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Biomarkers of Atherosclerosis: Clinical Applications

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Abstract

Current cardiovascular risk prediction models incorporate traditional risk factors to estimate 10-year cardiovascular risk. Numerous blood-based biomarkers have been identified which are associated with increased cardiovascular risk after adjusting for traditional risk factors. Many of these biomarkers, either alone or in combination, have been incorporated into risk prediction models to determine whether the addition of these markers increases the predictive ability of the model. We review the recently published literature on blood-based biomarkers and examine whether incorporation of these markers might improve clinical decision making.

Introduction

Traditionally, risk prediction models incorporate demographic and clinical variables like age, gender, blood pressure, cholesterol levels, diabetes status, and smoking status to risk-stratify individuals with known or suspected cardiovascular disease (CVD) [1,2]. Although these models perform well on a population basis, they misclassify some individuals and, having been designed with a 10-year time horizon, underestimate long-term cardiovascular risk [3]. Therefore, identifying new variables which, when used in addition to traditional risk factors, could improve the risk stratification of those with known or suspected CVD is of interest.

Numerous biomarkers independently predict cardiovascular events when added individually to models containing traditional demographic and clinical variables. Recently, investigators have attempted to construct multi-marker risk prediction models, incorporating traditional risk factors and multiple biomarkers simultaneously. In this paper, we review the most recently published literature investigating blood-based biomarkers used either individually or as part of multi-marker risk prediction models for the risk stratification of individuals with known or suspected CVD. Additionally, we examine whether incorporation of these biomarkers assists with clinical decision making.

Assessment of the Predictive Ability of a New Biomarker

Prior to reviewing the data on individual biomarkers, we will summarize the recent controversy about assessing the utility of a new biomarker. Traditionally, most investigators have used multivariable modeling to determine whether a biomarker is independently associated with cardiovascular events after adjusting for traditional risk factors. Once this association is

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demonstrated, the next logical step is to investigate the degree to which this biomarker improves the overall predictive ability of the model. This is usually accomplished by calculating the area under the receiver operating characteristic (ROC) curve, also known as the c-statistic, for the model containing only traditional cardiovascular risk factors and then again after the biomarker is added to the model. If the c-statistic increases significantly after the addition of the biomarker, inclusion of the biomarker is said to increase the overall predictive ability of the model [4]. However, the sole reliance on changes in the c-statistic to evaluate the utility of biomarkers has been questioned [5].

Two important properties to consider when evaluating the overall predictive ability of a model are discrimination and calibration. The area under the ROC curve assesses model discrimination, which evaluates how well the model differentiates between individuals with and without disease. This is useful to evaluate the utility of a diagnostic test when the disease is either present or not present currently; however, the c-statistic may not be as useful in evaluating models that stratify individuals into groups of various risk for future events [5]. Cook indicates that an odds ratio (OR) of 3 may not be large enough to significantly increase the c-statistic, but it could be the difference between someone having a risk of 8% (low risk) and 24% (high risk) and would likely alter treatment [5]. So, Cook argues that model calibration and reclassification are important and often overlooked properties of predictive models. If individuals are not reclassified into different risk strata with the addition of a new biomarker, the biomarker will not change management decisions. Calibration evaluates how well the predicted probabilities from the model for each of these risk strata agree with the actual observed risk in each subgroup [5]. Despite the limitations outlined by Cook [5], most studies to date have relied solely on the c-statistic to investigate the utility of new biomarkers.

Lipoproteins

Recently, a consensus conference convened to discuss lipoprotein management in patients with cardiometabolic risk [6]. Although low-density lipoprotein cholesterol (LDL-C) remains the primary target of therapy, the measurement of apolipoprotein (apo) B is receiving increasing interest as a summary measure of atherogenicity of plasma and as a treatment target. In addition to LDL, apo B is present on chylomicrons, very low- and intermediate-density lipoproteins, and lipoprotein(a), all atherogenic particles. Many, but not all, previous studies in middle-aged populations demonstrated that apo B was superior to LDL-C in predicting cardiovascular risk [7,8]. However, a recent analysis from the Bogalusa Heart Study suggests that non-high-density lipoprotein cholesterol (HDL-C) measured in childhood performs as well as apo B in predicting subclinical atherosclerosis in adulthood [9]. Recently, increased attention has been directed at the apo B:apo A-1 ratio. After a median follow-up of 15 years, the apo B:apo A-1 ratio predicted incident coronary heart disease (CHD) in 3,322 individuals in the Framingham Offspring Study (hazard ratio [HR] per standard deviation increase 1.39, 95% confidence interval [CI] 1.23-1.58 in men; HR 1.40, 95% CI 1.16-1.67 in women), adjusting for non-lipid risk factors [10]. In a nested case-control study of 2,380 individuals enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study, the apoB:apo A-1 ratio was associated with increased coronary artery disease (CAD) events after a mean follow-up of 6 years (OR 1.77, 95% CI 1.31-2.39), adjusting for the Framingham risk score [11]. However, in both of these studies, the apo B:apo A-1 ratio did not improve the c-statistic and did not improve the reclassification of individuals when compared to the total cholesterol:HDL-C ratio, limiting the utility of apo B in settings where traditional lipid values are available [10, 11]. The consensus conference did, however, emphasize the utility of Apo B as it does not require fasting status and may be a good predictor of residual cardiovascular risk in patients receiving statin therapy [6]. Recommended apo B targets are <90 mg/dL for individuals with diabetes or 2 CVD risk factors and <80 mg/dL in those with known CVD or diabetes with an

additional CVD risk factor [6]. Routine lipoprotein(a) measurement was not recommend as its clinical utility was felt to be uncertain [6].

Inflammatory Markers

The predictive abilities of numerous inflammatory biomarkers have been investigated. Myeloperoxidase (MPO), stored in leukocyte granules and released with neutrophil activation [12], may have a role in cardiovascular risk prediction [13]. In a nested case-control study of 3,375 individuals in the EPIC-Norfolk cohort with a mean follow-up or 8 years, MPO levels in the highest quartile were associated with CAD events (OR 1.36, 95% CI 1.07-1.73) compared to those in the lowest quartile, adjusting for traditional cardiovascular risk factors [14]. Lipoprotein-associated Phospholipase A_2 (Lp-PLA_2) is a pro-inflammatory substance produced by monocytes, lymphocytes, and mast cells; 80% is bound to LDL-C, and 20% to HDL-C [12]. Garza and others meta-analyzed 14 studies investigating the association between Lp-PLA_2 and CVD [15]. After adjustment for conventional cardiovascular risk factors, elevated Lp-PLA_2 levels were associated with CVD (OR 1.60, 95% CI 1.36-1.89) [15]. In an additional study not included in the Garza meta-analysis, Ballantyne and others evaluated the ability of Lp-PLA_2 to predict ischemic stroke in 960 individuals using a case-cohort design in the Atherosclerosis Risk in Communities (ARIC) study [16]. Compared to individuals in the lowest tertile of Lp-PLA_2 levels, those in the highest tertile had increased risk for ischemic stroke after a mean of 4.4 years (HR 1.93, 95% CI 1.14-3.27), adjusting for traditional cardiovascular risk factors [16].

C-Reactive protein (CRP) is an acute phase reactant and inflammatory marker primarily produced by the liver in response to interleukin-1, interleukin-6, and tumor necrosis factor-alpha. Local production of CRP by cells in atherosclerotic plaques may also be possible [12]. Ridker recently summarized the large body of data supporting the use of a high-sensitivity CRP (hsCRP) assay to predict cardiovascular events [17]. Since 1997, hsCRP has been demonstrated to predict myocardial infarction (MI), ischemic stroke, cardiovascular death, incident diabetes, and incident hypertension in over 20 epidemiologic cohorts, including individuals with and without CVD and in those experiencing acute coronary syndromes (ACS) [17].

Most recently the prognostic significance of hsCRP has been evaluated in individuals with stable CAD. The Prevention of Events With Angiotensin-Converting Enzyme Inhibition (PEACE) trial randomized individuals with stable CAD to the angiotensin-converting enzyme inhibitor trandolapril or placebo [18]. Based on the hsCRP level, Sabatine and colleagues divided the PEACE trial participants into 3 risk groups, as defined by the Centers for Disease Control and Prevention and the American Heart Association: <1, 1-3, and >3 mg/L [19]. As expected, compared to individuals with a hsCRP level of <1 mg/L, individuals with a hsCRP level of 1-3 mg/L (HR 1.39, 95% CI 1.09-2.81) and >3 mg/L (HR 1.52, 95% CI 1.15-2.02) had an increased risk of the combined endpoint of cardiovascular death, MI, or stroke, adjusting for traditional risk factors [18]. Additionally, when compared to individuals with a hsCRP level of <1 mg/L, individuals with a hsCRP level of 1-3 mg/L and >3 mg/L each had increased risk for new-onset diabetes (HR 1.80, 95% CI 1.34-2.42 for hsCRP 1-3 mg/L; HR 1.96, 95% CI 1.43-2.68 for hsCRP >3 mg/L) and new-onset heart failure (HR 1.55, 95% CI 0.83-2.92 for hsCRP 1-3 mg/L; HR 2.83, 95% CI 1.54-5.22 for hsCRP >3 mg/L) [18].

Vidula et al evaluated the prognostic significance of CRP in patients with peripheral arterial disease (PAD) [20]. At 4 years of follow-up, each 50% increase in CRP level was associated with an increased risk of all-cause mortality (HR 1.14, 95% CI 1.05-1.24) and CVD mortality (HR 1.17, 95% CI 1.05-1.30) [20]. On further analysis, CRP was a significant predictor of mortality only during the first 2 years of follow-up, suggesting that elevated CRP levels may

effectively predict short-term cardiovascular risk, but not long-term risk, in individuals with PAD [20].

Data from the Women's Health Study suggest that the addition of hsCRP to standard Framingham risk factors improves the estimation of future risk [21]. In this large cohort of women free of baseline CVD, the addition of hsCRP to a risk prediction model containing only traditional Framingham risk factors had only modest effects on the c-statistic [21]. However, the predicted risk from the model with hsCRP included demonstrated closer agreement to the observed events during follow-up than did the model with only traditional Framingham risk factors [21]. Approximately 20% of women with an estimated 10-year CVD risk of >5% were reclassified with the addition of hsCRP. Importantly, those reclassified appeared to be reclassified more correctly into different risk strata [21].

Using data from 24,558 women without prevalent CVD in the Women's Health Study, Ridker et al developed the Reynolds Risk Score [22]. The score was developed using data from 16,400 of these women and was subsequently validated in the other 8,158 [22]. A total of 35 potential variables were analyzed and the final, most parsimonious model contained the 8 most clinically applicable variables that maximized cardiovascular risk prediction (age, hemoglobin A1C if diabetic, smoking status, systolic blood pressure, HDL-C, total cholesterol, parental history of MI <age 60, and hsCRP) [22]. The Reynolds Risk Score did not increase the c-statistic significantly when compared to traditional Framingham risk factors; however, among women at intermediate risk based on Framingham criteria, approximately 40-50% were re-classified [22]. Furthermore, for the majority of those reclassified, the observed event rate more closely resembled the predicted event rates after reclassification with the Reynolds Risk Score than those initially predicted by traditional Framingham risk factors, suggesting that the Reynolds Risk Score did produce clinically meaningful risk prediction in women beyond that provided by traditional Framingham risk factors [22]. However, the Reynolds Risk Score has yet to be validated in a separate cohort. This is particularly important as the Women's Health Study relied on participant self-report of many cardiovascular risk factors, thus adding "noise" to the traditional model and possibly resulting in misclassification of cardiovascular risk.

Coagulation Markers

Plasma fibrinogen levels are associated with increased cardiovascular risk [23]. Two recent studies from the Cardiovascular Health Study have concluded that this association is stronger in men than in women. After adjustment for traditional risk factors in 5,828 participants with and without baseline CVD, fibrinogen levels in the highest quartile were associated with death during the first year of follow-up in men (HR 4.11, 95% CI 2.66-6.35) compared with those in the lowest quartile but not in women (HR 1.31, 95% CI 0.79-2.15) [24]. After a mean of 9 years of follow-up, each standard deviation increase in fibrinogen among 4,510 individuals without baseline CVD was associated with cardiovascular events in men (HR 1.12, 95% CI 1.04-1.22) but not in women (HR 1.01, 95% CI 0.93-1.09) after adjustment for traditional risk factors [25] In the previously mentioned study by Vidula et al, elevated D-dimer levels, similar to hsCRP, were associated with mortality occurring less than 1 year after measurement (HR 1.20, 95% CI 1.08-1.33) and between 1 and 2 years after measurement (HR 1.14, 95% CI 1.02-1.27] but not with deaths occurring more than 2 years after biomarker measurement [20].

Cardiac Troponin-I

Cardiac troponins are used to establish the diagnosis of MI, assess the prognosis of individuals presenting with ACS, and select those most likely to benefit from early invasive management [26-28]. However, troponin elevations below the diagnostic threshold for MI, even in individuals without ACS, may signal the presence of CAD and increased future cardiovascular

risk. Schulz and colleagues evaluated the troponin-I values of 47 patients referred for elective coronary angiography, excluding individuals with recent rest angina or accelerating anginal patterns to avoid including individuals with persistently elevated troponins soon after an acute cardiovascular event [29]. Individuals underwent symptom limited bicycle stress testing prior to undergoing angiography with troponin-I measured before and after the stress test [29]. Troponin-I values did not increase following stress testing when compared to the baseline values [29]. When compared to individuals with coronary stenoses <50%, those with stenoses ≥70% had higher mean baseline troponin-I values (0.021±0.021 vs. 0.005±0.005 ng/mL, p<0.001) [29]. Using a troponin-I of 0.02 ng/mL as a diagnostic cut-point for the presence of a coronary stenosis ≥70%, elevated troponin-I correctly classified 65% of individuals, similar to the predictive accuracy of stress testing with imaging (70%) and better than the electrocardiogram recorded during stress testing (53%) in this cohort. This cut-point was far below the troponin-I value corresponding to the 99th percentile of a reference population (0.07 ng/mL) for this assay [29]. Similarly, using a different troponin-I assay, Agewall and others studied 468 consecutive patients admitted to the coronary care unit with suspected MI. Unadjusted mortality rates after a mean follow-up of 40 months in those with undetectable troponin-I was 5.9% compared with 23.2% (P<0.01) in those with detectable troponin-I values below the diagnostic threshold for MI, which for this assay was near the 99th percentile of a reference population [30]. These studies demonstrate that even mild troponin-I elevations, including levels below the 99th percentile of a reference population, may predict the presence of angiographic CAD and future cardiovascular events.

The above studies were performed in individuals with suspected CAD referred for coronary angiography or admitted to the coronary care unit for suspected MI, respectively. Zethelius and others have evaluated the prognostic significance of mildly elevated troponins in a cohort of 1,203 men with a mean age of 71 years [31]. A troponin-I value ≥0.04 mcg/L, corresponding to the 99th percentile of a reference population, was associated with an increased risk for all cause mortality after a median follow-up of 7.9 years in all individuals (HR 2.76, 95% CI 1.77-4.30) as well as only in those without baseline CVD (HR 2.12, 95% CI 1.06-4.22), adjusting for traditional risk factors [31]. Using a troponin-I of ≥0.04 mcg/L as a cut-point in those without baseline CVD, troponin-I correctly predicted mortality and incident CHD events in 80 and 85% of individuals, respectively [31].

Brain Natriuretic Peptide

Brain Natriuretic Peptide (BNP) is synthesized by and released from the ventricular myocardium primarily in response to myocardial stretch, but a variety of pro-inflammatory cytokines and neurohormones may also stimulate its release [32,33]. BNP and its amino-terminal fragment N-terminal pro-BNP (NT-proBNP) have been investigated as risk predictors in individuals with and without CVD. As recently reviewed by Omland et al, higher levels of NT-proBNP are associated with increased long and short-term mortality in individuals with stable CAD and in those presenting with ACS [33]. Recently, 3 studies have further examined the prognostic utility of NT-proBNP in patients with ACS. Khan et al examined the ability of NT-proBNP measured <24 hours after symptom onset in 473 consecutive patients with ST-segment elevation MI (STEMI) [34]. NT-proBNP levels significantly predicted mortality after a median follow-up of 272 days (HR 3.82 per 10-fold rise in NT-proBNP, 95% CI 1.89-7.78), adjusting for demographics, MI location, pharmacologic management, and troponin and creatine kinase levels [34]. The area under the ROC curve for NT-proBNP was greater (0.79) than for the TIMI risk score (0.67), suggesting that following STEMI, NT-proBNP levels may provide additional prognostic information beyond traditional clinical variables [34]. NT-proBNP may also predict risk in individuals with ACS and normal troponin values. In both the Bad Nauheim ACS and the Prognosis in ACS (PACS) registries, NT-proBNP levels >474 pg/mL were associated with increased mortality (HR 9.56, 95% CI 2.42-37.7 and HR 5.02, 95%

CI 2.04-12.33, respectively) after a mean follow-up of 213 and 173 days, respectively [35]. Windhausen and colleagues investigated whether NT-proBNP predicts benefit from a routine invasive strategy in ACS patients with positive troponins in the Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) trial [36]. Although increased levels of NT-proBNP significantly predicted mortality at 1 year (HR 5.0, 95% CI 2.1-11.6 for the highest quartile compared to the lowest 3 quartiles), NT-proBNP did not independently predict recurrent MI during follow-up nor did it identify individuals who benefit from routine invasive management [36].

NT-proBNP may also have prognostic utility in individuals with stable CAD. After a mean follow-up of 3.7 years, each 1 standard deviation increase in NT-proBNP was associated with an increased risk for cardiovascular events and death in 987 individuals with CAD in the Heart and Soul study (HR 2.3, 95% CI 2.0-2.6), adjusting for clinical risk factors, echocardiographic parameters, treadmill exercise capacity, CRP, troponin, and New York Heart Association classification [37]. Furthermore, the addition of NT-proBNP increased the area under the ROC curve for cardiovascular events from 0.76 to 0.80 ($p=0.006$) when added to clinical risk factors and echocardiographic parameters [37]. After a median of 4.8 years of follow-up, each 1 standard deviation increase in log(NT-proBNP) levels in 3,761 individuals with CAD enrolled in the PEACE study was associated with increased risk for cardiovascular mortality (HR 1.69, 95% CI 1.38-2.07), fatal or non-fatal congestive heart failure (HR 2.35, 95% CI 1.86-2.98), fatal or non-fatal stroke (HR 1.63, 95% CI 1.26-2.12), but not fatal or non-fatal MI (HR 1.02, 95% CI 0.87-1.19) after multivariable adjustment [38]. The addition of NT-proBNP to a model of traditional risk factors increased the area under the ROC curve for cardiovascular mortality from 0.74 to 0.77 ($p<0.05$) [38]. Similarly in the Heart Protection Study, which followed 20,536 people for an average of 5 years, increased NT-proBNP levels (highest quintile compared to lowest quintile) were associated with a 2.3 fold increased risk for cardiovascular death, MI, stroke, or revascularization ($p<0.0001$) after multivariable adjustment [39].

These results have been replicated in a general population-based sample. Olsen et al studied the prognostic value of NT-proBNP in 2,656 randomly selected individuals in Denmark, only 5% of whom had a prior MI or stroke [40]. After a median follow-up of 4.9 years, each 1 standard deviation increase in log(NT-proBNP) was a significant predictor of the composite endpoint of cardiovascular death, non-fatal MI, or non-fatal stroke (HR 1.56, 95% CI 1.33-1.83), adjusting for traditional cardiovascular risk factors, echocardiographic parameters, hsCRP, and the urinary albumin to creatinine ratio [40].

Cystatin C

Cystatin C, a novel marker of renal function, is more sensitive than serum creatinine in diagnosing mild reductions in glomerular filtration rate and is associated with increased cardiovascular risk [41,42]. Ix et al studied 990 individuals with stable CAD in the Heart and Soul study [41]. After a median follow-up of 37 months, compared to those in the lowest quartile, individuals with cystatin C levels in the highest quartile had an increased risk for all-cause mortality (HR 3.6, 95% CI 1.8-7.0), cardiovascular events (HR 2.0, 95% CI 1.0-3.8), and incident heart failure (HR 2.6, 95% CI 1.0-6.9), adjusting for traditional cardiovascular risk factors [41]. Maahs and colleagues investigated the association between cystatin C and progression in coronary artery calcium scores in 509 adults with type-I diabetes mellitus and no history of CVD [42]. After a mean follow-up of 2.5 years, each 1 standard deviation increase in cystatin C was associated with an increased odds of coronary artery calcium progression (OR 1.44, 95% CI 1.00-2.18), adjusting for age, baseline coronary artery calcium score, gender, diabetes duration, systolic blood pressure, and HDL-C [42]. Cystatin C was a better predictor of coronary artery calcium progression than serum creatinine or glomerular filtration rate as estimated by the Cockcroft-Gault or Modification of Diet in Renal Disease equations [42].

Multi-Biomarker Scores

Recent investigations have focused on the incorporation of multiple biomarkers simultaneously into traditional risk prediction models in an attempt to improve risk prediction. Table 1 summarizes the findings from these studies. In most of these, the addition of multiple biomarkers resulted in only modest, but statistically significant increases in the c-statistic for the prediction of cardiovascular events or death. The most recent study by Zethelius et al also assessed the reclassification of individuals using a multi-marker model [46]. Among those free of CVD at baseline, the use of the multi-marker approach resulted in the reclassification of approximately 30% of individuals, and reclassification more accurately predicted cardiovascular events during follow-up [46]. These results have resulted in cautious optimism about the clinical utility of biomarkers, but this cohort consisted of only elderly men and needs further validation in more diverse populations before changes in clinical management can be recommended [47].

Clinical Utility of Biomarker Assessment

To be clinically useful, biomarkers must change management. In the setting of biomarker elevations, intensification of therapy might be directed towards either reducing the biomarker itself, if the biomarker is thought to directly contribute to cardiovascular risk, or at traditional risk factors with more aggressive treatment targets. However, the data on biomarkers thus far have been limited to the assessment of cardiovascular risk, with no studies examining whether changing treatment plans on the basis of these data modifies this risk. One recent study may provide the first data demonstrating a benefit from intensifying therapy in response to an elevated biomarker. The Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial randomized 17,802 men ≥age 50 and women ≥age 60 without baseline CVD who had an LDL-C <130 mg/dL and a hsCRP ≥2mg/L to rosuvastatin or placebo [48,49]. The trial was recently stopped early due to benefit in the rosuvastatin arm [50]. The full results of JUPITER have yet to be presented or published, but it would appear that the results of this trial will indeed change clinical management, as individuals without prevalent CVD who might not otherwise have an indication for statin therapy but who are at increased cardiovascular risk due to an elevated hsCRP level may benefit from treatment with rosuvastatin. Whether this benefit results from a direct reduction in hsCRP levels or further lowering of LDL-C levels in the setting of hsCRP elevations is unknown.

Conclusions

Recently published literature demonstrates that elevated levels of numerous biomarkers are associated with increased cardiovascular risk, even after adjustment for traditional cardiovascular risk factors. To date, there are no published studies demonstrating that intensifying treatment in response to elevated biomarker levels leads to risk reduction, thus limiting the clinical utility of biomarker measurement in clinical practice. The recently terminated JUPITER trial may provide the first data to demonstrate benefit of a biomarker-guided treatment strategy and, if replicated, may change our approach to management of individuals with biomarker elevations in the future.

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Table 1

Overview of the Studies Evaluating the Effect on the C-statistic of Including Multiple Biomarkers in Addition to Traditional Cardiovascular Risk Factors in Risk Prediction Models

				C-Statistic		
	Cohort	**Biomarkers**	**Outcome**	**CV Risk Factors Alone**	**CV Risk Factors Plus Biomarkers**	**P-Value**
Blankenberg et al [43]	HOPE Trial	NT-proBNP, sICAM-1, IL-1Ra, fibrinogen	CV death, MI, or stroke	0.65	0.69	<0.001*
Wang et al [44]	Framingham Offspring Study	hsCRP, BNP, NT-proANP, aldosterone, renin, fibrinogen, PAI-1, D-dimer, homocysteine, UACR	All-cause Mortality	0.80	0.82	NS
Shlipak et al [45]	Heart and Soul Study	NT-proBNP, cystatin C, albuminuria, hsCRP, IL-6, fibrinogen	CV death, MI, or stroke	0.73	0.77	<0.005
Zethelius et al [46]	Uppsala Longitudinal Study of Adult Men	Troponin I, NT-proBNP, cystatin C, hsCRP	All-cause Mortality	0.60	0.68	<0.001

*Additional analyses suggested that most of the benefit was from the addition of NT-proBNP and that the inclusion of the remaining biomarkers offered no additional benefit.

BNP = brain natriuetic peptide, CV = cardiovascular, hsCRP = high-sensitivity c-reactive protein, HOPE = Heart Outcomes Prevention Evaluation, IL-1Ra = interleukin-1 receptor antagonist, IL-6 = interleukin-6, NT-proANP = N terminal pro-atrial natriuretic peptide, NT-proBNP = N terminal pro-brain natriuretic peptide, PAI-1 = plasminogen-activator inhibitor type 1, sICAM = soluble intercellular adhesion molecule-1, UACR = urinary albumin-to-creatinine ratio