Editorial

Overhauling Cardiovascular Risk Prediction in Primary Prevention
Difficult Journey Worth the Destination

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First, current guidelines based on the ASCVD risk calculator have considerably broadened the scope of statin candidates. Among 101 million people aged 40 to 79 years in the US population without established CVD, 33% are expected to receive strong recommendation for statin because of 10-year ASCVD risk ≥7.5%. An additional 12% can be advised moderate dose statin based on estimated risk of 5% to 7.4%. If ACC/AHA risk estimates are applied, Ionannidis conservatively estimate 1 billion individuals worldwide are potential statin candidates, with generic therapy cost approaching $1 trillion by 2020.

Second, the dilemma with possible statinization of the population, along with added burden on an already cost-constrained healthcare system, is heightened by emerging data that suggest half of those eligible for statin therapy have a significantly lower 10-year risk than the threshold suggested by guidelines to consider them. Although the new risk calculator may favorably result in higher treatment rates among those expected to have future cardiovascular events, this benefit can only be realized if a significant proportion of patients at a much lower risk are willing to accept lifelong commitment to statins.

Third, our most important stakeholders (ie, patients) have made it absolutely clear in their desire for avoiding lifelong pills, however safe, cheap, and effective. Recent evidence suggests that patients are likely to decline statin treatment, even if it may potentially add years to their lives. In fact, 21% of adults considering would pay $1000 or more for information to avoid taking a pill each day for the rest of their lives.

These concerns are emphatically countered by arguments that these thresholds do not mandate a statin prescription rather specifically calls for clinician–patient discussion. However, I respectfully question, are we putting too much onus on patients to deal with these uncertain risk estimates, without arming them with tools to facilitate better informed decisions? If our fundamental objective lies in truly empowering the patients, the first step is to honestly acknowledge the challenges with ASCVD risk estimator in its present rendition.

The efforts by Jarmul et al in this issue of Circulation: Cardiovascular Quality and Outcomes are admirable for being among the first to pursue this challenging task. Leveraging the well-established National Health and Nutrition Examination Survey (NHANES) survey, the authors apply the what-if principle and report the impact of adding the widely available hemoglobin A1C (HbA1c) results to currently proposed ACC/AHA estimates for risk reclassification. HbA1c was categorized according to clinical relevance: normal (<5.7%), prediabetes (5.7–6.4%), and diabetes mellitus (≥6.5%). Because
there is no prospective follow-up information, the investigators extrapolated the potential shift in pretest ASCVD risk to post-test risk relying on adjusted hazard ratio estimates derived from Emerging Risk Factors Collaboration. The study found that HbA1c distribution had a modest effect in the magnitude with an absolute 0.4% to 2% downward and 1% to 2.5% upward reclassification. The authors optimistically conclude that because HbA1c testing is inexpensive, widely performed in primary care settings, and has few direct adverse effects, as a result even small changes in risk prediction can possibly add value to current risk prediction models.

The findings of this study raise several points worthy of discussion. Although not directly addressed by the study, it would be important to know to what degree the reclassification provided by HbA1c would affect patient management related to statin use? With respect to achieving the most optimal net reclassification, we need to consider what would our stakeholders value more, downregulation or upregulation of risk? In circumstances, when a substantial proportion of adult population are already statin candidates based on an estimator known to overestimate risk, the need to identify additional individuals for preventive treatment becomes less compelling. In 2015, our stakeholders are likely to place a higher value for information that can appropriately derisk allowing informed individual choices and limiting overtreatment at the population level.

So based on the case above, can HbA1c results afford reassurance to patients who may consider avoiding statins to focus on judicious lifestyle changes? Those interested in this key issue may not need to look beyond Tables 3 and 4 of the current article. Among those with average pretest risk of 7.5% who are recommended statin treatment having a normal HbA1c, at best, would lower the estimated post-test 10-year risk to 6.4%. Whether this difference is meaningful and would affect the decision to avoid statins is debatable, as the risk still remains above threshold suggested by guidelines for considering moderate intensity statins. Judging by Krumholz’s doctrine “what would anybody do differently because of the results of the research?” I am less confident that these findings will affect our current practices.

At this point, it is worth asking, given the plethora of biomarkers that have been associated with cardiovascular outcomes, why did the current risk prediction model still end up with 6 basic risk factors first established almost half a century ago? The reason is pretty simple. None of the contenders have meaningfully moved the needle to discriminate CVD risk for affecting clinical decisions. For example, in the original study, from which the authors derive risk estimates, although HbA1c levels are associated with worsening CVD risk, it provided little incremental benefit indicated by a mere change in C-index of 0.0018. More importantly, no improvement in reclassification of risk categories used to inform treatment intensity decisions was noted.

The same is true for other biomarkers. Even high-sensitivity C-reactive protein, one of the most extensively studied novel biomarker, only provides little incremental information for discerning cardiovascular risk. In a pooled analysis, from 52 prospective studies that included 246669 participants free of established CVD followed for 9 years, high sensitivity C-reactive protein increased the C-index by only 0.0027 and yielded minimal net reclassification improvement of 0.83%.

If we are truly motivated in accelerating development of personalized patient-centric risk prediction models, then our persistent resolve with biomarkers need to be critically reconsidered, as historically this approach has consistently yielded negligible dividends in CVD risk reclassification. Maybe its time we heed to the advice “If we produce food that no one eats, we need to consider different crops.” A good starting point would be to garner consensus among experts to shortlist target candidates and strategies that based on evidence generated are most promising in diminishing widespread heterogeneity within current CVD prediction models. This approach can be comparable with a drug development program, where billions of dollars are at stake, therapeutic molecules most likely to realize predefined targets are advanced in order of priority.

In this context, one could argue for paradigm shift in our attention from surrogate markers to actual detection of the disease process itself. It is clear that atherosclerosis acts as necessary mediator between risk factors and majority of preventable cardiovascular events. Among available choices, detection of coronary artery calcium (CAC) by noncontrast computed tomography is an attractive option for identifying and quantifying the actual amount of atherosclerosis for a given individual. Notably, this test is now widely available, can be performed at a cost of $75 to $100, and is associated with an extremely low radiation dose.

Strikingly, within primary prevention settings, no other test offers better prognostication, discrimination, and reclassification for CVD risk. To date, data have consistently shown that at least two-thirds of all events are concentrated among a quarter of the population that have at least a moderate amount of coronary plaque. Compared with limited performance with surrogate biomarkers, CAC testing provides net reclassification improvement in nearly two-thirds individuals with intermediate risk level to significantly influence treatment decisions.

I think that the true value of CAC testing can be unlocked by emphasizing on the absence rather than the presence of disease. A series of studies, including a meta-analysis, a large retrospective study, and data from the prospective Multiethnic Study of Atherosclerosis, that systematically pursued a focused question, What is the value of CAC=0? were first published in 2009. The results demonstrated low event rates of ≈1 per 1000 patient-years (≈1% per 10-year event rate). Justifiably, pre 2013, when we faced dilemma of missed opportunities for treatment in higher risk patients based on CVD risk models, the paradigm shifting notion of using a test to reassure garnered little attention.

However in 2013, with the pendulum abruptly shifted from under to overestimation of ASCVD risk affecting higher treatment rates, interest in CAC=0 resurfaced. This concept coined as power of zero, gained special traction from multiple studies that confirmed its ability to derisk higher risk individuals. A common theme in all these studies was that sizeable proportion likely to be considered for lifelong preventive medications have no signs of early atherosclerotic disease (CAC=0) and an extremely low risk of incident CVD. Although CAC testing seems an attractive proposition in guiding individual
informed decisions regarding statin use, valid societal apprehensions because of the challenges presented by upfront tests cost remain. However, Roberts et al⁹ recently demonstrated that among those with 10-year estimated risk of 6% to 20%, decision to avoid treatment among those with CAC=0 versus treat-all approach with generic statins is cost-effective, as long as CAC testing is priced less <235. Although we do not yet have answers for all the complex interplay balancing issues of costs, accuracy, access, and integration in shared decision-making protocols from stakeholders perspective, the untapped value of CAC=0 should not be discounted, as eloquently pointed by Greenland et al¹⁰ “here is truly a situation in which nothing is really something.”

In summary, if we truly aspire to “inform but not dictate, guide but not enforce, and support but not restrict,”¹¹ there must be room for those who raise uncomfortable questions highlighting our shortcomings. For this, Jarmul et al¹² deserve our deepest appreciation for cautiously taking the first step in confronting status quo.⁸ I sincerely hope that this study will accelerate the mission by encouraging many among us out of hibernation, who still believe that we can do better. It is a difficult journey, but worth the destination.

Disclosures
Dr Nasir is on the advisory board for Quest Diagnostic and consultant for Regeneron.

References

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