Curr Cardiovasc Risk Rep (2015) 9: 28
DOI 10.1007/s12170-015-0455-4

NOVEL + EMERGING RISK FACTORS (K NASIR AND R SANTOS, SECTION EDITORS)

Tools for Cardiovascular Risk Assessment in Clinical Practice

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Published online: 17 April 2015

Abstract Precise risk stratification of atherosclerotic cardiovascular disease guides best management and therefore is a public health priority. In addition to risk estimation using traditional risk factors, tools such as coronary artery calcium, high-sensitivity C-reactive protein, ankle-brachial index and carotid imaging, and clinical features such as family history of premature coronary heart disease may offer opportunities for a more personalized risk assessment. In this review, we discuss the strengths and limitations of each of these tools, focusing on the evidence provided by the latest studies relevant to the field. Among them, coronary artery calcium currently stands out as the most powerful tool for cardiovascular risk assessment, as recognized by the 2013 ACC/AHA Risk Assessment Guideline. Recent studies have expanded our knowledge regarding its value for improving the detection of both low and high absolute risk within clinically relevant subgroups, as well as for cost-effectively guiding preventive therapy allocation.

Keywords Cardiovascular disease · Atherosclerosis · Risk assessment · Absolute cardiovascular risk · Risk management · Prevention · Traditional risk factors · Risk scores · Coronary artery calcium · Family history · Serum biomarkers · High-sensitivity C-reactive protein · Ankle-brachial index · Carotid intima-media thickness · Carotid plaque

Abbreviations

ABI	Ankle-brachial index
ACC/AHA	American College of Cardiology/ American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
CAC	Coronary artery calcium
CAC=0	Coronary artery calcium score of zero
CIMT	Carotid intima-media thickness
CKD	Chronic kidney disease
CT	Computed tomography
CVD	Cardiovascular disease
hsCRP	High-sensitivity C-reactive protein
MRI	Magnetic resonance imaging
PAD	Peripheral arterial disease

This article is part of the Topical Collection on *Novel and Emerging Risk Factors*

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Introduction—Current Challenges in Cardiovascular Risk Assessment

Cardiovascular disease (CVD) remains a leading cause of death throughout the world. A large fraction is atherosclerotic CVD (ASCVD), including myocardial infarction and stroke. Even in those countries in which the combination of

primordial preventive interventions, improved risk factor management, and modern acute-phase pharmacologic and invasive therapies have resulted in a marked reduction in cardiovascular mortality, ASCVD still represents a major cause of morbidity, disability, hospital discharges, and healthcare costs [1, 2, 3•]. Furthermore, the growing prevalence of risk factors such as obesity and diabetes—with striking increases in their prevalence among young adults and the youth [1]—threatens to worsen this situation in the next few decades. These phenomena highlight the need for effective preventive interventions, among which the early, accurate detection of asymptomatic individuals at an increased cardiovascular risk is crucial.

On the other hand, increased life expectancy and population aging in Western countries have increased the size of the elderly population, a group often affected by multiple chronic diseases and treated with several pharmacotherapies at the same time. This context underscores the need for tools that accurately discriminate individuals who are likely to have ASCVD events and, thus, more likely to benefit from preventive pharmacotherapies, from those in whom costly treatments with potential drug-drug interactions and side effects could be downscaled or minimized.

Thus, the accurate detection of both high and low cardiovascular risk appears more important than ever and carries important clinical and public health implications. In this review, we address the strengths and limitations of currently available cardiovascular risk assessment tools, discussing the findings from the most recent, highest quality literature relevant to the field.

Traditional Cardiovascular Risk Factors and Risk Scores

The causal role of high blood pressure, dyslipidemia, diabetes, and tobacco use in the development and progression of atherosclerosis is undisputed [4, 5]. However, their performance as predictors of an individual's risk is modest. On the one hand, neither lifetime exposure nor individual/genetic susceptibility—which are believed to play a key role in the eventual development of disease [6•]—are captured by scores combining one-time measurements of a limited set of those factors. On the other hand, risk scores provide predictions based on group averages (with confidence intervals around the predictions) and may be helpful guiding preventive strategies at the population level. However, even though an individual patient may be classified in a group that is expected to derive net benefit from a preventive therapy, that does not mean that a specific patient will definitely benefit from it [7•].

Furthermore, as a consequence of the heavy weight of chronological age in risk scores, young adults with significant risk factors tend to be misclassified in lower risk categories [8–10]. This may result in the late treatment of those subjects likely to get the greatest benefit from timely interventions. In contrast, elderly adults are systematically classified into high-risk categories regardless of their risk factor profile [11, 12, 13•], leading to an expanded indication for preventive pharmacotherapies in that group. However, concentrating preventive therapies in the second half of life would seem to be a reactive approach that is somewhat in conflict with the underlying principles of preventive healthcare.

Thus, even though traditional risk factors and risk assessment scores may provide a first approximation to an individual's absolute risk in clinical practice, there may be a wide range of scenarios in which they will fall short, providing an opportunity for other risk assessment tools for moving the risk needle to a more reliable, accurate evaluation.

The 2013 Risk Assessment Guidelines

The American College of Cardiology and the American Heart Association (ACC/AHA) released in November 2013 a new set of joint cardiovascular prevention guidelines, with recommendations for both ASCVD risk assessment [14••] and management [15••, 16, 17] in asymptomatic adults. These new guidelines addressed important limitations from previous versions, particularly by developing specific risk prediction equations for women and African-Americans. Stroke was included as part of an aggregated cardiovascular events outcome, and a lifetime risk estimator was provided for those aged 20–59 years.

Yet, this new version of the guidelines still relied on the traditional approach that started with the Framingham Risk Score to cardiovascular risk assessment—the use of a limited set of single-time measurements of traditional cardiovascular risk factors, combined in a 10-year risk score. Age, sex, levels of total and HDL cholesterol, systolic blood pressure, hypertension treatment use (yes/no), diabetes (yes/no), and smoking status (yes/no), which are indeed the same factors considered in previous versions of the guidelines, were combined in race/ethnicity specific equations as an ASCVD risk estimator. It was intended to be used in adults 20–79 years of age by the Risk Assessment Guideline (age 40–75 by the Cholesterol Guideline) without clinical ASCVD, LDL cholesterol ≥190 mg/dL, or diabetes plus LDL cholesterol ≥70 mg/dL (subgroups already considered to be at high risk) [14••]. Treatment algorithms were built on the results of the estimator by the Cholesterol Guideline Panel, which recommended a clinician-patient risk discussion including consideration of statin treatment for those subjects with a 10-year ASCVD risk ≥7.5 % (Class I, Level of Evidence A) [15••].

Beyond the inherent limitations of the traditional risk factors approach, immediately following the release of the guidelines, it was noted that application of the risk estimator in

modern cohorts resulted in an overestimation of risk up to 150 % [18•]. This phenomenon was consistent with some overestimation already detected in the external validation studies [19] and could not be fully explained by increased statin use or coronary revascularizations in modern cohorts nor by differences in event ascertainment [20•]. Thus, the causes remain unclear, although it has been suggested that discrepancies between modern cohorts and the ones used for developing the 2013 Pooled Cohort Equations may be in part attributed to temporal trends of cardiovascular risk factors and disease. The inclusion of stroke in the outcome, resulting in an increased sensitivity of the new risk calculator to chronologic age, may also play a role [21•]. Finally, another reasonable hypothesis is that traditional risk factors alone cannot account for the lower risk of those in a higher socioeconomic class.

Importantly, using the new risk estimator and following the related risk management algorithms overall reduces the threshold for initiating a clinician-patient risk discussion to consider statin treatment. It appears that a clinician-patient risk discussion is now indicated in almost every white man 65 years of age or older and in almost every African-American male age 55 and older [22]. This is a good step forward as too few patients are aware of their risk status and the potential options for managing it. However, treatment decisions must be individualized, and clinicians need to grow more comfortable using other risk assessment tools to help refine the score-based risk estimate. Specifically, while other tools are commonly thought of as useful for upgrading risk classification, downgrading score-based risk predictions is particularly important to consider in elderly groups that are classified as high risk entirely or predominantly on the basis of chronologic rather than biologic age.

These issues can be discussed between the patient and clinician, who together can use the model of shared decision-making to personalize treatment decisions. They can consider current best evidence, the clinician can offer clinical judgment, and the patient can state his or her preferences. Highlighting the clinician-patient risk discussion in the 2013 ACC/AHA is a key virtue of the guidelines [23, 24•], and we anticipate that more specific guidance to clinicians will be forthcoming.

The discussion is indeed an opportunity to address uncertainty in risk estimation and consider the use of other tools to refine the risk estimate, potentially allowing for more personalized management [25•]. Although an "intermediate risk" group is no longer specified in the guideline, we have proposed 5 to 15 % 10-year predicted risk to roughly define such a group [24•, 25•], but the performance of such an approach has not been formally tested. Ultimately, the goal is to match intensity of preventive interventions with absolute risk [26].

Family History of Premature Coronary Heart Disease

Given genetically based clustering of disease, family history is part of routine medical assessment, though greater attention to ascertaining it may be needed in some practices [27]. A family history of premature ASCVD may be considered present if ASCVD manifested in a first-degree male relative before <55 years of age or a first-degree female relative <65 years [14••, 28]. Such individuals are candidates for Lp(a) testing and management [29], which may be one avenue to address the need for greater mitigation of risk [30].

Observational studies of family history, albeit somewhat heterogeneous in definitions, have repeatedly shown an independent association with subclinical atherosclerosis [31–35]. For example, in the Multi-Ethnic Study of Atherosclerosis (MESA), a family history of coronary disease was independently associated with the presence and extent of coronary artery calcium (CAC) [32]. In addition, the Coronary Artery Risk Development in Young Adults (CARDIA) investigators observed an independent association of parental history of premature CVD with CAC and carotid intima-media thickness (CIMT), though it was limited to white participants [33].

In MESA, incidence and progression of CAC were most strongly related to family history in white individuals, though formal interaction testing by ethnicity was non-significant [34]. Considering risk of ASCVD events, another recent MESA analysis assessed risk associated with a positive family history in individuals with a baseline CAC score of 0 (CAC=0) [35]. Although the absolute event rate was low in these individuals, there was approximately a 70 % proportional increase in CVD events in those with a family history of coronary disease.

Overall, family history may provide a rough approximation of an individual's genetic susceptibility. Patients will vary in their ability to accurately report family history. The 2013 ACC/AHA guidelines recommend family history assessment "in subjects in whom treatment decisions are uncertain after quantitative risk assessment" [14••]. We also advise that clinicians consider assessing family history regularly—particularly in young adults—as a cheap way to contextualize the risk assessment approach.

Coronary Artery Calcium

Provided the limitations of traditional risk factors as predictors of risk, in the last two decades several tests including coronary atherosclerosis-imaging techniques, serum biomarkers and other diagnostic and prognostic tests have been developed, aimed to provide a more personalized, accurate cardiovascular risk assessment, and enhance subsequent decision-making.

Among them, since the publication in 1990 of Agatston's method for measuring the CAC score [36], a wealth of studies have shown CAC being the most powerful single tool for cardiovascular risk assessment. CAC is a reliable marker of total atherosclerotic plaque burden [37–39], is independently associated with CVD events and mortality in asymptomatic subjects, and improves risk predictions beyond traditional risk factors [40, 41, 42••, 43••, 44••, 45••]. Of note, high-quality studies have shown such improvement to be greater than that attained by any other currently available advanced risk assessment tool [42••, 43••, 44••] (Table 1).

Accordingly, the 2013 ACC/AHA guidelines consider CAC "likely to be the most useful of the current approaches to improving risk assessment among individuals found to be at intermediate risk after formal risk assessment" [14••, 46•]. Moreover, beyond the further risk assessment of subjects considered at intermediate risk (which, as noted above, is unclearly defined in the new guidelines though we have provided potential ranges to consider), CAC may be helpful in other relevant risk assessment scenarios as well (Table 2).

In the last year, several studies further expanded knowledge on the potential utility of CAC in clinical practice. In MESA, CAC improved CVD risk predictions among subjects at the extremes of traditional risk factor burden [47•], as well as among categories of number of lipid abnormalities, levels of LDL and non-HDL cholesterol, and quartiles of total/HDL cholesterol [48•] (Fig. 1.). Of note, in MESA, the threshold of a CAC score ≥100 was associated with CVD event rates similar to those of secondary prevention populations [48•]. Thus, the binary distinction between primary and secondary prevention becomes blurred from an absolute risk and management standpoint.

Moreover, in MESA, CAC improved the prediction of incident cerebrovascular events beyond clinical features [49], highlighting its potential value as a tool for guiding stroke prevention efforts. This makes sense given the shared underlying pathophysiology. Furthermore, CAC has been found to be a cost-effective strategy for guiding statin therapy [50•], as well as a potentially helpful tool for guiding aspirin allocation [51] and the use of the polypill [52]. In a context of cost-constrained healthcare systems, these findings are likely to have important public health and economic implications.

Beyond its performance identifying asymptomatic subjects at an increased risk, CAC may be particularly valuable as a "negative" test to downgrade risk or "de-risk" an individual. A CAC=0 is associated with an excellent 10-year prognosis [53] and may aid the detection of true low risk among subjects stratified as intermediate or high risk by clinical scores, leading to a more selective use of preventive pharmacotherapies. Importantly, recent research has expanded our understanding regarding the stability or "warranty period" of a CAC=0 over time, assessing the potential role of combining information derived from different imaging techniques and measurements for predicting calcium conversion (the development of detectable coronary calcium in a subject with CAC=0 in a first scan) [54]. In the future, the interplay between clinical features and the information derived from imaging techniques will likely allow building personalized, safe, and cost-effective follow-up strategies for subjects with CAC=0 on a first scan [55].

Finally, the performance of new CAC scoring modalities for risk assessment has also been tested recently. The regional distribution of CAC among the coronary arteries has been found to be strongly and independently associated with frequency and mode of future coronary revascularization [56•]. Coronary calcium density has shown an inverse, independent association with CVD at any level of CAC volume [57•]. In the next years, the combination of improved CAC scoring methods such as CAC density with the information provided by regional patterns will likely further improve risk assessment beyond the standard CAC score.

CAC also has limitations that must be considered. No randomized, adequately powered trial has assessed the use of CAC for guiding preventive interventions and their impact on cardiovascular outcomes. Moreover, because of technical and funding reasons, such trial is unlikely to be performed in the near future [58]. However, this limitation also applies to the guideline-supported strategy of statin allocation guided by risk scores, as well as to any other advanced risk assessment tool. In such context, the results from carefully designed observational studies have provided consistent evidence regarding the superiority of CAC compared to any other risk assessment approach [42••, 43••, 44••, 45••].

Second, computed tomographic (CT) scanning for CAC scoring involves radiation exposure, even though with modern scans, the associated radiation dose is ≤1.0 mSv. This amount of radiation is roughly equivalent to two transatlantic flights or a bilateral mammogram. When considering the importance of radiation, one should also take into account the age of the patient. It is generally felt that the importance of radiation exposure may be greater in a younger patient.

Third, CAC may fail to detect early non-calcified atherosclerotic plaque. Nevertheless, recent evidence has shown that asymptomatic subjects with CAC=0 have a very low presence of non-calcified atherosclerotic plaque, including only a 1 % of subjects with obstructive, non-calcified plaque, and a very low event rate after a median follow-up of 22 months [59]. Fourth, there needs to be greater consideration of whether examination of the lung window during a CAC scan is truly justified, and, if so, whether routine follow-up CT scans add clinical value.

Finally, a recent propensity-score matched study suggested that the use of CAC for risk assessment may be associated with increased downstream testing and healthcare costs compared to other risk assessment tools [60•]. Nonetheless, in the same study, CAC-guided management was associated with lower CVD event rates. Furthermore, it is unknown whether

Table 1 Key studies comparing advanced cardiovascular risk assessment tools

Study	Study location and population	Tests compared	Mean follow-up	Study outcomes	Key results
MESA Yeboah J et al. Ref: [42••]	USA Population-based *N*=6814	ABI, brachial FMD, CAC, CIMT, FH, hsCRP	7.6 years	CHD events CVD events	ABI, CAC, hsCRP, and FH were independently associated with CHD and CVD. CAC had the strongest association with both CHD and CVD. CIMT and brachial FMD not independently associated with CHD or CVD. CAC afforded the greatest increment in the AUC when added to the FRS plus race/ethnicity for both CHD and CVD. The NRI with CAC was also the greatest for both CHD and CVD events.
Rotterdam Kavousi M et al. Ref: [43••]	The Netherlands Population-based *N*=5933	CAC, CIMT, CRP, PWV, CKD, PAD, NTProBNP, von Willebrand factor antigen, fibrinogen, leukocyte count, homocysteine	6.8 years	CHD events	Adding CAC to the FRS significantly improved the accuracy of risk predictions. Adding NTProBNP to the FRS also improved risk predictions, but to a lesser extent than CAC. Improvements in predictions with other markers were marginal.
EISNER Rana JS et al. Ref: [44••]	USA Clinical cohort *N*=1286	CAC, CRP, IL-6, myeloperoxidase, NTProBNP, plasminogen activator-1	4.1 years	CVD events	CAC was independently associated with increased hazards for CVD after adjusting for FRS. Multiple biomarkers score was also associated with increased risk beyond FRS. The c-statistic did not increase significantly when the multiple biomarkers score was incorporated into FRS. The c-statistic increased when CAC was incorporated into FRS without or with multiple biomarkers score. Addition of CAC to FRS resulted in significant reclassification, whereas addition of the multiple biomarkers score did not.
Heinz Nixdorf Erbel R et al. Ref: [45••]	Germany Population-based *N*=4129	CAC	5 years	CHD events	Reclassifying intermediate-risk subjects (defined as 10–20 % and 6–20 %) with CAC<100 to low risk and with CAC≥400 to high-risk yielded NRIs of 21.7 % (p<0.001) and 30.6 % (p<0.001) compared to the FRS, respectively. Adding CAC to the FRS resulted in an IDI of 1.52 % (p<0.001). Adding CAC to the FRS and NCEP-ATP III categories improved the AUC from 0.681 to 0.749 (p=0.003) and from 0.653 to 0.755 (p<0.001), respectively.

Abbreviations: *MESA* multi-ethnic study of atherosclerosis, *EISNER* early identification of subclinical atherosclerosis by noninvasive imaging research, *ABI* ankle-brachial index, *FMD* flow-mediated dilation, *CAC* coronary artery calcium, *CIMT* carotid intima-media thickness, *FH* family history, *hsCRP* high-sensitivity C-reactive protein, *CRP* C-reactive protein, *PWV* pulse wave velocity, *CKD* chronic kidney disease, *PAD* peripheral arterial disease, *NTProBNP* N-terminal fragment of prohormone B-type natriuretic peptide, *IL-6* interleukin-6, *CHD* coronary heart disease, *CVD* cardiovascular disease, *AUC* area under the curve, *FRS* Framingham risk score, *NRI* net reclassification improvement, *IDI* integrative discrimination index, *NCEP-ATP III* national cholesterol education program adult treatment panel III

Table 2 Potential indications of CAC scoring for cardiovascular risk assessment of asymptomatic adults in clinical practice

1) Further risk assessment + aid decision-making in patients considered at intermediate risk by scores. Especially useful in the context of:
Family history of premature cardiovascular disease
Metabolic syndrome
Men with erectile dysfunction of a suspected vascular mechanism
Women with a history of pre-eclampsia
Inflammatory systemic vascular diseases, rheumatic diseases
Statin-reluctant patients
2) Further risk assessment + aid decision-making in patients considered at high risk by scores, if:
Optimal levels of risk factors and the high risk prediction is driven exclusively by chronological age
Patients using multiple treatments and at risk of drug-drug interactions
Motivate statin-reluctant patients
3) Other uses:
Further assessment + aid decision-making in young adults with "low" predicted risk but several non-traditional risk factors
Aid decision-making for non-statin therapies

that increased testing and cost offsets the potential savings of a more accurate risk assessment attained with CAC.

High-Sensitivity C-Reactive Protein

Inflammation is believed to have a critical role in the development and stability of coronary atherosclerotic plaque [61]. Accordingly, in the last two decades, a number of serum biomarkers have been tested for their association with CVD events, as well as for their potential value for improving risk predictions beyond traditional risk factors. Among them, high-sensitivity C-reactive protein (hsCRP), which was first linked with coronary artery disease risk in 1996 [62], has gained the greatest attention.

Studies have shown hsCRP being independently associated with CVD events and mortality [63, 64]. The 2013 risk assessment guidelines recommend considering hsCRP testing selectively for further risk assessment when clinical management is uncertain. However, widespread use of hsCRP in

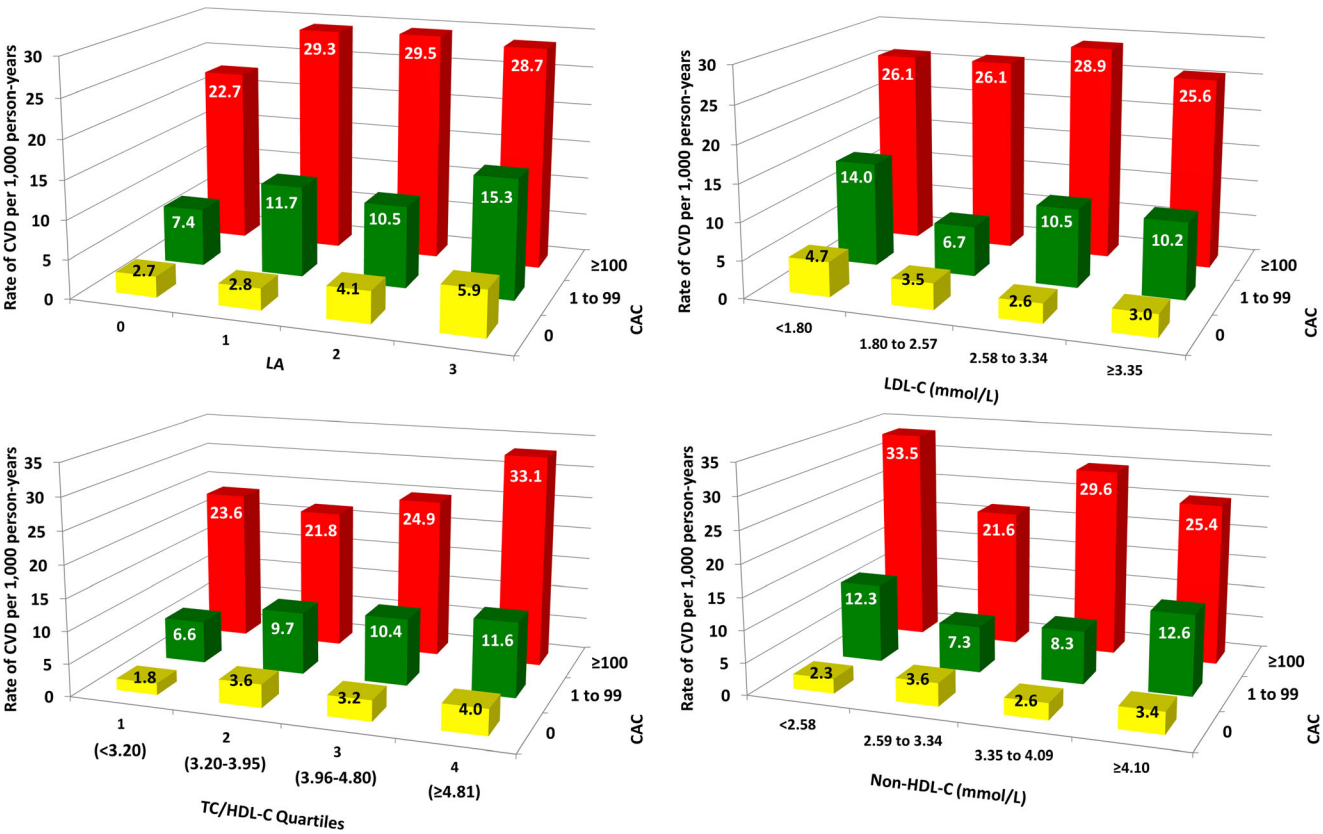

Fig. 1 Atherosclerotic cardiovascular disease event rates per 1000 person-years by number of lipid abnormalities (*upper left*), LDL cholesterol levels (*upper right*), quartiles of total/HDL cholesterol (*lower left*) and non-HDL cholesterol levels (*lower right*), and coronary artery calcium score. *Abbreviations*: *CVD* cardiovascular disease, *LA* lipid abnormalities, *CAC* coronary artery calcium, *LDL-C* low-density lipoprotein cholesterol, *TC* total cholesterol, *HDL-C* high-density lipoprotein cholesterol. Reproduced with permission from Martin SS et al.: dyslipidemia, coronary artery calcium, and incident atherosclerotic cardiovascular disease: implications for statin therapy from the multi-ethnic study of atherosclerosis. *Circulation. 2014 Jan 7;129(1):77-86*

clinical practice either as a tool for risk assessment or for the allocation of statin therapy—as suggested by the JUPITER trial [65]—is currently not justified [66•]. In intermediate-risk subjects in MESA, the majority of events actually occurred in subjects with hsCRP <2 mg/L, whereas approximately 90 % occurred in individuals with CAC>0 [67]. Finally, a recent study reported that 440 intermediate-risk individuals would have to be screened using hsCRP levels—and treated with statins accordingly—in order to prevent one additional CVD event over the course of 10 years [68].

Hence, currently available evidence suggests that the performance of hsCRP as a tool for risk assessment or preventive therapy allocation is modest. Indeed, hsCRP has a marked ethnic, sex-related, and intra-individual short-term variability [66•, 69], and its ability for capturing long-term exposure is limited. Moreover, whereas other tests such as CAC improve risk predictions among hsCRP categories [67], the value of hsCRP for improving risk predictions beyond the information provided by those tools is unknown.

Ankle-Brachial Index

Endothelial dysfunction and atherosclerosis are systemic processes, and subjects with a diseased vascular bed are more likely to have disease in other locations as well [70]. Accordingly, a number of tests aimed at detecting atherosclerosis in territories other than the coronary arteries have been proposed as tools for improving coronary and cerebrovascular risk assessment in clinical practice. Among them, the ankle-brachial index (ABI) and carotid ultrasound imaging have generated the greatest research interest.

Beyond its role as a surrogate marker for peripheral arterial disease (PAD) [71], the ABI is robustly and independently associated with incident CVD events [72] including recurrent stroke [73]. The 2013 ACC/AHA guidelines support the use of ABI for further cardiovascular risk assessment in subjects for whom risk-based decision-making is uncertain after risk estimation using traditional risk factors, specifically by "revising risk assessment upward" in subjects with an ABI <0.9 [14••]. Such a cut point has a high specificity, but its sensitivity for detecting increased CVD risk is low [74], with only 5 % of the US population ≥40 years of age without known CVD having an ABI ≤0.9 [75].

Moreover, a recent systematic review on the added value of ABI in risk prediction noted that, currently, there is insufficient evidence to assess the balance of harms and benefits of CVD risk assessment using the ABI [76•, 77]. The same review also found limited trial evidence regarding treatment of CVD in persons with asymptomatic or minimally symptomatic PAD [76•, 77]. Specifically, the value of the ABI in risk reclassification is considered almost non-existent in adults <65 years of age. Finally, a recent study detected important technical issues associated with the measurement of ABI in clinical practice [78].

Thus, even though the ABI may be an informative test in the elderly and in subgroups of subjects with high CVD event rates [76•, 77], its widespread use as a tool for further risk assessment is likely to provide limited information in most patients.

Carotid Ultrasound Imaging

CIMT and the presence of carotid plaque can be assessed non-invasively using ultrasound imaging. Regarding CIMT, baseline [79] and some progression measurements [80] have each shown an independent association with incident CVD events. Furthermore, CIMT in MESA was a better predictor of incident stroke than CAC [81]. However, the 2013 AHA/ACC guidelines recommend against the routine measurement of CIMT for CVD risk assessment in clinical practice (class of recommendation III, level of evidence B) based on concerns regarding measurement quality and standardization, as well as on the evidence provided by recent studies [82] and a meta-analysis [83•] of 14 population-based cohorts (N=45,828) showing a very modest performance of CIMT to improve risk predictions beyond traditional risk factors [14••]. More recent studies published after the release of the guidelines have reported similar findings [84•].

On the other hand, the prognostic value of CIMT increases when combined with measurements of carotid plaque [85, 86], a strategy not addressed in the 2013 ACC/AHA guidelines [14••] but which has been suggested as a reasonable screening strategy by expert consensus documents [87]. Interestingly, the combination of CIMT and carotid plaque measurements may be particularly useful for downgrading risk estimates in subjects unlikely to have events [88]. Finally, a recent MESA study on carotid plaque measurements using magnetic resonance imaging (MRI), which provides insight into carotid plaque morphology, composition, and remodeling, reported improved risk predictions when carotid plaque measurements were added to traditional risk factors [84•]. Future studies will expand our understanding regarding the potential role of combined measurements of CIMT and plaque and of carotid MRI, as well as their performance and cost-effectiveness compared to other tests.

Other Potential Risk Assessment Tools

Coronary computed tomography angiography, which allows for the detection of non-calcified atheroma, and the detailed study of coronary plaque using MRI, offer opportunities for advanced imaging in selected individuals and specific clinical scenarios, but currently are not recommended as tools for

routine risk assessment in asymptomatic subjects [14••, 89–91]. Similarly, stress testing is not routinely recommended for risk stratification in asymptomatic adults [14••, 89, 90].

Measurements of arterial reactivity (such as brachial flow-mediated dilation) and stiffness (such as pulse wave velocity) are independently associated with CVD events [92, 93]; however, their clinical role remains unclear. A number of serum biomarkers beyond hsCRP have also been considered as potential risk assessment tools, either individually or combined in "multiple biomarker" panels; however, their performance seems to be modest [42••, 43••, 44••].

In addition to the standard lipid profile, multiple other lipid tests are available, such as apolipoprotein B and LDL particle concentration. Recent studies have demonstrated the importance of lipid discordance, an under-detected but common phenomenon that may lead to risk misclassification [94, 95•, 96]. Additional discordance analyses are warranted, and future guidelines may clarify the groups of patients that may benefit from additional lipid testing at baseline and on-treatment.

Chronic kidney disease (CKD) is strongly associated with incident CVD in the general population [97] and has been proposed as a coronary heart disease risk equivalent [98]. Furthermore, preventive treatments reduce CVD events in this group [99]. Thus, some scientific societies consider CKD patients at high CVD risk and advocate for the aggressive management of their risk factors [28, 90].

Cardiorespiratory fitness is considered an integrative predictor of all-cause mortality and may offer complementary information to that provided by atherosclerosis-imaging techniques such as CAC [100•]. However, the role of fitness measurements in the prediction of cardiovascular events is currently unclear, and further research is needed.

Finally, despite the identification of genetic variants that predispose to the development of CVD, whether the results of genotype testing alter management or improve clinical outcomes is currently unknown, and current guidelines do not recommend genetic testing as part of a cardiovascular risk assessment strategy [14••, 89, 90].

Conclusion

CAC, the flagship of a personalized atherosclerosis-imaging, disease-detection paradigm, is the best single tool for cardiovascular risk assessment. CAC refines risk predictions within clinically relevant subgroups and among a wide range of risk assessment scenarios, and offers opportunities for a more cost-effective allocation of preventive pharmacotherapies. On the other hand, recent evidence has shown that the improvement in risk prediction with hsCRP and ABI is likely to be modest.

Future iterations of the risk assessment guidelines should incorporate the findings from the latest, highest quality studies regarding the role that advanced risk assessment tools can play in clinical practice. Thus, beyond traditional risk scores and easy-to-follow recommendations, by providing decision-makers with clear guidance regarding the use of such personalized risk assessment tools, the accurate stratification and management of absolute cardiovascular risk in clinical practice will be closer to becoming a reality.

Acknowledgments MC-A was funded by a research grant from the Spanish Society of Cardiology. SSM is supported by the Pollin Cardiovascular Prevention Fellowship, Marie-Josée and Henry R Kravis endowed fellowship, and a National Institutes of Health training grant (T32HL07024). RSB is supported by the Kenneth Jay Pollin Professorship in Cardiology.

Compliance with Ethics Guidelines

Conflict of Interest Michael Blaha served on an Advisory Board for Pfizer and Luitpold Pharmaceuticals and received grant support from the FDA, all outside of the scope of the present work. Roger Blumenthal, Miguel Cainzos-Achirica and Kieran Eissler have no relevant disclosures to report. Seth Martin is listed as a co-inventor on a pending patent filed by Johns Hopkins University for a method of low-density lipoprotein cholesterol estimation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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