Overhauling Cardiovascular Risk Prediction in Primary Prevention

Difficult Journey Worth the Destination

Khurram Nasir, MD, MPH

The 2013 American College of Cardiology and the American Heart Association (ACC–AHA) Prevention guidelines offers a refreshing approach to cardiovascular risk management.\(^1\) The guidelines part the emphasis on cholesterol concentrations and target goals, instead accentuate the importance of absolute risk in guiding treatment decisions.\(^1\) This conceptual shift tempered the dogma of relentlessly chasing low-density lipoprotein targets, a goal often achieved by prescribing additional drugs with uncertain impact on cardiovascular disease (CVD) risk reduction. With lipid control, no longer a particular focus, the role of statin medication is elevated as a proven risk reduction agent rather than merely a driver of reduced surrogate numbers. In addition, the guidelines underscore the matching of statin intensity with increasing individualized risk and support flexible goals for those with lower risk. Most importantly, it firmly placed the patient in driver seat to make informed choices based on their preferences, values, understanding of risk, and whether estimated benefit is worth considering decades of statin therapy.\(^1\)

Although the guidelines deserve credit for simplifying the decision-making framework, at the same time, we must be pragmatic to recognize that there is no such thing as too much of a good thing. Although there seems to be a consensus that the current guidelines point in the right direction as far as management approaches are concerned, criticism about miscalculation with guidelines proposed atherosclerotic cardiovascular disease risk-estimates and consequential impact cannot be overlooked.\(^2\) The underlying fundamental disagreement is not what and how we lower cardiovascular risk, but how we choose the target patient population.

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%.\(^2\) 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, Ioannidis conservatively estimated 1 billion individuals worldwide are potential statin candidates, with generic therapy cost approaching $1 trillion by 2020.\(^3\)

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.\(^2\) 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.\(^1\) 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.\(^3\)

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\(^4\) 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 investiga-
tors 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 reclassifica-
tion provided by HbA1c would affect patient management
related to statin use? With respect to achieving the most opti-
mal 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 estima-
tor 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 popula-
tion 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
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sidering moderate intensity statins. Judging by Krumholz’s
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doctrine “what would anybody do differently because of the
results of the research?” I am less confident that these find-
ings will affect our current practices.

At this point, it is worth asking, given the plethora of bio-
markers that have been associated with cardiovascular out-
comes, 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 lit-
tle incremental benefit indicated by a mere change in C-index
of 0.0018. More importantly, no improvement in reclassifica-
tion of risk categories used to inform treatment intensity deci-
sions was noted.

The same is true for other biomarkers. Even high-sensi-
tivity C-reactive protein, one of the most extensively studied
novel biomarker, only provides little incremental informa-
tion 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 reconsi-
dered, 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 tar-
get 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 reclas-
sification 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 reclas-
sification 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
focussed 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
CAC testing, 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 treat-
ment 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 propor-
tion likely to be considered for lifelong preventive medica-
tions 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 al⁸ 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 al²⁵ deserve our deepest appreciation for cautiously taking the first step in confronting status quo.⁴ 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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