test to downgrade risk estimates in individual patients. In 2016, we adopted a technique developed by statisticians Gu and Pepe (6) for calculating multivariable-adjusted diagnostic likelihood ratios (DLRs) for binary test results (5); this approach has become the new standard for evaluating negative risk factors.

FIGURE 1 Conceptual Difference

Conceptual difference between the traditional approach to risk factors and the concept of the negative risk factor.

The DLR is a measure of the value of a new test, measuring the change from the pre-test risk to the post-test risk in individual patients, conditional on their unique set of demographics and risk factors. Clinicians know well that a test can have great value as a univariate predictor but may offer little value after accounting for individual patient characteristics (e.g., a D-dimer test, although valuable in certain settings, is a poor test for pulmonary embolus in young asymptomatic patients). Thus, DLR is flexible to a range of patient characteristics, and it may suggest greater value of a test in certain individuals and less value in others. For example, it has been shown that CAC = 0 is a more powerful negative risk factor (lower DLR) in borderline- to intermediate-risk patients (5% to 20% 10-year ASCVD risk) than in unselected low-risk patients (<5% risk).

Surprisingly, despite concerns about competing noncardiovascular risks, little is known about the comparative value of negative risk factors in adults aged older than 65 years and in older adult patients (age older than 75 years) who are nearly all at elevated risk using conventional risk scores such as the pooled cohort equations. A strong negative risk factor may have great value in these populations because of uncertainties regarding polypharmacy and medication side effects.

In this issue of the *Journal*, Mortensen et al. (7) evaluated 13 candidate markers in 5,805 participants (mean age 69 years, mean estimated 10-year ASCVD risk of 16.4%) from the well-regarded BioImage study. Prevalence of the potential negative risk factors was calculated, and the strength of the negative risk factors was evaluated using patient-specific DLRs. Candidate negative risk factors ranged from atherosclerosis imaging tests (CAC = 0) to absence of family history to low levels of various serum biomarkers (e.g., hs-CRP and pro-B-type natriuretic peptide [pro-BNP]).

Consistent with the imaging hypothesis of risk prediction, and previous data from MESA, Mortensen et al. (7) found that CAC = 0 (present in 32% of the cohort) and CAC <10 (present in 38% of the cohort) were the strongest negative risk factors (mean DLRs of 0.20 and 0.20 for coronary heart disease and 0.48 and 0.41 for ASCVD, respectively), followed by absence of carotid plaque on ultrasound testing (0.39 and 0.65). Results for absence of family history and serum biomarkers, including various lipid tests, were generally unimpressive. The lone exception was galectin-3 levels below the 25th percentile, which was a moderately strong negative risk factor for coronary heart disease (0.44) and ASCVD (0.43), a finding that is novel, highly interesting, and deserving of further study.

The study by Mortensen et al. (7) has many strengths, including the use of a well-phenotyped cohort with physician-adjudicated outcomes, an older population with a high baseline ASCVD risk, secondary analysis of older adult participants (age older than 75 years), and use of patient-level DLRs for evaluation of 13 commonly encountered negative risk factors. The primary weakness was the limited follow-up time, because the BioImage study only recorded events over a median 2.7 years of follow-up, rather than the typical standard of 10-year risk.

The primary takeaway is that atherosclerosis imaging tests are perhaps the strongest negative risk factors in cardiovascular medicine today. The results are clinically actionable and should shape our approach to these tests in clinical practice. Fortunately, clinical guidelines have taken notice of this emerging consensus. For example, the new 2018 American College of Cardiology/American Heart Association (ACC/AHA) prevention guidelines assigned a Class IIa recommendation for CAC testing in selected adults aged 40 to 75 years at borderline to intermediate risk to guide individualized management decisions. In addition, these guidelines stated that it is reasonable to use CAC to reclassify risk in adults 76 to 80 years of age.

For the first time, the ACC/AHA guidelines devoted a section to negative risk factors, specifically highlighting the value of CAC = 0 and stating that intensive statin therapy is of less value in such patients and can potentially be avoided. Similarly, the 2017 Society of Cardiovascular Computed Tomography guidelines state that aspirin therapy should nearly always be avoided in primary prevention patients with CAC = 0.

The consistent results in the older adult subgroup may prove to be the most intriguing aspect of the Mortensen et al. study. Because of significant uncertainty about risks and benefits of statin treatment in those age older than 75 years, the National Heart, Lung, and Blood Institute has called for a "pragmatic trial from a network or consortium of health care delivery systems" to address critical knowledge gaps regarding risks and benefits of statins in this population (8). We believe there is a tremendous opportunity to incorporate baseline CAC testing in such a study to additionally address the hypothesis of limited statin benefit in the nearly 1 in 3 older adults with low CAC (<10).

In summary, we have evolved a much more nuanced view of risk factors since the landmark work by Kannel et al. (1). Some novel risk factors are best suited to upgrade risk and trigger increased preventive medications use (risk-enhancing factors, like high lipoprotein(a) or South Asian ancestry). The data from Mortensen et al. (7) remind us that other risk factors, like atherosclerosis imaging tests, have particular value as negative risk factors and may be key to limiting potential overuse of primary prevention pharmacotherapies in older adults.

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