ABSTRACT

Introduction: Current primary prevention guidelines do not strongly support the use of cardiovascular imaging and circulating biomarkers in the risk assessment. Still, an increasing body of evidence suggests that important prognostic information can be obtained from imaging and biomarker measurements.

Areas covered: In this review, we will describe the most important imaging modalities (coronary computed tomography, myocardial perfusion imaging, carotid intima media thickness, echocardiography and cardiac magnetic resonance imaging) and circulating biomarkers (cardiac troponins, B-type natriuretic peptides and C-reactive protein) for risk prediction in people without known cardiovascular disease. We will discuss both the prognostic performance and clinical utility of these biomarkers in the era of primary prevention with increased focus on precision medicine. Finally, we will comment on the use of cardiac biomarkers in screening for additional work-up with cardiac imaging and the combination of the entities in risk prediction.

Expert opinion: We believe future primary prevention should to a larger extent integrate measurements of cardiovascular biomarkers and non-invasive imaging to enhance the precision of subclinical disease detection and risk stratification. The use of cardiovascular biomarkers as a screening tool for further testing with non-invasive imaging may be a cost-effective strategy.

ARTICLE HIGHLIGHTS

- Cardiovascular biomarkers and non-invasive cardiac imaging are not strongly recommended by current primary prevention guidelines despite convincing evidence demonstrating clinical importance.
- In the era of precision medicine health care providers and patients are expected to increasingly request assessment with novel imaging modalities and cardiovascular biomarkers.
- Integration of cardiovascular biomarkers and non-invasive imaging in a stepwise approach may be a cost-effective strategy in risk stratification and identification of subclinical disease in the general population.

1.0 INTRODUCTION

The focus on primary prevention and intensive risk factor control has resulted in a dramatic reduction in mortality from cardiovascular disease (CVD) over the last decades. From 2004 to 2014 death rates attributable to CVD declined 25% in the United States, yet CVD still accounts for about a third of deaths in industrialized countries [1]. Still, due to an aging population and increases in lifestyle-related disease, as many as 44% of the US adult population is projected to have some form of CVD by 2030 [1]. Thus, primary prevention of CVD remains critical to continue the global improvement in cardiovascular morbidity and mortality.

Early detection of CVD is a key factor in the next generation of primary prevention. Current risk-stratification guidelines [2] [3] are based on probabilistic risk scores including the Framingham Risk Score [4] and Systematic COronary Risk Evaluation (SCORE) [5]. These include population-based cardiovascular risk factors, such as age, sex, cholesterol levels, blood pressure, smoking habits and comorbidities. There are however well-documented limitations to this approach for preventing CVD [6], and the focus on early screening tests has increased as the traditional risk factors do not fully explain inter-individual variation in cardiovascular risk. Indeed, the landscape of primary prevention has shifted with the rapid technologic advances in cardiovascular imaging and development of high sensitivity assays for circulating cardiovascular biomarkers. These two areas have made important contributions to the emerging field of individualized cardiovascular precision medicine. However, the utilization and integration of the numerous imaging modalities and biomarkers in cardiovascular risk prediction may prove challenging to clinicians.

Herein, we review the literature regarding cardiovascular imaging, cardiovascular biomarkers and the combination of these two entities, for primary prevention of CVD. As many of the biomarkers included are relevant in primary prevention of more than one cardiac condition, this review is structured by the biomarker candidates and not by different cardiac condition.

2.0 CARDIAC IMAGING IN PRIMARY PREVENTION

A wide range of techniques for imaging of the cardiovascular system has been developed during the recent decades. The majority of current examinations are performed in symptomatic patients to diagnose specific disease. However, many of the imaging modalities

are non-invasive and therefore safe to use also in the primary prevention setting. Still, to promote imaging modalities for primary prevention will require that the examinations provide incremental information to the information obtained from standard risk assessment, and that benefit outweighs costs. Of note, most current guidelines do not recommend universal routine screening with imaging to predict future cardiovascular events [2, 3]. Still, with the increased focus on personalized medicine among health care providers *and* the general population, it is expected that the demand for noninvasive cardiovascular imaging in primary prevention will increase in the near future.

2.1 Coronary computed tomography

When addressing the use of computed tomography (CT) in the evaluation of coronary artery disease in primary prevention, there are primarily two modalities of interest; coronary calcium scoring (CAC) and coronary CT angiography (CCTA). CAC scoring is a non-contrasted automated protocol that provides a quantitative estimate of the total coronary calcium burden, and CCTA a contrast enhanced evaluation of coronary anatomy and plaque morphology. These modalities are usually compared with invasive coronary angiography, the reference standard for identification of coronary artery disease [7], for diagnostic purposes.

2.2 Coronary Artery Calcium Score

The extent of coronary calcifications assessed by radiography has been shown to be an independent marker of poor cardiovascular prognosis for decades [8, 9]. In asymptomatic individuals, CAC score improves risk stratification in addition to current guidelines for statin treatment [10], and is a robust predictor of long-term cardiovascular risk, both alone and as an adjunct to global risk stratification tools [11*, 12*, 13*]. Recently, several studies have attempted to explore not only the diagnostic and prognostic aspects of CAC scoring, but also its *therapeutic* merits in the primary prevention setting. To date, the evidence for outcome related improvements by use of CAC are few, and the majority of available studies are underpowered to detect significant effects on adverse outcomes [14]. The Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) study attempted intensified primary prevention counseling in older individuals with available CAC scores. The availability of CAC scores did not affect outcome, though there seemed to be a favorable trend towards lower risk [15]. Comparable results were seen in the Prospective Army

Coronary Calcium (PACC) trial [16]. In the Multi-Ethnic Study of Atherosclerosis (MESA) study, CAC score added incremental prognostic value to traditional risk stratification tools and was a strong predictor of incident coronary heart disease, but did not add therapeutic benefit [17**]. Moreover, CAC score ≥100 identified subjects from MESA with favorable risk/benefit for aspirin use, while subjects with zero CAC score were estimated to receive net harm from aspirin [18*]. Currently, guidelines recommend the use of CAC scoring as an adjunct to quantitative risk assessment in asymptomatic low to intermediate risk individuals where risk-based treatment decisions are uncertain [3, 19]. Given the additional healthcare costs, radiation exposure and inconvenience associated with a screening strategy using CAC, it is important to consider cost-effectiveness [20]. The few studies that investigated this in general favored a CAC strategy, particularly in men [21, 22, 23]. Still, there is a need for large, international clinical trials assessing the net cost-effectiveness by using CAC to stratify the intensity of preventive treatment.

2.3 Coronary Computed Tomography Angiography

As an imaging modality, CCTA has unique benefits related to accurately identifying plaque morphology and quantifying obstructive disease. As opposed to CAC, CCTA can identify non-obstructive high-risk plaque both in asymptomatic and symptomatic individuals. In a systematic review of studies employing 64-slice CT in the evaluation of *symptomatic* patients, negative CCTA reliably ruled out significant CAD, but the positive predictive values were somewhat low suggesting a need for additional diagnostic testing [24]. In the recent Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) study, the prognostic efficacy of CCTA, CAC and functional testing was compared in symptomatic patients. CAC was found to be more sensitive, while functional testing was more specific, for future cardiovascular events [25*]. However, CCTA was superior to both CAC and functional testing [26*]. Few studies have been performed with the intent to examine the role of CCTA in *primary prevention*. In the Screening For Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography, Following Core 64 (faCTor-64), diabetic patients without known cardiovascular disease were randomized to receive either CCTA guided primary prevention therapy or standard of care. Although there was more aggressive treatment and additional diagnostics in the CCTA arm, no significant difference in outcome was observed between the groups [27*]. Notably, there was a promising signal in the CCTA arm after longer (three years) follow-up. As for the CAC

studies, insufficient statistical power remains a problem due to the low event rates in asymptomatic populations. Another consideration in the role of CCTA in primary prevention is the low, but unneglectable risk associated with radiation exposure. The current primary prevention guidelines do not recommend the routine use of CCTA in primary prevention and the field remains controversial [3, 19]. Future trials should examine whether CCTA improves clinical outcome when added to standard of care in patients free of cardiovascular disease, similar to what was recently demonstrated for patients with stable CAD in the Scottish Computed Tomography of the Heart (SCOT-HEART) trial [28*].

2.4 Myocardial perfusion imaging

Although myocardial perfusion imaging is recommended in secondary prevention for risk stratification among patients with suspected or known coronary artery disease [29], few studies have investigated the role of myocardial perfusion imaging in the primary prevention setting. The Diagnostic Imaging in Asymptomatic Diabetes (DIAD) trial was designed to assess whether screening with single-photon emission computed tomography myocardial perfusion imaging (SPECT-MPI) improved risk stratification in patients with type 2 diabetes [30]. Although the study was limited by a low event-rate, the main finding was that SPECT-MPI screening did not reduce cardiac events. Taken together with the time and resources (either exercise stress testing or pharmacologically-induced stress testing) required to complete myocardial perfusion imaging, the test does not seem to have a role in primary prevention, even in high-risk individuals.

2.5 Carotid intima media thickness

Ultrasonography for the measurement of carotid intima media thickness (cIMT) and carotid plaque has become the standard reference method for assessing the presence and amount of atherosclerosis in living humans [31]. Population-based studies have shown robust correlations between the severity of atherosclerosis in one arterial territory and the involvement of other arteries [32**], and with superior accessibility the carotid has been most studied. Several reports suggest an association between greater cIMT and increased cardiovascular risk, starting already in childhood [33, 34, 35, 36]. The presence of carotid

plaque has also been shown to have prognostic importance [37]. Given the increase in cIMT with increasing age and hypertension, carotid plaque is probably a better measure of cardiovascular risk in the elderly [33]. In addition to being a robust modality in predicting cardiovascular events, carotid ultrasound may also have a role in assessing treatment response, i.e. by intensive lipid-lowering that have been demonstrated to induce regression of atherosclerosis measured by cIMT [38, 39, 40]. However, a large meta-analysis from 2012 failed to demonstrate any incremental predictive value of cIMT to the Framingham Risk Score [41*].

2.6 Echocardiography and cardiac magnetic resonance imaging

Assessment of cardiac structure and function does not have a central role in current primary prevention. However, a wealth of important information in the setting of personalized risk prediction can be obtained from echocardiography and cardiac magnetic resonance imaging (CMR). Echocardiography is the most available modality for assessment of cardiac structure and function, whereas CMR is more accurate and reproducible [8] In addition, the application of gadolinium-enhanced MRI in later years has made precise identification and quantification of myocardial scar and fibrosis available [42] [43].

The prognostic importance of echocardiographic variables are well established in patients with established CVD. In primary prevention, data from the Framingham Heart Study first demonstrated the association between left ventricular (LV) dimension (measured by M-mode echocardiography) and the risk of heart failure [44]. Later, in the Olmsted County Study, LV mass, LV systolic function, LV diastolic function and left atrial volume were all shown to be independent predictors of CVD after adjusting for all of the traditional risk factors [45*]. Furthermore, echocardiography provided incremental prognostic information in this elderly cohort, which has been validated in other cohorts [46] [47]. Importanly, novel and more sensitive measures of LV dysfunction such as global longitudinal strain has been demonstrated to be a superior predictor of risk as compared to other echocardiographic measures and conventional risk scores [48] [49]. Still, echocardiographic screening in the general population for structural and valvular heart disease provided no benefit for mortality or the risk of myocardial infarction or stroke

[50].

The clinical use of CMR in the primary prevention setting is limited, as the modality is resourceful, time-consuming and with restricted availability. Hence, this highly sensitive method of assessing cardiac structure and function is primarily reserved for symptomatic individuals and secondary prevention. However, CMR plays an important role in research, also of the general population, to enhance understanding of cardiovascular pathophysiology and subclinical disease. The Dallas Heart Study (DHS) and the MESA study are two large community-based studies with CMR measurement, which has yielded invaluable knowledge about cardiovascular disease progression in presumably healthy adults. Results from DHS has demonstrated a strong association between LV hypertrophy with adverse outcome in the general population [51] [52]. The MESA investigators have also demonstrated that subtle age-related ventricular remodeling confers significant cardiovascular risk, particularly when present early in life.[53] The presence of scar assessed by contrast-enhanced CMR was also strongly associated with CV events [54].

3.0 CARDIAC BIOMARKERS IN PRIMARY PREVENTION

A large number of circulating biomarkers with association to cardiovascular risk have emerged in the recent years. Still, only a few biomarkers have reached the high bar for clinical implementation in primary prevention. Morrow and de Lemos have suggested 3 benchmark criteria for evaluating novel biomarkers: 1) Ease of measurement, 2) Incremental information and 3) Impact on clinical management [55]. The two latter criteria exclude most novel biomarkers from clinical practice as the information provided is usually not superior to existing tests, has limited ability to improve risk-classification and most importantly does not change patient management. Indeed, the 2016 European Guidelines on cardiovascular disease prevention in clinical practice states that “CV circulating and urinary biomarkers have either no or only limited value when added to CVD risk assessment with the SCORE system” [2]. This review therefore focuses on three biomarkers that are already commonly measured in current clinical practice for other reasons than primary prevention, but still provide incremental prognostic information in cardiovascular risk prediction: Cardiac troponins, B-type natriuretic peptides (BNP) and C-reactive protein (CRP).

3.1 Cardiac troponins

Measurement of cardiac troponins is fundamental in the diagnosis of acute coronary syndromes and has been part of the universal definition of acute myocardial infarction since 2000.[56] With the evolution of high-sensitivity cardiac troponin assays, it is now possible to quantify concentrations of cardiac troponin in large proportions of the presumably healthy population and low-grade increases in cardiac troponin are associated with increased risk of fatal and non-fatal cardiovascular disease.[57, 58, 59]. In 2018, the high-sensitivity cardiac troponin I assay from Abbott was the first to receive the European CE mark for risk prediction in primary prevention.

With regard to the development of cardiovascular disease, systolic blood pressure and blood cholesterol are currently treatment targets in primary prevention and the use of both antihypertensives and lipid modifying therapy have beneficial impact on cardiovascular risk [60, 61]. Two important studies have explored the use of cardiac troponins in risk assessment of patients with hypertension and increased blood cholesterol. In 2015, Pokharel et al. investigated the impact of concentrations of cardiac troponin T and systolic blood pressure on the risk heart failure, coronary heart disease and stroke.[62] For most categories of systolic blood pressure, higher concentrations of cardiac troponin T were associated with increased cardiovascular risk. In contrast, increasing systolic blood pressure within categories of cardiac troponin T did not convey an increase in risk. In 2016, Ford et al. demonstrated the effects of statin therapy on cardiovascular risk and concurrent changes in concentrations of cardiac troponin I.[63*] Men with increased concentrations of low-density lipoprotein cholesterol were randomized to statin therapy or placebo for 5 years, and cardiac troponin I was measured at baseline and after 12 months. In this trial, statin therapy reduced concentrations of cardiac troponin I by 13%, and participants with the largest decreases in cardiac troponin I had the lowest risk of incident coronary events. Similar findings were done in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPTIER) trial.[64*] These studies support the notion that concentrations of cardiac troponin reflect cardiovascular risk and that changes in cardiac troponin concentrations could be an important index of response to preventive therapy. More aggressive medical intervention may accordingly be warranted in subjects with high baseline concentrations of cardiac troponin.

3.2 B-type natriuretic peptides

Among the natriuretic peptides, B-type natriuretic peptide (BNP) and N-terminal pro–B-type natriuretic peptide (NT-proBNP) are the most commonly used in clinical practice. BNP opposes activity of the renin-angiotensin-aldosterone and the adrenergic system, and promotes natriuresis and vasodilatation in response to myocardial ischemia and stress.[65] Concentrations of both BNP and NT-proBNP have their applicability in the diagnosis and prognosis of heart failure, but are also associated with cardiovascular risk in presumably healthy individuals from the general population,[66*, 67] as well as in patients with coronary artery disease.[68, 69]

Two important trials have explored the use of natriuretic peptides in subjects at risk of developing cardiovascular disease. In 2013, Huelsmann et al. published data from the NT-proBNP Guided Primary Prevention of CV Events in Diabetic Patients (PONTIAC) trial.[70] In this report, patients with diabetes mellitus free from cardiovascular disease with concentrations of NT-proBNP ≥125pg/ml were randomized to standard care or intensified care with cardiac follow-up and neurohumoral medication (i.e. renin-angiotensin system antagonists and β-blockers). For the primary endpoint of hospitalization or death due to cardiac disease, there was a significant reduction of 64.9% in the intervention group after two years of follow-up. Despite being statistically significant for the primary end-point, this study ended up being underpowered to detect a clinically relevant difference between the groups, and the 95% confidence intervals were wide (hazard ratio 0.13-0.98). Accordingly, these findings are now being investigated in the much larger, multicenter, PONTIAC II trial, which is expected to be completed in 2021. Although by definition not purely primary prevention in subjects free from known cardiovascular disease, the work of Ledwidge et al.[71*] from 2013 merits mentioning. In this report, the authors detailed the results from the St Vincent's Screening to Prevent Heart Failure (STOP-HF) trial. Patients at increased risk of developing heart failure were randomized to conventional care or screening with BNP testing. Subjects in the intervention arm with BNP concentrations ≥50pg/ml underwent echocardiography and specialized cardiac follow-up. For the primary endpoint of incident LV dysfunction and heart failure, there was a significant reduction of 45% in the intervention group after 4.2 years of follow-up. As for cardiac troponins, both studies elegantly illustrate the benefit of screening with natriuretic peptides for patients most likely to benefit from medical intervention preventing the development of cardiovascular disease.

3.3 C-reactive protein

CRP is an acute-phase reactant of hepatic origin that is released into the circulation as a response to increased interleukin-6 and tumor necrosis factor α signaling [72]. In Europe, CRP has for years been used in the diagnostic assessment of infectious diseases and is an established marker of inflammation. Liuzzo et al demonstrated the prognostic importance of CRP in patients with unstable angina pectoris in 1994 [73]. Work from 1997 led by Dr. Ridker extended this inflammatory link to atherosclerosis and CVD in the primary prevention setting, by demonstrating that subjects with elevated levels of CRP were at increased risk of myocardial infarction and stroke [74*]. These discoveries, together with pioneering work by Dr. Libby, Dr. Hansson and Dr. Ross, led to the recognition that atherothrombosis is no longer considered solely a disorder of lipoprotein accumulation in the arterial wall, but also involves important inflammatory pathways. This initiated a fascinating scientific treasure hunt for anti-inflammatory therapies for CVD [75]. For now, the story has culminated with the recent Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) demonstrating that interleukin-1beta-inhibition reduces cardiovascular risk in patients with elevated CRP in the secondary prevention setting [76]. In contrast, the Cardiovascular Inflammation Reduction Trial (CIRT) did not see a reduction in cardiovascular events by low-dose methotrexate [77].

Numerous epidemiological trials have also supported the association between elevated CRP measured by high-sensitivity assays and risk of cardiovascular events [78*] [79, 80], and a large meta-analysis showed that CRP concentrations ≥3.0 mg/L were associated with 58% greater risk of incident coronary heart disease compared with levels less than 1.0 mg/L [81]. Moreover, the information provided by measuring CRP in people without known CVD are incremental to the established risk factors and improves reclassification models [82]. Still, recent studies have found CRP to be an inferior prognostic marker as compared to cardiac troponin and BNP [59].

4.0 USE OF CARDIAC BIOMARKERS IN SCREENING FOR ADDITIONAL CARDIAC IMAGING

Most imaging examinations are resource demanding and not readily available in most primary prevention settings. The application of such tests should accordingly be reserved to patients that will benefit from deeper phenotyping in assessing their cardiovascular risk. The circulating biomarkers are superior in accessibility compared to all imaging modalities. Although easy to measure, the interpretation of biomarker measurements demands insights into the biology and mechanisms underlying expression and release of the biomarker. With knowledge about clinical characteristics and comorbidities that associate with higher concentrations of the biomarker, the physician can get a wide range of information about cardiac structure and function, in addition to cardiovascular risk. Both cardiac troponins and BNP have been demonstrated to correlate with specific cardiac imaging indices. In the general population higher concentrations of cardiac troponins are known to be significantly related to greater LV mass [83*] and LV dysfunction [83] [84] [85]. As for BNP, higher concentrations associate with a number of measures of LV structure and function [86], and in agreement with the hypothesized release mechanisms by cardiomyocyte stretch, the strongest correlate seems to be measures of diastolic dysfunction and wall stress [87, 88] Thus, the use of these cardiac biomarkers as a first-line screening tool may guide more effective use of echocardiography and CMR in assessing asymptomatic LV dysfunction. In addition to this, several studies have demonstrated an association between elevated levels of cardiac biomarkers and ischemia, even in the stable setting. Although results are diverging, elevated concentrations of cardiac troponins seems to reflect reversible ischemia [89][90][91][92] [93][94], and this association seems to be independent of LV mass [92*]. A similar association to ischemia for BNP has also been demonstrated, particularly among those with a history of myocardial infarction. [95]

5.0 COMBINING CARDIAC IMAGING AND CARDIAC BIOMARKERS IN RISK PREDICTION

The cardiac imaging modalities and circulating biomarkers included in this review are all prognostic markers. A few studies have tried to determine which imaging modality is the most powerful predictor of risk, and whether biomarkers add incremental prognostic information. Investigators from the MESA study aimed to compare CAC score, carotid cIMT, ankle-brachial index, brachial flow-mediated dilatation and CRP on top of the Framingham Risk Score in predicting risk of coronary heart disease [13**]. They found that

CAC score provided the best discrimination and risk classification compared to the other markers (**Figure 1**). The same superior finding of CAC score was done in the Rotterdam Study, where also NT-proBNP improved risk prediction (but to a lesser extent) [96]. A community study from Denmark demonstrated that NT-proBNP, and not CRP, predicted CV events after adjusting for measures of echocardiographic measures of LV structure and function [97]. The combination of NT-proBNP and E/e' may additionally identify those patients at highest cardiovascular risk [98]. Similarly, cardiac troponins have been demonstrated to provide incremental prognostic information on top of both measures of cardiac structure and function, as well as BNP and CRP [52, 83, 99*]. Finally, it is critical to appreciate the incremental value of adding biomarkers to a model. Although each of the biomarkers are excellent predictors of risk, the combination of these will not necessarily improve the prognostic performance. This relates to the degree of collinearity and is illustrated in a simulation by M. Pencina, PhD, Boston University[100] (**Figure 2**). A moderate biomarker correlation of r=0.40 require >50 biomarkers to increase the C-statistics by 0.05. In contrast, with a weak biomarker correlation of r=0.05, <10 biomarkers are needed to raise the C statistic by 0.05, which is considered a substantial improvement in prognostic accuracy.

6.0 CONCLUSION

Numerous imaging modalities and biomarkers assays have been studied in association with future cardiovascular events and detection of subclinical disease in subjects without established cardiovascular disease. CAC is a highly sensitive test for CAD and is recommended by current guidelines for risk assessment in asymptomatic low to intermediate risk individuals where risk-based treatment decisions are uncertain. CCTA is less frequently utilized in primary prevention although the test has a high specificity for CAD and accurately identifies plaque morphology and allows quantification of obstructive disease. SPECT-MPI is an accurate functional test for reversible ischemia that should be reserved for patients with suspected CAD given the resources required for the examination. In contrast, cIMT is a quick and readily available test for detection of atherosclerosis, and the measurement provides important prognostic information. Circulating concentrations of cardiac troponin is a robust predictor of future cardiovascular events, and correlate strongly with measures of cardiac structure in the general population. Elevated levels of BNP correlate with measures of cardiac function in the general population and associate with cardiovascular risk, specifically for

incident heart failure. CRP is an unspecific marker of inflammation that associates with the risk for incident CAD in the general population, presumably reflecting the progress of atherosclerosis.

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6.1 EXPERT OPINION

Although not strongly recommended by current European or US guidelines [2, 3], the application of cardiac imaging and circulating biomarkers in primary prevention is expected to increase during the next decade with the shift towards cardiovascular precision medicine [101]. However, it appears to be a widening gap in the pace of technological development in medicine and implementation in clinical practice. The incorporation of novel imaging modalities and measurement of biomarkers with high sensitivity assays will enhance personalized medicine and could play a central role in the next generation of primary prevention. Additionally, biomarkers are increasingly used for several purposes in clinical trials, including diagnostics, monitoring, safety, risk enhancement and surrogate endpoint, as recently reviewed by Arrigo and Gayat [102].

There is convincing evidence that certain imaging indices and circulating biomarkers can provide incremental value in risk assessment (prognosis) and identification of subclinical disease (diagnosis) in subjects without known cardiovascular disease. Among imaging modalities, CAC seems to be particularly powerful in predicting future CAD in the general population. In light of the recent randomized clinical trials on aspirin in primary prevention, the identification of subjects at particularly high risk of CAD where the benefit of the treatment outweighs the risk of bleeding is critical [103]. CAC may be a useful test in selecting these patients [18]. Still, clinical trials are warranted to estimate the net cost-effectiveness of primary prevention using a CAC strategy. For cardiovascular biomarkers, cardiac troponin measured by high-sensitivity assays appears to be the most robust in predicting cardiovascular death, while natriuretic peptides are particularly important in predicting incident heart failure. Thus, these biomarkers are complementary and may both provide clinically relevant information in primary prevention. The cardiovascular biomarkers have been shown to be especially useful in ruling out cardiovascular disease and concentrations within the normal range have a high negative predictive value. Given the availability and low cost associated with measuring circulating biomarkers in primary care, we suggest a four-step strategy for primary prevention in the era of precision medicine

(**Figure 3**). *Step 1* includes a thorough assessment based on clinical examination, medical history and environmental exposures according to current guidelines and risk scores. Based on the findings in the first step, patients with elevated cardiovascular risk or findings that are suspicious of subclinical cardiovascular disease should have cardiovascular biomarkers, including at least cardiac troponin and natriuretic peptides, measured in *Step 2*. The need for non-invasive cardiovascular imaging (*Step 3)* should be decided based on traditional risk assessment in Step 1 together with concentrations of cardiovascular biomarkers (Step 2, potentially adjusted for age, sex, race and renal function). The selection of modality depends on the individual risk assessment. *Step 4* includes more advanced imaging and possibly invasive examination and intervention according to current recommendations based on findings from non-invasive testing.

We believe the approach of integrating circulating biomarkers and imaging by using circulating biomarkers to identify subjects that need extended work-up with non-invasive cardiac imaging is a novel and possibly cost-effective approach in this regard, but this approach will need to be validated in clinical studies before introduced into clinical practice. The results from this thorough risk assessment can be used in preventive efforts tailored for each individual, including life-style interventions, pharmaceutical therapy and intensity of monitoring.

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Figure 1. Receiver-operating characteristics (ROC) curves demonstrating the incremental value of coronary artery calcium score, carotid intima-media thickness, brachial flow-mediated dilatation, C-reactive protein, family history and ankle-brachial index.
Adapted with permission from JAMA 2012 Aug 22;308(8):788-95, *Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals*, by Yeboah et al.

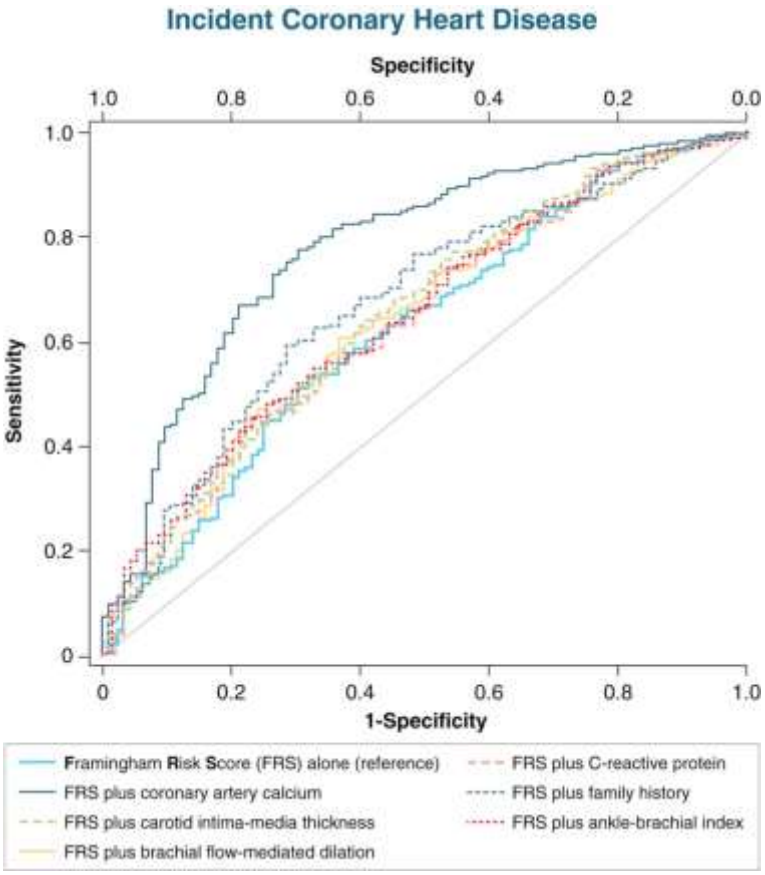

Figure 2 Increment in discrimination from adding hypothetical biomarkers, according to the degree of marker-marker correlation (r). The simulated hazards ratio for the outcome is 1.35 per SD increment in the biomarker. The y axis shows the C statistic from a model containing traditional risk factors plus a variable number of simulated biomarkers (x axis), each with a fixed association with the outcome. The simulation was performed by Michael Pencina, Boston University © 2007.

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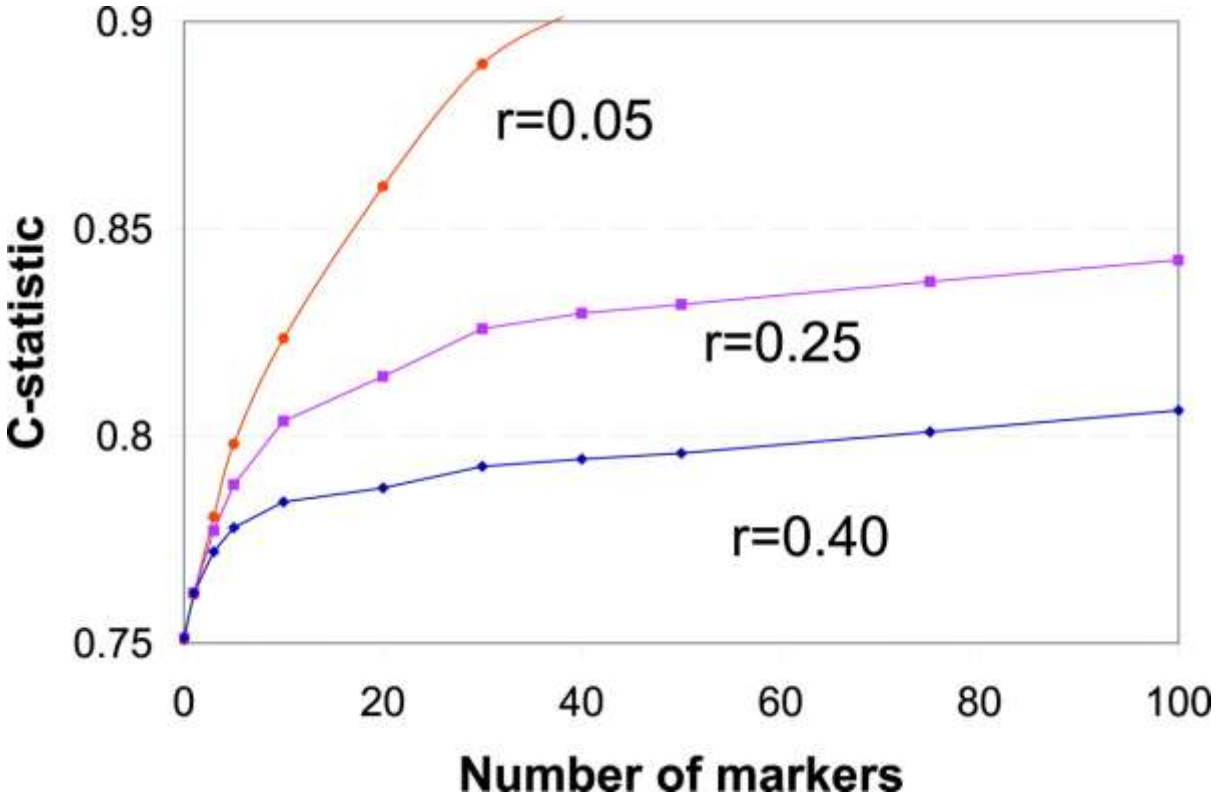

Figure 3. A suggested four-step strategy for primary prevention in the era of precision medicine