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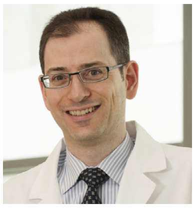

Forecasting Preventive Care Effectiveness With Imaging

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In 1987, a series of predictive models were published to predict future risk of coronary heart disease and to simulate the effects of varying risk factors on clinical outcomes, thereby informing the potential effectiveness of various therapeutic interventions to reduce population risk (1). At the time, this coronary heart disease policy model was revolutionary; over time, it has evolved into models of primary and secondary prevention, and more recently, global burden of disease models have been developed and validated (2,3). These predictive models have largely ignored imaging markers as a means to reduce population risk, with clinical practice guidelines focusing on the application of global risk score cutoffs as a threshold for targeted intensive preventive care (4). The parameters underlying most predictive equations are indirect surrogates of the main reason for CV events—the presence of atherosclerotic disease and thus they "guess" the risk rather than see atherosclerosis directly. This has real world consequences - prescribing preventive therapies based on the predicted absolute risk of ASCVD or on using criteria from primary prevention trials, has been shown to allot treatment to a large group of patient with low risk as per imaging criteria, like CAC. Imaging, however, allows one to "see atherosclerosis" and might refine predictive models (5,6) and better direct therapy to those who will benefit from it and avoid it in those unlikely to do so. Throughout the years, imaging approaches have been put forth, but most have focused on risk reduction with coronary revascularization (7). There have been some efforts to better predict risk (8) or modulate risk reduction with imaging but these have been small or were modeling estimates from current studies. One example would be using coronary artery calcification (CAC) for focusing the use of trial based efficacy of statin treatment to patients most likely to benefit from them (9).

Most risk prediction is in the asymptomatic patient but the symptomatic patient also needs intermediate to long-term risk prediction beyond severity of stenosis and strategies to modulate that over and beyond detecting and managing flow limiting coronary artery disease (CAD). Computed tomographic angiography (CTA), currently indicated only in the symptomatic patient, can also allow for this refined risk prediction and guidance for therapy (10) with its ability to detect prognostically important nonobstructive CAD (11), high risk plaque (12), the progression of disease that underlies future risk (13) and ACS events (14–16).

In this issue of *iJACC*, Mortensen et al. (17) propose a novel approach employing anatomic findings from coronary CTA as a basis for therapeutic risk reduction.

Findings from the Western Denmark Heart Registry (WDHR) reveal the potential for coronary CTA detection of nonobstructive and obstructive CAD to reduce population risk by nearly one-third, with numbers needed to treat over 6 years, with a number needed to prevent atherosclerotic cardiovascular events of 27 for nonobstructive CAD and a number as low as 8 for 3-vessel CAD. Although this model requires external

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validation across varied patient cohorts, there are decided advantages and unique concepts put forth that should stimulate lively discussion as to how imaging should be used to inform prevention care strategies to reduce risk.

First, we know that imaging, with its unique ability to visualize disease, can be very impactful and enhance patient and physician adherence to preventive care (18-20). Second, the model put forth from the WDHR incorporates what has traditionally been a population approach to risk reduction into a patient-level approach. The relative hazard for cardiovascular events is orders of magnitude higher for patients with symptoms and prevalent CAD risk factors when compared with the general population. Thus, the potential for a risk-based treatment approach applied to a patient population would be more effective in terms of the proportion of event-free lives saved. We know that approximately 33% and 20% of patients undergoing coronary CTA have nonobstructive and obstructive CAD, respectively. Based on the WHDR estimates, if 20 million patients are tested, then nearly 3.2 million events could be prevented during 6 years of follow-up, if they follow a coronary CTA-guided care algorithm. Third, when applying the WDHR approach, findings from coronary CTA (or, conceptually, from any imaging modality) could be used to formulate not only evaluation pathways, but also targeted treatment algorithms, with the goal to seamlessly integrate imaging data with effective treatment. So many of the current imaging consensus statements focus on appropriate clinical indications for testing and stop short of guided treatment, leaving imaging as operating in isolation of patient care. This inability of imaging to be integrated into clinical care hurts not only the imaging modality, but also the patients, and explains why imaging findings often fail to exert influence or change clinical management (i.e., initiation or intensification of anti-ischemic or preventive medical therapy). Furthermore, while Mortensen et al. provide a conservative estimate of the potential event reduction that can be observed with statin therapy, it is likely that that the identification of significant atherosclerosis, especially when severe, could influence many other beneficial therapies (e.g., add-on lipid-lowering agents, antithrombotic therapies, blood pressure-lowering agents). Indeed, as the armamentarium of preventive therapies continues to expand, the potential role of imaging for identifying high-risk individuals most likely to benefit from these second- or third-line treatment options will become even more important.

Of course, there is a paucity of therapeutic treatment trials based on imaging markers, and when available, they often enroll small patient samples and are often more mechanistic in design (e.g., surrogate outcome trials). Larger imaging trials are often pragmatic in design, without guidance on the type and intensity of treatment based on the imaging findings. This renders many treatment patterns following an imaging procedure to diverge from potential optimal standards of care, and they often lack the sufficient intensity of treatment that is warranted based on the expected risk based on the imaging results. Few large trials are available to help integrate imaging findings into a pathway of care. A central role of imaging in future trials should be to select patients who will have sufficient risk (and the appropriate underlying pathophysiology) to be included in clinical trials and who will derive the greatest benefit, thereby enhancing the efficiency, cost, and efficacy of cardiovascular outcomes trials. One such example in which this is being performed is the use of coronary artery calcium and coronary CTA testing as a possible inclusion criterion in the VESALIUS-CV (Effect of Evolocumab in patients at high CV risk without prior myocardial infarction or stroke) trial.

Given the enormous cost of cardiovascular outcomes trials, one should posit whether the lack of such data is a compelling enough reason to consider developing imaging-guided care strategies. At the heart of the discussion is the concept of the preventable burden of cardiovascular disease among the nearly 20 million patients who undergo cardiac imaging each year. Absent such clinical care guidance, millions of lives are placed at risk. A great example of lacking clinical care guidance is the patient with nonobstructive CAD with evidence of atherosclerosis—a progressive disease that will only worsen, have signatures that could indicated heightened risk of major CAD events (14,21), or predict response to therapy (21) and, yet, prompt care is largely not initiated. While routine use of CTA in the asymptomatic population is clearly not justified, opportunistic detection of non-obstructive CAD, especially in those with high CAC too, can provide a unique chance to initiate preventive therapies (18) that might stick over the long term once the patient is shown evidence of disease. Developments like automated plaque quantitation (22) might make risk estimation even more feasible in these patients. Such patients are clearly at a heightened risk of major CAD events, and yet, prompt preventive measures are only rarely initiated. So, what is our pathway forward? Who will take up the charge to embark on this brave new world of imaging-guided treatment? Some guidelines are starting to find a way to use imaging in such decision making (23) but more needs to be done, especially in accumulating the evidence base needed for a major reorientation and soon. It is clearly time for revolutionary ideas in cardiac imaging to produce evolutionary changes in our approaches to patient care!

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