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EDITORIAL COMMENT

Planning a Research Agenda to Incorporate Imaging Into Clinical Practice*

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The paradigms for prevention guidelines continue to evolve (1). The recent 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guideline is based on the concept of a net atherosclerotic cardiovascular disease (ASCVD) risk reduction benefit for guiding treatment decisions (2). Estimation of a net benefit can inform the decision to initiate statin therapy, as well as nonstatin therapy in statin-treated patients with or without ASCVD (1,3). In addition to identifying 4 patient groups for whom there was a clear ASCVD risk reduction benefit from statin therapy, the 2013 ACC/AHA cholesterol guideline also recommended that when the treatment decision is unclear, assessment of atherosclerotic burden by coronary artery calcification (CAC) or ankle brachial index can be considered in selected primary prevention patients (2,4). Carotid intimal medial thickness did not contribute additional risk information and so was not recommended (4).

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Data to evaluate other measures of atherosclerotic burden such as computed tomography angiography (CTA) were not available for the 2013 ACC/AHA guidelines (4). To begin to address this evidence gap, in this issue of *iJACC*, Emami et al. (5) undertook a modeling exercise to evaluate whether CTA has the potential to reclassify patients with nonobstructive coronary artery disease (CAD) (defined as <50% luminal narrowing in at least one coronary artery) for statin treatment. They found only 2 studies with ASCVD endpoints, one each in symptomatic and asymptomatic individuals. The presence of nonobstructive CAD increased ASCVD risk by about 3-fold over a mean follow-up of 4.2 years. They then applied this information to an observational cohort who presented to the emergency room with chest pain and underwent CTA as part of the ROMICAT (Rule Out Myocardial Infarction with Computer Assisted Tomography) trial, but were subsequently determined to have noncardiac chest pain and were, therefore, eligible for primary prevention. Nonobstructive CAD upclassified 14% of women and men with a 10-year ASCVD risk of <7.5%, based on the pooled cohort equations, to a 10-year ASCVD risk of ≥7.5%, a level of risk at which primary prevention statin therapy should be strongly considered (2). The degree of reclassification was more prominent in African Americans than in Caucasians, and more prominent in men than women. Conversely, they found 12% of those with a 10-year ASCVD risk of ≥7.5% by the Pooled Cohort Equations would be downclassified to a 10-year ASCVD risk of <7.5% based on the absence of nonobstructive CAD.

Based on this modelling exercise, further research to define the role of CT angiography seems reasonable. CAC has already been shown to upclassify or downclassify 10-year ASCVD risk estimates in a significant proportion of intermediate risk patients (6). However, CAC may not reflect the evolution of the underlying severity of atherosclerosis adequately, or the burden of disease in statin-treated patients (7).

Lessons from CAC investigations may prove instructive for developing the evidence base for incorporating CTA into clinical prevention efforts. In light of changes in ACC/AHA guideline development toward rigorous evaluation of evidence, the foremost lesson is that a Class IA recommendation ("must do") will require 2 or more trials that clearly demonstrate that CTA meaningfully reclassifies the risk of

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patients, and that such reclassification improves ASCVD outcomes (8). However, lower levels of evidence or lower classes of recommendation (IIa "it is reasonable" or IIb "may be considered") may be based on improved ASCVD risk assessment.

Clearly, development of the evidence base for CTA will require the development of prospective cohorts with careful assessment baseline and follow-up biomarkers and medication use. Evaluations of CAC and long-term ASCVD outcomes have been challenging in the face of contemporary trends of increasing statin use. Therefore, appropriate statistical methods for time-varying exposures will be required. Moreover, statin therapy increases dense calcium volume, suggesting that CTA could provide a better estimation of treatment response than CAC (9).

In addition, ASCVD as defined in the 2013 ACC/AHA risk assessment guideline is the most pertinent risk prediction outcome. ASCVD (nonfatal myocardial infarction and stroke and cardiovascular death) is a more robust endpoint for non-Hispanic white women and African American women and men who have a higher risk of stroke than non-Hispanic White men, who have a predominance of coronary heart disease, the focus in most of the CAC literature (10).

Whether CTA adds enough new information to the Pooled Cohort Equations, or other region- or country-specific equations, and CAC to reclassify patients toward or away from treatment will need to be determined. Cutpoints for reclassification evolve or differ among guidelines; a range of cutpoints should be examined in more extensive supplementary sensitivity analyses. Analyses by gender and race are also important, analyses that also have been largely missing from the CAC literature until very recently.

The net benefit of a treatment strategy also includes a consideration of harm, and this should be included formally in all analyses of the benefits of reclassification. Although radiation dose continues to decrease for CTA, use in low-risk situations or repeated use remains a concern, as does downstream testing or treatment in asymptomatic patients.

Finally, any evaluation of CTA for informing treatment decisions in primary prevention requires an evaluation of cost effectiveness. Broad treatment with generic statins has been shown to more cost effective than CAC reclassification (11). CAC would only be cost effective if statins were expensive or if they significantly affect quality of life. Neither condition seems to be the case. Six of 7 statins are generic and the rate of adverse events, including muscle events, is similar in the control and statin groups (12). Recent data further suggest that statins reduce the relative risk of cardiovascular events more in lower risk than higher risk patients, which may further alter the benefit and risk of reclassification across the range of ASCVD risk (13). Although CTA might provide additional information for risk stratification of statin-treated patients, assessment of plaque vulnerability remains an important consideration and perhaps an important limitation. On the other hand, knowledge of plaque burden could improve adherence to preventive therapy. However, CAC studies have been equivocal in this regard (14).

Risk prediction remains at best an inexact science—for the individual patient the risk of event is either zero or 100%. Therefore, improving ASCVD risk estimation remains an area of intense interest. Although CTA could provide a better tool for guiding statin intensity, lifestyle, or nonstatin therapy, much work remains to be done. Before undertaking further investigation in this area, it would be prudent to determine the bounds for the treatment scenarios in which the additional information provided by CTA, or any other test, would be cost effective or cost saving in an increasingly limited health care resource environment.

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REFERENCES

1. Robinson JG, Ray K. Moving toward the next paradigm for cardiovascular prevention. Circulation 2016;133:1533–6.

2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2889–934.

3. Robinson J, Huijgen R, Ray K, et al. Determining when to add nonstatin therapy: a quantitative approach. J Am Coll Cardiol 2016;68:2412–21.

4. 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;63:2935–59.

5. Emami H, Takx RAP, Mayrhofer T, et al. Nonobstructive coronary artery disease by coronary CT angiography improves risk stratification and allocation of statin therapy. J Am Coll Cardiol Img 2017;10:1031–8.

6. Nasir K, Bittencourt MS, Blaha MJ, et al. Implications of coronary artery calcium testing among statin candidates According to American College of Cardiology/American Heart Association cholesterol management guidelines: MESA

(Multi-Ethnic Study of Atherosclerosis). J Am Coll Cardiol 2015;66:1657–68.

7. Zoccali C, Bolignano D, D'Arrigo G, et al. Validity of vascular calcification as a screening tool and as a surrogate end point in clinical research. Hypertension 2015;66:3–9.

8. Labarthe DR, Goldstein LB, Antman EM, et al. Evidence-based policy making: assessment of the American Heart Association's strategic policy portfolio: a policy statement from the American Heart Association. Circulation 2016;133:e615–53.

9. Auscher S, Heinsen L, Nieman K, et al. Effects of intensive lipid-lowering therapy on coronary plaques composition in patients with acute myocardial infarction: assessment with serial coronary CT angiography. Atherosclerosis 2015;241:579–87.

10. Karmali KN, Goff DC Jr., Ning H, et al. A systematic examination of the 2013 ACC/AHA pooled cohort risk assessment tool for atherosclerotic cardiovascular disease. J Am Coll Cardiol 2014;64:959–68.

11. Pletcher MJ, Pignone M, Earnshaw S, et al. Using the Coronary Artery Calcium Score to guide statin therapy: a cost-effectiveness analysis. Circ Cardiovasc Qual Outcomes 2014;7:276–84.

12. Collins R, Reith C, Emberson J, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016;388:2532–61.

13. Robinson JG. Starting primary prevention earlier with statins. Am J Cardiol 2014;114:1437–42.

14. Whelton SP, Nasir K, Blaha MJ, et al. Coronary artery calcium and primary prevention risk assessment: what is the evidence? An Updated meta-analysis on patient and physician behavior. Circ Cardiovasc Qual Outcomes 2012;5:601–7.

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