

## Clinical imaging for prevention: Directed strategies for improved detection of presymptomatic patients with undetected atherosclerosis—Part I: Clinical imaging for prevention

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### INTRODUCTION

Nuclear cardiology has flourished within the past decade by developing extensive risk-stratification evidence to guide effective patient management.<sup>1,2</sup> The detection of a prognostically significant, flow-limiting coronary stenosis has been the focus of nuclear cardiology practices for decades. Moderate to severe myocardial perfusion abnormalities are typically observed in the setting of 1 or more significant obstructive coronary stenoses.<sup>1</sup> Considerable development and refining of computed tomography (CT), cardiovascular (CV) magnetic resonance, and other CV imaging techniques have coincided with growth in nuclear cardiology. With the introduction of new technologies and our evolving evidence on risk assessment, we are now at the precipice of a new era in CV imaging—one that includes a more comprehensive assessment of atherosclerotic disease burden and vascular function. Furthermore, the development of new CV imaging techniques allows us to use gated myocardial perfusion single photon emission computed tomography (MPS) as well as noninvasive imaging of coronary stenosis and atherosclerotic plaque burden and, to

some extent, plaque composition. Today, the defining of plaque burden potentially expands our risk-detection paradigm considerably. The CV imager is now faced with a barrage of imaging technologies with an ever-expanding role as more than a diagnostician but an evolution to that of an imaging vascular biologist.

Rapid technologic developments that include dramatic visualization of calcified and noncalcified plaque as well as noninvasive assessment of coronary stenoses support this transition beyond diagnosis of obstructive coronary artery disease (CAD) to defining the global burden of cardiovascular disease (CVD). Although risk-stratification evidence with MPS is robust and varied,<sup>1,2</sup> with a depth that is unparalleled in CV imaging, previously undetected risk with non-stenotic, diseased coronary arteries without functional or hemodynamic significance remains a concern. Furthermore, accuracy limitations associated with attenuation artifacts impose interpretive deficiencies in MPS that could be aided by the support of alternative or hybrid imaging techniques, leading to improved test accuracy for important patient subsets (eg, obese patients and women).

Moreover, evidence from serial angiographic reports notes that subcritical stenoses are prone to rupture with ensuing presentation as acute myocardial infarction (MI)<sup>3</sup>; thus searching solely for an obstructive stenosis by use of any testing paradigm will fail to detect a sizeable proportion of at-risk patients. These latter statements are further supported by recent ran-

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domized trial evidence noting that targeted risk-reducing medical therapies, with demonstrable anti-ischemic and antiatherosclerotic properties, are equally effective as strategies focusing on improving blood flow to a stenotic lesion via percutaneous coronary intervention.<sup>4</sup>

This notion of disease beyond obstructive lesions is not new to nuclear cardiologists, who have relied on defining prognostically significant, flow-limiting disease as a standard for clinical management for years.<sup>1,2,5-7</sup> In this paradigm flow limitations may include an intermediate or severely stenotic lesion but also may be elicited as a result of endothelial dysfunction. Positron emission tomography and evolving single photon emission computed tomography strategies for measuring alterations in myocardial blood flow or perfusion reserve are noninvasive methods by which to evaluate markers of endothelial function.

This expanded testing model, which includes a focus on diagnosis of obstructive CAD as well as atherosclerotic plaque, coincides with parallel research focusing on the importance of lifetime risk of coronary heart disease (CHD).<sup>8,9</sup> The American Heart Association (AHA) may eventually expand the focus of risk detection beyond the Framingham risk score (FRS) estimation of 10-year risk to predict a patient's lifetime risk of CVD. The reason for this change is that many patients may be at low risk over a period of 10 years but their lifetime risk of CHD is substantive. This is best illustrated by examining the frequency of a low FRS in women, where approximately 90% are categorized into this risk class.<sup>10</sup> However, the lifetime risk of incident CAD is 39% for a 50-year-old woman.<sup>8</sup> The latter 2 statements appear incongruous but, in reality, reflect a vision of near-term (ie, 10-year) versus long-term (ie, lifelong) disease risk. Focusing solely on short-term risk assessment fails to identify the burden of disease in women and other important patient subsets. In many cases, the unfolding CV risk-detection strategy will be to assess both near-term and long-term risk. Clinicians will have to judge the impact of each risk assessment by using an integrative approach that considers both short-term and long-term risk in guiding decisions regarding the intensity of management. Berman et al<sup>5,6</sup> were the first investigators to introduce this concept of short-term and long-term information regarding risk from different imaging tests. This concept focuses on the utility and strength of a particular modality. For the high-risk patient, in general, detection of nonobstructive atherosclerosis provides a long-term estimation of risk, which may guide the intensity of preventive strategies. By comparison, the detection of ischemia for those who proceed to gated MPS provides an estimation of elevated short-term risk and may guide decisions regarding the need to consider revascularization.

Given the high standard set by MPS in outcomes evidence, what is currently required from these new CV imaging modalities is compelling evidence that includes incremental prognostication by use of risk markers of plaque morphology or vulnerability and vascular function. A natural expansion of current testing strategies would focus on detection of nonobstructive atherosclerosis. Moreover, expanded testing algorithms that target "high-risk" yet asymptomatic patients could be another method to further reduce the burden of symptomatic disease and death. In this expanded testing paradigm, CV imaging would focus on the identification of risk in early or "preclinical" disease states with ensuing aggressive preventive strategies aimed at further reducing the burden of CV morbidity and death.

Within this vision of testing high-risk asymptomatic patients, we introduce this concept of selective imaging for prevention, where the goal of testing is to target downstream therapeutic intervention with the endpoint of improved patient outcome. This concept of imaging for prevention links test utilization in appropriate clinical indications with targeted effective treatment strategies that result in improved patient outcomes. We believe that future developments in the field of CV imaging should be focused to this end so that additional reductions in the global burden of CVD may be achieved. Persons in the field of CV imaging are challenged to define the role of various CV imaging modalities to successfully achieve this goal. For most of this statement, we will be discussing testing strategies that are under development, not all of which are ready for routine clinical practice. Yet, in this way, we believe this provides a template on which to guide future imaging research in the area of preventive cardiology. Furthermore, we hope that members of the American Society of Nuclear Cardiology (ASNC) and clinical cardiologists will find this discussion of interest and use this as a guide for tracking developments in the field of CV imaging.

## STRATEGIC PRIORITIES FOR EXPANDING CV IMAGING

Since the 1990s, research efforts have concentrated on devising comprehensive diagnostic and therapeutic strategies for risk reduction of the symptomatic patient.<sup>9-11</sup> Our goal when considering expanding our current testing paradigm is to devise appropriate imaging strategies without generating excessive cost. Our strategic priorities for current practice must include an action plan that provides guidance in our role as stewards to our patient population. Thus, at the core of this project is defining appropriate imaging targets for risk detection and setting priorities for valid and valued future developments in the field of CV imaging. To that end, all of

our discussion will focus on defining optimal imaging strategies that mirror the excellent, unparalleled evidence base supporting the cost-effectiveness of gated MPS patient management strategies.

### Strategies for Radiation Dose Reduction

A critical requirement for the use of subclinical disease testing in asymptomatic patients is that radiation exposure be as low as possible. This is not an issue for coronary artery calcium (CAC) testing, where the effective radiation dose is approximately 1.0 to 1.8 mSv. (The yearly radiation exposure for an average adult is approximately 3.0 mSv.) However, in a recent report, Einstein et al<sup>12</sup> evaluated the lifetime cancer attributable risk with 64-slice multidetector computed tomography (MDCT) for evaluation of non-invasive angiographic CAD. Their results supported cautious utilization of MDCT in younger patients because of a higher lifetime cancer risk, especially for women. This report serves to highlight the significance of radiation exposure and its ensuing long-term cancer risk in our adult population and should give pause to both the referring physician and the CV imager particularly when considering radiation-based imaging modalities for the most vulnerable subset of patients (eg, young women).

Therefore, for effective CT examinations in subclinical disease testing, radiation dose must be minimized. Effective patient radiation doses with state-of-the-art MDCT scanners can range from 6 to 25 mSv for imaging of the heart depending on the specific scan and patient parameters. Radiation dose–reduction strategies for cardiac MDCT are the focus of much ongoing research. Recently, Earls et al<sup>13</sup> described an exciting development in radiation dose reduction for cardiac MDCT using a novel adaptive, prospective electrocardiography (ECG)–gated axial CT technique. In this study of 203 patients, the coronary arteries of 82 consecutive patients were evaluated by use of retrospective ECG-gated helical techniques whereas 121 patients were evaluated by use of prospective ECG-gated axial MDCT. Of the prospectively gated axial MDCT scans, 119 examinations (98%) were diagnostic, with only 2 patients requiring repeat scanning.<sup>13</sup> Image quality was significantly better with the axial technique ( $P < .001$ ), with no significant difference in assessing coronary segments (98% for both). Most importantly, the mean radiation dose was reduced by approximately 85% with prospective ECG-gated axial MDCT (2.8 mSv vs 18.4 mSv,  $P < .0001$ ). This important advance in cardiac MDCT via axial imaging is one step toward using this technology for lower-risk patient populations.

### Defining Clinically Effective Presymptom Risk Assessment

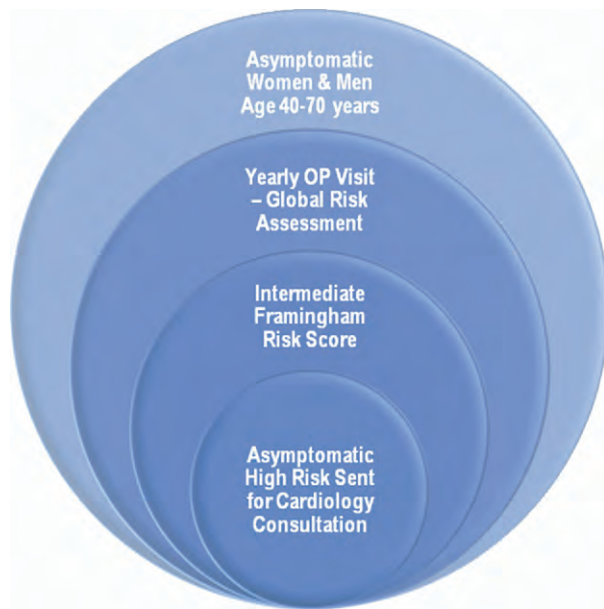
The ideal scenario is one in which subclinical disease may be accurately detected and there is an established, effective therapy to treat preclinical or presymptomatic atherosclerosis. The success of such an approach requires demonstration of clinical effectiveness and global cost advantages of any imaging strategy in today's health care environment with limited resources.<sup>14</sup> The optimal imaging strategy may involve more than 1 approach or technique for the detection of risk, measurement of global risk, and assessment of the response to lifestyle or medical interventions in terms of risk reduction. Imaging strategies ideally will reduce costs and not impose an added financial encumbrance on an already overburdened economy that spends a measurable percentage of its gross domestic product on health care. In design, a clear strategy must exist to understand and evaluate both effectiveness and cost-saving opportunities with CV imaging. Testing strategies must target a sufficient level of pretest risk to ensure incremental value and cost-effective imaging while distinguishing this effort from inappropriate or harmful testing practices in low-risk populations.

Thus, our discussions will be framed within the context that a clinical test is useful if it (1) effectively identifies patients at high and low risk of future adverse events, (2) effectively defines targeted treatment strategies that result in decreased future adverse events for those selected high-risk patients, and (3) establishes cost-effectiveness—namely, that the cost of the test, treatments for high-risk individuals, and savings incurred by nontreatment of low-risk individuals result in a cost-efficient strategy and treatments reduce adverse outcomes.

We believe that this paradigm for patient testing should supplant other strategies requiring a test to produce improvements in patient outcomes (ie, save lives).

### Early-Detection Strategies Versus Population Screening

A key difference between the current document and other reviews (eg, US Preventive Services Task Force) is that we are focusing on patient cohorts. Our early-detection strategies are those aimed at defining risk within patient populations and differ from CHD screening that targets population screening<sup>15</sup> (Figure 1). Public and most private insurers have yet to evolve to support routine screening for CHD; however, there is a large evidence base on the role of carotid artery intima-media thickness (CIMT) and CAC scoring as effective risk stratifiers.<sup>16,17</sup> For Medicare patients, lipid screening is the only recommended screening option. Population screening ef-



**Figure 1.** Selecting patient candidates for subclinical disease testing from the general population of adult men and women. This figure highlights the difference between asymptomatic screening that generally considers evaluation of the entire adult population whereas the current proposal focuses on the need for subclinical disease testing in selected patient cohorts that are at high risk for CVD. *OP*, outpatient.

forts (eg, lung or breast cancer screening) are evaluated by the US Preventive Services Task Force, and a recent report failed to support most CHD screening techniques, including the rest electrocardiogram, exercise treadmill test, and CT measurement of CAC.<sup>15</sup> Our document does not seek to put forth evidence on population-wide screening efforts but seeks to provide support and guidance to cardiologists who see higher-risk patient subsets with multiple risk factors or markers of CHD. This document will focus solely on the referred, potentially high-risk asymptomatic patients who could benefit from presymptom risk stratification.

We define the term *presymptom risk stratification* as the evaluation of risk in asymptomatic individuals whose underlying hazard for CHD events exceeds that of other low-risk asymptomatic cohorts. In fact, the evidence would support the idea that selected subsets of asymptomatic patients may have CHD event rates, including death or MI, that place them in “risk-equivalent” status. That is, their underlying risk is equivalent to a patient with known CAD, which is defined by the National Cholesterol Education Program as having an annual rate of CV death or nonfatal MI of 2% or higher.<sup>18</sup> A list of CHD risk-equivalent patient subsets is detailed in [Table 1](#). Although not all of these individuals meet the criteria for initiating aggressive preventive therapies, such as statins and aspirin, a sizeable portion of these individuals are likely to harbor a higher

**Table 1.** CHD risk-equivalent asymptomatic patient subsets

Known vascular disease
PAD
Cerebrovascular disease
CHD risk equivalent
Diabetic patients
CKD
Degree of comorbidity
Elderly
Functionally impaired (<5 metabolic equivalents of exercise)
Intermediate FRS + high-risk CAC score ( $\geq 400$ )

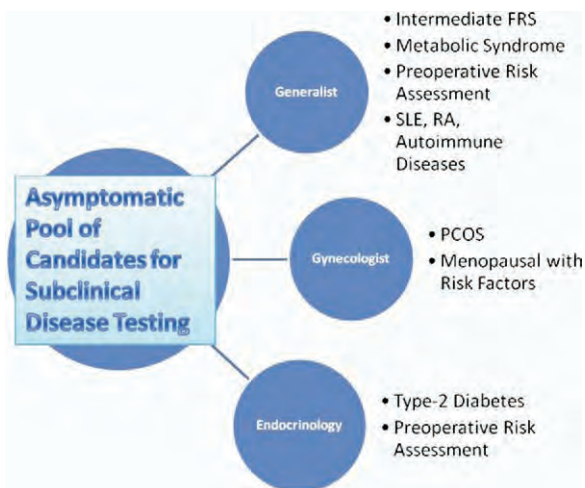
underlying atherosclerotic burden and are probably at a higher-than-desired risk of subsequent CV events.

## DESCRIBING THE INITIAL ENCOUNTER WITH THE PATIENT

### Risk Stratification for Generalists

For cardiologists, the majority of global risk assessment is undertaken by their general medicine colleagues ([Figure 2](#)). Global risk scores, within the outpatient setting, play a central role in the treatment of hypertensive and hyperlipidemic patients. The global risk score that is most commonly applied in the United States is the FRS.<sup>18,19</sup> By use of the FRS, asymptomatic individuals are categorized as low risk if the expected CHD death or MI event rate over a 10-year period is 10% or less, intermediate risk if the expected CHD death or MI event rate over a 10-year period is 10% to 20%, or high risk if the expected CHD death or MI rate over a 10-year period is greater than 20%.<sup>18,19</sup> Individuals classified as high risk are already candidates for very aggressive preventive management, including aspirin and lipid-lowering therapy, with an optional low-density lipoprotein goal of less than 70 mg/dL, and generally do not benefit from CV imaging. Testing of low-risk, largely younger patients with minimal risk factor burden could be cost-ineffective, but cost-effective alternatives for imaging in this group are discussed later in this document.<sup>16,17</sup> The previously mentioned discussion will be evolving with the introduction and refocusing of risk assessment by use of lifetime risk estimates. As we stated previously, this will most dramatically affect the large pool of low-risk individuals. For patients with a low FRS, a reassessment of risk should especially be focused on young men (aged <60 years) and women in the setting of multiple cardiac risk factors or even those patients with several borderline risk factors.

The current guidelines from the American College of Cardiology (ACC) and AHA state that subclinical



**Figure 2.** Potential sources of high-risk patients by type of referring physician. *FRS*, Framingham risk score; *SLE*, systemic lupus erythematosus; *RA*, rheumatoid arthritis; *PCOS*, polycystic ovary syndrome.

disease testing (eg, CAC scoring) may be considered in selected patients with an intermediate FRS.<sup>16,17</sup> Educational opportunities should be undertaken to guide general medicine and family practice physicians with regard to decision making and utilization of additional subclinical disease testing for patients with an intermediate FRS. Recent guidelines have considered it reasonable to use CAC or CIMT scoring in such patients based on available evidence demonstrating incremental risk prediction information.<sup>16,17</sup> This conclusion is based on the possibility that such patients might be reclassified to a higher-risk status based on high CAC or CIMT scores, and subsequent patient management may be modified. Recent evidence shows that as many as 50% of intermediate-risk patients are reclassified based on subclinical disease testing.<sup>20-22</sup>

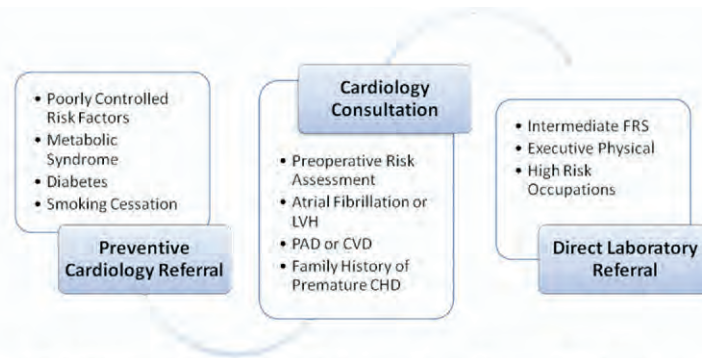
### Improving the Catchment of Candidates for Subclinical Disease Testing

Further improvement in identifying high-risk individuals, especially among younger women or men with multiple risk factors, those with a family history of premature CVD, or those with the metabolic syndrome can be achieved by focusing on risk factors not included in the FRS.<sup>23,24</sup> Recently, it has been shown that among individuals with a family history of premature CHD with 0 or 1 traditional risk factors, nearly one quarter will have significant CAC (ie,  $\geq 100$ ).<sup>21,25</sup> It is important that newer strategies broaden our ability to identify high-risk individuals currently considered at lower risk (based on the FRS) who may benefit from appropriate preventive and therapeutic interventions.

As stated previously, current AHA and ACC guide-

lines do not endorse testing in patients with a CHD risk estimate of less than 10%.<sup>15</sup> Although this statement fits many low-risk patients, it does require further scrutiny. National statistics indicate that 50% of men aged 50 to 59 years and 80% of men aged 60 to 69 years are at intermediate risk according to the FRS.<sup>10</sup> Thus, some patients may be candidates for further CHD testing by use of CAC scoring as a potential means of modifying risk prediction and altering therapy. On the other hand, the majority of women without diabetes (ie, 92%) aged below 70 years are considered at low risk.<sup>26,27</sup> Only a negligible percentage (1.4%) of women aged 50 to 69 years are classified as being at intermediate risk, with very few (8.2%) women aged 60 to 69 years attaining a 10-year CHD risk in the 10% to 20% range.<sup>5</sup> A critical point is that the FRS underestimates risk in certain patient populations. Historically, CHD risk in women has been insufficiently recognized, diagnosed, and treated. Thus very few women, as per the current consensus document,<sup>4</sup> will be candidates for CAC testing compared with a significant proportion of adult men who are eligible for further risk stratification. This is despite the fact that although men in the United States have experienced a decline in CHD deaths, the total number of CV deaths in women has remained stable or has increased.<sup>28</sup> A further limitation to the FRS is that it may also underestimate risk in young men (ie, aged  $< 60$  years) with risk factors.<sup>21</sup>

On the basis of this information, it may be prudent to consider some women (and perhaps younger men) for additional CV imaging if their risk factor burden is excessive (ie,  $\geq 2$  risk factors with the FRS failing to define intermediate risk) despite their FRS categorization. In addition, women with risk factors who underwent surgical or natural menopause early in life (ie,  $< 40$  years of age) have had a longer duration of exposure to diminished endogenous estrogen, which may further accelerate their CHD risk, and may also be candidates for risk assessment with CV imaging. Other female candidates may be those with (1) with poorly controlled hypertension or hyperlipidemia, (2) with polycystic ovary syndrome (PCOS), or (3) meeting criteria for the metabolic syndrome. PCOS is a hyperandrogen state that is associated with multiple risk factors and is a strong determinant of diabetes.<sup>29</sup> It is estimated that approximately 10% of women have the PCOS phenotype of thinning hair, androidal shape (ie, waist circumference  $> 35$  inches), menstrual irregularities, and a history of infertility. As these women are largely cared for by their gynecologists, educational programs should be considered to provide additional risk assessment of PCOS women for their diabetes and CV risk. Other female patients who should also be considered for additional CV imaging include those with rheumatoid arthritis and systemic lupus erythematosus.<sup>30-32</sup> These autoimmune



**Abbreviations:** LVH=Left Ventricular Hypertrophy, PAD=Peripheral Arterial Disease, CVD=Cerebrovascular Disease, CHD=Coronary Heart Disease, FRS=Framingham Risk Score

**Figure 3.** Patient candidates for subclinical disease testing. The following should be noted: (1) Patients with diabetes at high risk include those with poor glucose control or a diagnosis of 5 years or greater. (2) Perioperative risk assessment includes major general or vascular surgery. (Further details can be found in the ACC/AHA guidelines.)<sup>35</sup> (3) Patients with PAD may also include those with an ankle-brachial index of 0.90 or less. (4) CVD patients may include those who have had transient ischemic attacks. (5) Patients with a family history of premature CHD include those with a primary relative having early atherosclerosis (<65 years of age for a female relative and <55 years of age for a male relative). (6) Patients with high-risk occupations include firefighters, police, and pilots.

disorders occur with a greater frequency in female patients and are associated with a large increase in atherosclerotic plaque burden.<sup>30</sup> There are growing data illustrating the superiority of atherosclerosis imaging over FRS assessment in guiding the intensity of medical management in a lower-risk population.<sup>21,33,34</sup>

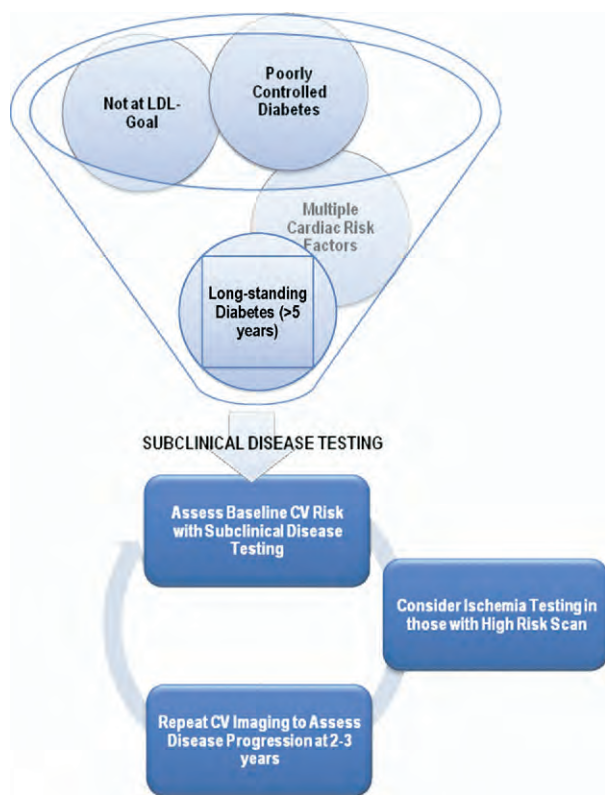
### APPROPRIATE SELECTION OF HIGH-RISK ASYMPTOMATIC PATIENT CANDIDATES FOR SUBCLINICAL DISEASE TESTING

#### Sequential Monitoring of Risk in Diabetic Patients

Preventive cardiologists form a core referral base for identifying candidates for CV imaging with their regular evaluation of patients with multiple risk factors (Figure 3). As stated previously, ACC and AHA guidelines fail to support imaging of patients with a high-risk FRS. However, there may be reasons for evaluating certain high-FRS patients in routine clinical practice. Diabetic patients, for example, have a high rate of CV events and, according to the guidelines, should already have been treated to achieve secondary-prevention goals. Diabetic patients with CAC have a substantially higher mortality rate when compared with nondiabetic patients with CAC and, importantly, diabetic patients without CAC.<sup>36</sup> Given the same burden of subclinical atherosclerosis, a diabetic patient is at substantially higher risk when compared with a nondiabetic patient. In one report nondiabetic patients and diabetic patients without CAC had similar 5-year survival rates.<sup>36</sup>

Thus, it may be prudent to consider a baseline CV imaging modality to define index risk and to further serve as a guide for sequential monitoring or reassessment of disease progression.<sup>37,38</sup> Repeat imaging has not been rigorously studied with the exception of one report, which found that a second scan at 5 years after the index CAC score of 0 was deemed appropriate.<sup>39</sup> A recent report from Budoff et al,<sup>40</sup> using a repeat scan at 2 years, noted that diabetic patients treated with statins had significantly less CAC progression when compared with untreated patients. Greater rates of progression were reported for diabetic patients with poorly controlled glucose levels (ie, hemoglobin A<sub>1c</sub> >7 mg/dL). In clinical practice one may consider testing diabetic patients with a diabetes diagnosis of 5 years or longer, those with poorly controlled diabetes, or those who have not achieved secondary-prevention goals, although this statement is an extrapolation from observational data.

Evidence suggests that patients who exhibit marked progression (ie, change in CAC by  $\geq 15\%$ ) on sequential CAC imaging have a decidedly higher risk of incident MI.<sup>41</sup> Of course, the larger the baseline CAC scores, the greater the expected change and the more rapid and higher the risk of incident MI. Conversely, one should take care to interpret changes in patients with low CAC scores (ie, <10), as they do not carry the same prognostic weight as changes in patients with a greater extent of atherosclerosis. To that extent, we have devised a strategy for selected subsets of diabetic patients that is detailed in Figure 4. This algorithm for testing is one that is not currently accepted by the ACC or AHA but that we



**Figure 4.** Potential diabetic patient candidates for subclinical disease testing. *LDL*, low-density lipoprotein.

believe is reasonable, given the high CV risk associated with diabetes mellitus.

For diabetic patients, sequential monitoring may not only include late repeat CT scanning for disease progression after several years of follow-up but may also include an early stress MPS study in those with significant CAC (ie,  $\geq 100$ ). Current evidence is substantial as to the role of MPS and CAC scoring in diabetic patient cohorts.<sup>24,42</sup> In a recent controlled clinical trial including 510 patients with type 2 diabetes, the frequencies of perfusion abnormalities were 23%, 48%, and 71% in patients with CAC scores of 101 to 400, 401 to 1000, and greater than 1000, respectively ( $P < .0001$ ).<sup>42</sup>

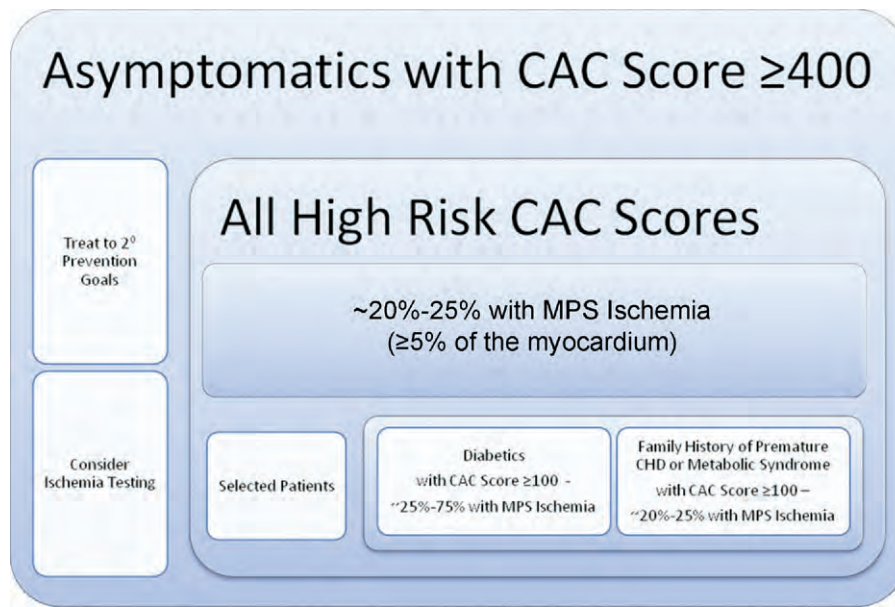
It is important to select the appropriate diabetic patient subset. Data from the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study revealed that universal testing of all diabetic patients with MPS is unlikely to yield a sizeable number of patients with a significant ischemic burden.<sup>43</sup> However, it may be reasonable to consider subclinical disease testing as an initial step in risk assessment, especially in patients with poorly controlled diabetes or those with multiple other cardiac risk factors who may have an elevated subclinical CAD burden (Figure 5). Additional candidates may also be those diabetic patients with a long-standing

diagnosis (ie,  $>5$  years). Raggi et al<sup>36</sup> also identified additional high-risk diabetic patients, including those who are female, hyperlipidemic, hypertensive, or aged 70 years or older. Evolving strategies may also unfold to consider patients who are insulin-resistant or those with the metabolic syndrome because of their mildly elevated risk of CV events.<sup>44,45</sup>

### Subclinical Disease Testing of Asymptomatic High-Risk Patients

There are additional subsets of patients defined as asymptomatic high-risk patients who may be referred for a cardiology consultation or evaluation in the outpatient setting. The first type of patient is one with evidence of peripheral arterial disease (PAD), including patients with an impaired ankle-brachial index. With regard to the latter patient subset, there is strong evidence to suggest that, even if asymptomatic, this group has a high atherosclerotic disease burden and an increased risk of CV events.<sup>46,47</sup> Similarly, patients with cerebrovascular disease or prior stroke or even those with documented transient ischemic attacks also have a high likelihood of CAD and could be candidates for subclinical disease testing. ACC/AHA guidelines have long supported diagnostic testing for patients in high-risk occupations including firefighters, pilots, and police.<sup>48</sup>

There is some controversy about screening for patients with PAD because they generally present late in the course of their disease with a considerable burden of not only peripheral but also coronary atherosclerosis. Clinicians should realize that an absence of CAC does not result in a reclassification of such a patient into a low-risk category, but the lack of calcified coronary arteries may result in an estimation of low risk of ischemic (but not other CV) events; however, this is speculation on our part. Furthermore, the evidence may unfold that patients with PAD or cerebrovascular disease may be better served by evaluation of not only CAC but a fully angiographic assessment of obstructive and non-obstructive CAD burden by use of CT. It may be possible that after a finding of an abnormal ankle-brachial index, a combined peripheral and coronary computed tomography angiography (CTA) may be the most expeditious manner of assessing risk in this patient subset. The published evidence is unclear as to whether this latter statement is best geared toward those with symptoms of vascular insufficiency or asymptomatic patients. An alternative approach could consider the addition of CTA in patients with significant CAC (ie,  $\geq 100$ ). There is no evidence to support these past few sentences, but these assertions are based on clinical reasoning and expert opinion guided by current management and expected underlying risk in this patient cohort. However, what is



**Figure 5.** Frequency of inducible ischemia in high-risk asymptomatic patients with (1) CAC scores of 400 or greater or (2) CAC scores of 100 or greater in those who are diabetic, those with metabolic syndrome, or those with family history of premature CHD.

clear is that all patients with PAD and cerebrovascular disease should be treated to achieve low-density lipoprotein goals of less than 70 mg/dL with additional aggressive treatment for their remaining risk factors.

### Patients With Chronic Kidney Disease

Chronic kidney disease (CKD), with moderate to severely reduced glomerular filtration rates between 15 and 60 mL · min<sup>-1</sup> · 1.73 m<sup>-2</sup> (ie, stage 3 or 4), has an estimated prevalence of approximately 8 million adults.<sup>49</sup> The association between renal dysfunction and increased risk of CV death has been known since early reports from the Framingham study.<sup>50</sup> Given the frequency of common cardiac risk factors, such as hypertension and diabetes, CKD is an independent risk factor for CVD.<sup>51-53</sup> Patients with CKD have a higher relative risk of CV death, with risk-adjusted ratios from 1.4- to 3.7-fold.<sup>54</sup> The association between CV events and renal failure is even stronger among those with end-stage renal disease (ESRD).<sup>55</sup> Approximately 50% of those with ESRD die from CV causes. Furthermore, it is estimated that 40% of those starting dialysis have clinical evidence of CAD, placing CKD patients at CHD “risk-equivalent” status.

From the perspective of CV imaging, patients across the spectrum of CKD, from mild renal insufficiency to ESRD, appear to be ideal candidates for presymptomatic testing. Indeed, Charytan et al<sup>56</sup> have recently shown that in a small asymptomatic cohort of 67 hemodialysis patients, 42% had at least 1 obstructive lesion on coro-

nary angiography. Although the prevalence of CAD has been quite high in small patient series, there are no large-scale studies on which to guide definitive management strategies that include initial testing by use of CTA.

However, initial testing with CAC imaging has been evaluated. Robinson et al<sup>57</sup> recently reported that among those with CKD, a CAC score of 400 or greater had a sensitivity of 86% and specificity of 83% for the detection of epicardial coronary artery stenosis of greater than 50% on subsequent coronary angiography.<sup>57</sup> Despite this preliminary evidence, the previous statements highlight the need for further studies in this high-risk group, where appropriate use of noninvasive testing including CAC scoring, myocardial perfusion imaging, and CTA may play a role in the evaluation of CV risk in patients with CKD. In the interim CV imagers should consider ongoing educational programs oriented toward the needs of nephrologists including cardiology consultation and, perhaps, selective use of CV imaging for high-risk CKD patients.

### Subclinical Disease Testing in Smokers

Within the CAC scoring literature, smokers comprise another subset of patients whose event risk is elevated.<sup>58</sup> Smoking is the prominent risk factor for acute coronary thrombosis,<sup>59,60</sup> and detection of at-risk patients may profoundly influence future CHD fatality statistics. In one report by Shaw et al,<sup>58</sup> smokers had a significantly higher frequency of CAC, and in particular, women and those with other cardiac risk factors had a

worsening survival rate with CAC and, therefore, may be candidates for subclinical disease testing. The fatal combination of age and smoking is also notable for targeting candidates for CV imaging. Smokers aged 60 years or older had a mortality risk that was elevated by 5.3- to 11.0-fold for CAC scores from greater than 100 to greater than 1000 when compared with nonsmokers.

Data are also abundant on the role of other imaging modalities besides CT. Cigarette smoking has been consistently associated with greater CIMT measurements, greater plaque burden, and carotid stenosis.<sup>61,62</sup> Smokers with elevated CIMT measurements also have a higher incidence of CHD events.<sup>63</sup> Smoking also accelerates the rate of PAD, and smokers with an abnormal ankle-brachial index have a higher risk of CV events.<sup>64,65</sup>

### **Subclinical Disease Testing in Patients With a Family History of Premature CHD**

Patients with a primary relative with premature atherosclerosis are also frequently referred for a cardiology workup. This variable is not included within the present FRS and is a potential source of unmeasured risk. Several reports from Johns Hopkins University (Baltimore, Md) have evaluated the accuracy of MPS and CAC scoring in patients with a family history of premature CHD.<sup>66-68</sup> Notably, patients with a family history of premature CHD have a high rate of significant CAC (eg,  $\geq 100$ ) and should be considered candidates for subclinical disease testing if the decision of whether to treat with lifelong aspirin and lipid-lowering therapy is unclear.<sup>68</sup> These results apply to women with a low FRS and a family history of premature CHD.<sup>69</sup> In a recent report nearly one third of women with a family history of premature CHD had significant CAC scores greater than the 75th age- and gender-based percentile rank. In addition, 20% to 37% of individuals in a multiethnic cohort, considered low risk by the FRS, were observed to have significant CAC, defined as greater than or equal to the 75th percentile for age, gender, and race.<sup>70</sup> Thus, for both women and men across all ethnic groups, the presence of a family history of premature CHD is substantially associated with a higher atherosclerotic burden, and these patients are strong candidates for additional subclinical disease testing.

### **Role of Stress MPS in High-Risk Asymptomatic Patients**

Additional high-risk subsets of asymptomatic patients include those with left ventricular hypertrophy (LVH) or new-onset atrial fibrillation. Current guidelines support the use of stress MPS in these patient cohorts.<sup>71-73</sup> Generally, these published series include a

mixture of symptomatic and asymptomatic patients, and one cannot fully infer that the benefit will apply to lower-risk patients without symptoms. Despite this caveat, there is evidence as to the role of stress MPS in patients with LVH and atrial fibrillation. In one recent report, patients with LVH and a normal stress MPS study had a low risk of CV events.<sup>71</sup> CAD mortality or nonfatal MI rates increased linearly with the extent and severity of stress MPS and reached as high as 10% in LVH patients with moderate to severe perfusion abnormalities.

For patients with new-onset atrial fibrillation, the use of stress MPS is supported by recent appropriateness criteria.<sup>64</sup> In a recent report by Abidov et al,<sup>73</sup> among patients with atrial fibrillation, the cardiac mortality rate was 1.6%/y for those with a normal stress MPS study, whereas it was 0.4%/y for those without atrial fibrillation ( $P < .0001$ ). CAD mortality rates continued to accelerate for patients with atrial fibrillation and abnormal stress MPS studies, with risk ratios up to 6-fold higher than those for patients without atrial fibrillation.<sup>74</sup>

Other potential asymptomatic patients may be those with a new left bundle branch block (LBBB) or those with poor exercise capacity (ie,  $< 5$  metabolic equivalents). For patients requiring a stress examination with LBBB, current guidelines from the ACC/AHA/ASNC support its utility.<sup>1</sup> Currently, pharmacologic stress testing is indicated because of the high frequency of false-positive perfusion defects in the interventricular septum.<sup>75</sup> Effective risk stratification has been reported in several series for LBBB patients undergoing pharmacologic stress MPS, by use of adenosine or dobutamine.<sup>76-79</sup> It remains possible that CT measurements of CAC may provide an initial testing strategy or serve as a guide to MPS results in patients with LBBB, although this strategy has yet to be reported.

Preoperative risk assessment is also a frequent indication for cardiology consultation. The referral for preoperative risk assessment is an important opportunity for cardiologists to evaluate the patient's lifetime risk of CAD as well as his or her near-term likelihood of perioperative complications. In fact, with several controlled clinical trials reporting a reduction in ischemic events after intraoperative  $\beta$ -blockade or statin use, longer-term risk stratification is becoming increasingly important.<sup>80</sup> One potential method by which to evaluate the patient in the preoperative setting is to determine (1) near-term risk of ischemic complications and (2) long-term risk of atherosclerosis. We envision that the combination of near-term and long-term risk stratification (as stated previously) may be required at several times in the course of a patient's life. As such, several investigators have introduced the concept of lifetime risk.<sup>8</sup> However, we wish to expand this concept to include a combined short-term and long-term assessment

of risk, with the former being evaluated as ischemic risk and the latter using some assessment of atherosclerotic risk.

CAC scoring or other subclinical disease tests are also effective at risk stratification in these patients. In one recent series CAC scoring was highly effective at identifying near-term risk of events in patients undergoing preoperative risk assessment before elective vascular surgery.<sup>81</sup> However, to date, a large number of reports have evaluated the prognostic accuracy of stress MPS in this setting.<sup>1</sup> Moreover, a recent ACC/AHA taskforce devised guidelines for CV evaluation<sup>35</sup> and identified MPS patient candidates as those meeting at least 2 of the following criteria: (1) intermediate clinical predictors (Canadian class I or II angina, prior MI, congestive heart failure, or diabetes mellitus); (2) poor functional capacity (<4 metabolic equivalents); or (3) high-risk surgical procedure (emergency major operation, aortic repair, peripheral vascular surgery, or prolonged surgical procedure with large fluid shifts or blood loss).<sup>73</sup> As stated previously, if arteriography is indicated for patients with PAD, the most expeditious test may include coronary and peripheral CTA. Given the randomized trial evidence on the intraoperative use of  $\beta$ -blockers and statins, a reappraisal of the “fit” for MPS is indicated.

The role of MPS after an initial CAC scan was synthesized in a prior information statement by ASNC.<sup>82-84</sup> The clinical message from this statement has not changed since its publication in 2005. That is, patients with a high-risk CAC score of 400 or higher have a high rate of inducible ischemia and should be referred for stress MPS after their index CAC scan. For diabetic patients, those with a family history of premature CHD, or those with the metabolic syndrome, the threshold for referral to stress MPS is lower, at a CAC score of 100 or higher.<sup>65,82,83,85</sup> Approximately one fourth of the asymptomatic patients overall as compared with nearly half of the higher-risk diabetic patients with CAC scores of 400 or greater will have significant MPS ischemia.<sup>82-84</sup> Rozanski et al<sup>86</sup> have shown the safety of relying on a normal MPS study to imply a benign prognosis in patients with extensive CAC, provided that effective medical therapy is used. They demonstrated that after risk adjustment, in the setting of a normal MPS study, there was no difference in 4-year cardiac event rates in patients with CAC scores of greater than 1000, 400 to 999, or less than 400.

### **Role of Coronary CTA in High-Risk Asymptomatic Patients**

This document has focused on CT for CAC measurement and MPS. Recent advances in coronary CTA have led to multiple reports demonstrating the high

accuracy of this method for detecting CAD. Preliminary data have also suggested that coronary CTA has considerable prognostic power.<sup>87</sup> Although current appropriateness criteria have listed coronary CTA as inappropriate in high-risk asymptomatic patients, it is anticipated that this application may emerge as another method for further characterizing risk in the high-risk asymptomatic patient (eg, multiple risk factors and diabetes) beyond that provided by other CV imaging techniques.

## **CONCLUSIONS**

The aim of this statement was to introduce the concept of imaging for prevention. When applying this new testing paradigm, the sole purpose of imaging is to target treatments based on identified atherosclerotic or ischemic risk markers. For example, statin therapy has been shown to exhibit substantive anti-ischemic effects that are associated with dramatic reductions in CV risk. In this manner, imaging is more closely aligned with treatment, extending the concept of matching the intensity of therapeutic intervention to the underlying clinical hazard of the patient.<sup>9</sup> This concept of matching treatment intensity to risk was initially based on clinical history and angiographic data but should now include the gamut of atherosclerotic and ischemic risk markers.

We further put forth the concept of presymptom risk assessment to focus on the clinical value of imaging high-risk asymptomatic patients. We identified a number of high-risk asymptomatic patient cohorts who we believe are underserved by CV imaging. The full breadth and depth of diagnosis and the potential for improved clinical outcomes have yet to be realized. Although testing may be underused in certain key patient subsets (eg, women and those with a family history of premature CHD), growth and expansion of CV volume for any imaging laboratory should be based on sound clinical effectiveness evidence and not solely on the desire for increased revenues. To that extent, much of the content of this document was based on expert opinion and should serve as a focus for future research in CV imaging. We hope that this document will serve as guidance for the expansion of appropriate imaging in order to yield optimal risk detection.

This document also questions the validity of our current paradigm for CV imaging that is based on population screening. Cardiologists see a selected higher-risk patient cohort. At ASNC, we believe guidelines should reflect the patient referral base in order to improve the efficiency and effectiveness of testing strategies. To that end, we have included selected circumstances in which testing of high-FRS patients (eg, diabetic patients) may be clinically useful. This contradiction with the current ACC/AHA statements on the evaluation of low- and high-FRS

patients should be formally evaluated in controlled clinical trials, but the presentation herein is a first step to devise clinically based CV imaging strategies for high-risk asymptomatic patients. Furthermore, clinical “appropriateness” is a work in progress, and it is recommended that the appropriateness statements be adaptive in their recognition of clinical effectiveness and the rapidly expanding evidence base on atherosclerosis imaging.

Finally, on the basis of the current document, we would like to make the following recommendations:

1. Current guidelines support the use of CAC and CIMT as effective risk stratifiers in both patient and population cohorts.<sup>16,17</sup> However, given the small sample sizes as well as other methodologic limitations, additional validation from controlled clinical series would help in improving the predictability of these imaging modalities in diverse patient subsets.
2. The addition of an atherosclerotic imaging test should be considered in appropriate patients with an intermediate FRS.
3. Clinicians should take care to examine vulnerable low-FRS patient subsets whose risk may be underestimated, notably women and younger men, and who may benefit from atherosclerosis imaging.
4. Risk factors that are not included in the FRS should also be used to define candidates for CV imaging risk detection, including patients with a family history of premature CHD or those with the metabolic syndrome.
5. Patients who may also be candidates for CV imaging include those with a higher risk of atherosclerosis, including (a) women with PCOS or early menopause (ie, <40 years of age) and (b) patients with rheumatoid arthritis, systemic lupus erythematosus, or other autoimmune diseases.
6. Although diabetic patients are classified as CHD risk equivalents, an index risk assessment that includes imaging may serve as an important guide to assess disease progression. Of those diabetic patients in whom imaging may seem prudent, those with long-standing diabetes (ie, >5 years) or with poorly controlled diabetes may be reasonable candidates for CV imaging. We also consider testing in other CHD risk equivalents to be of value for index risk assessment, including those with PAD, cerebrovascular disease, or CKD.
7. Other notable patient candidates within current testing guidelines include those undergoing preoperative risk detection, as well as those with new-onset atrial fibrillation or LVH.

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