

EDITORIAL COMMENT

The Future of CV Risk Prediction

Multisite Imaging to Predict Multiple Outcomes*



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Despite decades of observations establishing atherosclerosis as a systemic disease associated with multiple adverse outcomes, most risk assessment tools are designed to predict just one atherosclerosis-related condition: coronary heart disease (CHD). Thus, the most notable change in the new American College of Cardiology/American Heart Association (ACC/AHA) Risk Assessment Guidelines is the inclusion of stroke as a co-primary outcome (1).

What are the implications of modeling a broader set of cardiovascular diseases? From one perspective, this shift toward the more inclusive endpoint of atherosclerotic cardiovascular disease (ASCVD) is a welcome change, as stroke is common, frequently preventable, and associated with marked morbidity and mortality. However, from the perspective of risk prediction, inclusion of a disparate and heterogeneous outcome like stroke reduces the specificity of the prediction tool (2). How does one maintain highly personalized risk estimates while simultaneously considering multiple different cardiovascular outcomes?

RISK PREDICTION HYPOTHESIS 1. *It is likely impossible for a simple equation using 1-time measures of traditional risk factors (such as the Framingham Risk Score or the new Pooled Cohort Equations) to capture the complexity of atherosclerosis as a systemic disease.*

There has been contentious debate over the perceived level of personalization in the new ACC/AHA prevention guidelines. Despite some advances in the long-awaited Pooled Cohort Equations Risk Estimator, such as separate equations for African

Americans, it is critical to note that the new algorithm incorporates the same traditional risk factors as the original Framingham Risk Score published in 1998 (age, sex, race, systolic blood pressure, smoking, diabetes, total and high-density lipoprotein cholesterol). Chronological age of the patient, now more than ever, is the dominant factor in determining risk. Thus, while the new guidelines have expanded the scope of outcomes, the scope of the risk factors has not changed in over 25 years. This presents distinct challenges for multi-outcome risk prediction because the age and risk factor determinants differ for CHD and stroke (for example, cholesterol is important for CHD but less so for stroke, whereas the reverse is true for hypertension). As a result, it remains unclear whether the shift toward a single risk model incorporating a composite outcome leads to more personalized—or potentially less personalized—risk assessment (3).

Personalization of risk has long been considered the primary advantage of imaging (4). Traditional risk factors are limited by their reflection of a biological state at a single point in time (for example, blood pressure of a patient at one moment during a clinical encounter). In contrast, by integrating the lifetime exposure to both measured and unmeasured risk factors, atherosclerosis imaging allows direct visualization of the cumulative effect of all risk determinants *in an individual patient in the vascular bed of interest*. As such, imaging appears better suited to reflect the complex biological interaction networks and multiorgan crosstalk that underpins the remarkably complex pathogenesis of atherosclerosis as a systemic disease.

RISK PREDICTION HYPOTHESIS 2. *The best way to predict a particular ASCVD outcome is to directly image the vascular bed of interest.*

It is now well-known that coronary artery calcium (CAC) scoring is a powerful predictor of CHD that adds substantial predictive power to conventional risk scoring (5). CAC not only identifies those at high risk

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of CHD (6), but also those at very low risk of the development of CHD (7) and thus can be used to facilitate personalized decision making when deciding whether to treat with aspirin or a statin (4). CAC receives a class IIB recommendation in the new guidelines for patients in whom “the decision to treat with a statin is unclear” (1), although frustratingly the optimal interpretation of this phrase remains equally “unclear.”

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However, despite the power of CAC in predicting CHD, CAC is less effective for the prediction of stroke. In fact, measurements of carotid intima-media thickness, carotid plaque, and possibly aortic and/or intracranial carotid calcification may predict stroke better than CAC (8,9). In this issue of *iJACC*, Naqvi et al. (10) provide a wonderful review and critique of the current state of carotid ultrasound and the potential for various techniques including 3-dimensional ultrasound to improve risk prediction, particularly for stroke. Therefore, if the goal is to predict CHD, CAC is likely the optimal imaging test. However, if the goal is to predict stroke, incorporating imaging of the carotid or the thoracic aorta may be superior. Likewise, the optimal approach may vary further if the goal is to predict heart failure, peripheral vascular disease, or ASCVD-related death. As our understanding of the implications of atherosclerosis broadens, new outcomes will need to be modeled. Also in this issue of *iJACC*, Friedman et al. (11) discuss the role of identifying early abnormalities on brain imaging. Perhaps brain imaging will be the best way to anticipate the important outcome of vascular dementia.

RISK PREDICTION HYPOTHESIS 3. *Disease-specific, empirically derived combinations of multisite imaging measures will improve prediction across the spectrum of ASCVD outcomes.*

Multisite imaging studies have opened our eyes to the remarkable heterogeneity in atherosclerosis across multiple vascular beds. For example, Wong et al. (12) used data from the MESA (Multi-Ethnic Study of Atherosclerosis) to show that ~30% of individuals with abdominal aortic calcium (AAC) do not have CAC, whereas >30% of individuals without AAC have abnormalities in another vascular bed. Similarly, studies have shown distinct risk factor patterns for disease in each vascular territory (for example, CAC is more associated with dyslipidemia and male sex, whereas AAC is more associated with smoking with equal association with female sex) (13). Multiple studies have now shown that

although CAC predicts CHD and ASCVD events, AAC is more predictive of cardiovascular and all-cause death (14).

With the shift toward a multiple outcome (i.e., systems-based) approach to cardiovascular risk assessment, how can we leverage this heterogeneity for improving risk prediction? First of all, future multisite imaging studies must shift toward closely examining the *heterogeneity* in atherosclerosis rather than simply reporting concordance across measures. Reports stressing concordance of atherosclerosis measure 1 to measure 2 are extremely common and are probably less helpful. From an epidemiological perspective, the degree of heterogeneity is the most critical determinant of incremental risk prediction (15).

More importantly, future studies should look to derive disease-specific combinations of imaging measures aimed at predicting particular cardiovascular outcomes (15). The weighting of each factor should be empirically derived from the relative risk observed in well-designed prospective studies like MESA. For example, on a noncontrast cardiac computed tomography scan, a combination of CAC and thoracic aorta calcium may best predict CHD. A combination of mitral annular calcium, aortic valve calcium, and thoracic aorta calcium may best predict stroke. CAC plus 3-dimensional ultrasound for carotid plaque assessment may be the most parsimonious combination to address the new ACC/AHA guidelines outcome of CHD + stroke (ASCVD). The ideal combination of imaging measures for predicting heart failure, peripheral vascular disease, and vascular dementia is almost completely unknown.

What are the challenges to successful implementation of multisite imaging? The first is cost. The second is radiation. Combining noncontrast CTs of the brain, neck, chest, and abdomen may markedly increase mean radiation dose, although this could be mitigated by combining CT with ultrasound. Third is patient selection. Who is the ideal patient to undergo multisite imaging? Clearly the yield would be low in both young patients and elderly patients and unlikely to change clinical management in very low risk patients or very high risk patients. The final problem is incidental findings. Incidental pulmonary nodules are already a barrier to more widespread appropriate use of CAC. Until there is consensus about the clinical value of following low-risk incidental findings, multisite imaging will not withstand rigorous cost-effectiveness analysis.

In conclusion, the future is bright for using multisite imaging to improve multioutcome risk

prediction. At present, the new Pooled Risk Equations represent a useful starting point to the clinical risk discussion. However, many would agree that the future of risk prediction will include the upfront use of imaging. Based on the cumulative results from a variety of imaging studies—spanning vascular beds and imaging modalities—now may be the time for us

to initiate a complete rethinking of the conventional approach to risk prediction.

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REFERENCES

1. Goff DC Jr., Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63 (25 Pt B):2935-59.
2. Amin NP, Martin SS, Blaha MJ, Nasir K, Blumenthal RS, Michos ED. Headed in the right direction but at risk for miscalculation: a critical appraisal of the 2013 ACC/AHA Risk Assessment Guidelines. *J Am Coll Cardiol* 2014;63 (25 Pt A): 2789-94.
3. Blaha MJ, Blumenthal RS. Risk factors: new risk-assessment guidelines—more or less personalized? *Nat Rev Cardiol* 2014;11:136-7.
4. Blaha MJ, Silverman MG, Budoff MJ. Is there a role for coronary artery calcium scoring for management of asymptomatic patients at risk for coronary artery disease?: Clinical risk scores are not sufficient to define primary prevention treatment strategies among asymptomatic patients. *Circ Cardiovasc Imaging* 2014;7:398-408.
5. Detrano R, Guerci AD, Carr JJ, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. *N Engl J Med* 2008;358: 1336-45.
6. Patel J, Blaha MJ, McEvoy JW, et al. All-cause mortality in asymptomatic persons with extensive Agatston scores above 1000. *J Cardiovasc Comput Tomogr* 2014;8:26-32.
7. Blaha M, Budoff MJ, Shaw LJ, et al. Absence of coronary artery calcification and all-cause mortality. *J Am Coll Cardiol Img* 2009;2: 692-700.
8. Folsom AR, Kronmal RA, Detrano RC, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). *Arch Intern Med* 2008;168:1333-9.
9. Bos D, Portegies ML, van der Lugt A, et al. Intracranial carotid artery atherosclerosis and the risk of stroke in whites: the Rotterdam study. *JAMA Neurol* 2014;71:405-11.
10. Naqvi TZ, Lee M-S. Carotid intima-media thickness and plaque in cardiovascular risk assessment. *J Am Coll Cardiol Img* 2014;7:1025-38.
11. Friedman JI, Tang CY, de Haas HJ, et al. Brain imaging changes associated with risk factors for cardiovascular and cerebrovascular disease in asymptomatic patients. *J Am Coll Cardiol Img* 2014;7:1039-53.
12. Wong ND, Lopez VA, Allison M, et al. Abdominal aortic calcium and multi-site atherosclerosis: the Multiethnic Study of Atherosclerosis. *Atherosclerosis* 2011;214:436-41.
13. Criqui MH, Kamineni A, Allison MA, et al. Risk factor differences for aortic versus coronary calcified atherosclerosis: the multiethnic study of atherosclerosis. *Arterioscler Thromb Vasc Biol* 2010;30:2289-96.
14. Criqui MH, Denenberg JO, McClelland R, et al. Abdominal aortic calcium, coronary artery calcium, and cardiovascular morbidity and mortality in the Multi-Ethnic Study of Atherosclerosis. *Arterioscler Thromb Vasc Biol* 2014;34:1574-9.
15. Tison GH, Blaha MJ, Nasir K. Atherosclerosis imaging in multiple vascular beds—enough heterogeneity to improve risk prediction? *Atherosclerosis* 2011;214:261-3.

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