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Cardiovascular biomarkers and their utility in the older adult

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Abstract

Cardiovascular disease is the leading cause of morbidity and mortality in individuals over the age of 65 yet diagnosis, risk stratification and management continue to be more challenging than in younger adults due to the vast heterogeneity seen in this population. The current literature validates the use of biomarkers in addition to traditional risk assessment tools in younger and middle aged adults. The evidence for biomarkers in this older population is sparse; this review examines the epidemiological association of current biomarkers in the field and the utility of these markers in the diagnosis, risk discrimination and management of cardiovascular disease.

Keywords

Biomarkers; Inflammation; Cardiovascular risk; Elderly; C-reactive protein; Aging; Heart failure; Cardiovascular disease

Introduction

Currently, 13% of the United States population is over the age of 65, including 1.8% aged 85 years or older (US 2010 Census data). However, as survival rates increase, individuals over the age of 65 are predicted to make up 19% by the year 2030, with 2.6% over 85. Prevalence of cardiovascular disease (CVD) among this burgeoning population of older survivors is extremely high, and is the most common cause of morbidity and mortality. Nonetheless, diagnosis, risk stratification, and management of CVD are more challenging in relation to advanced age. Symptoms are less specific and susceptibility to subclinical disease increases, both contributing to delays or omissions of vital therapy. Likewise, heterogeneity among elderly is vast; some experience a quiescent CVD whereas others have a fulminate course, but there remains little to predict which is likely and to guide the most appropriate therapeutic strategies. Adding to the challenge, therapy itself is more problematic with age; polypharmacy and iatrogenesis increase, and cost implications are often more challenging. Ideally treatments should only be administered when there will be unambiguous benefits relative to therapeutic risks. For all these reasons, increased diagnostic and risk discrimination for older adults are key management priorities.

The field of biomarkers has expanded rapidly as a possible means to improve management of CVD with obvious relevance to the challenges pertaining to older patients. “Biomarker” is a general term used to describe a wide range of biological parameters, from measurable substances such as enzymes or hormones to characteristics on physiologic testing such as vital signs or electrocardiograms, which can be used in the assessment of disease. More recently, the term biomarker has become associated particularly with the inflammatory cascade that underlies atherosclerosis pathophysiology, i.e., key constituents of this pathway can serve as markers of diagnosis and risk stratification.

Many practitioners currently base their assessment of cardiovascular risk on validated instruments such as the Framingham Risk Score [1]. These risk assessment tools have considerable substantiation as a means to discriminate high or low risk, but also often distinguish only intermediate risk, which fails to point toward clear management rationales. Furthermore, many traditional risk assessment tools were validated on patients in their 50’s and 60’s, and do not differentiate risk in units that are clinically relevant for older adults. The concept of a “10 year risk” that is found in the Framingham score is not, for example, relevant for the many older CVD patients who have already exceeded their life expectancy. Therefore, the field of biomarkers developed rapidly, spurred in large part by the need to respond to these clinical needs.

Inflammation and Biomarkers

Inflammation is now understood to be an elemental factor in the pathophysiology of CAD, and it thereby has been applied as basis of an extensive group of diagnostic and prognostic biomarkers. Even traditional cardiovascular disease risk factors are now understood to exert injurious effects primarily in terms of their impact on the inflammation.

Cigarette smoking, hypertension, hyperlipidemia and hyperglycemia, contribute to the progression of atherogenesis through initiation of the inflammatory cascade as a result of endothelial injury. Monocytes migrate and attach to the endothelial surface after leukocyte soluble adhesion molecules and chemotactic factors are released by these noxious stimuli. These monocytes then transition into macrophages, leading to uptake of circulating cholesterol and development of the fatty streak on the endothelial surface. Additional injury then leads to propagation of the cascade and activation of inflammatory cytokines and hepatic production of acute phase reactants, such as C-reactive protein (CRP). Over time, the repetitive activation of these cytokines leads to the development of atherosclerosis and plaque [2].

Activation of the inflammatory cascade is also responsible for intrinsic instability of the plaque and potential for thrombosis. The lipid rich, atheromatous lesion is protected by a fibrous cap. Activated monocytes as well as activated vascular smooth muscle cells trigger metalloproteinases, proteolytic enzmyes, which can disrupt the vulnerable fibrous cap. This exposes the plaque contents to blood which can lead to activation of platelets and thrombogenesis [3].

Impact of the proinflammatory state on endothelium-derived nitric oxide (NO) is also critical. NO normally counteracts many of the steps in the inflammatory cascade by inhibiting platelet activation, promoting vasodilation, reducing leukocyte adherence, and suppressing proliferation of vascular smooth muscle cells. CRP moderates activity and production of NO [3] essentially facilitating progression of atheroscrerotic pathophysiology

The presence of circulating factors generated along the causal atherosclerotic pathway are applied as convenient markers of ongoing inflammation and increased cardiovascular risk. Particular markers that have been studied in relation to cardiovascular disease include high sensitivity C-reactive protein (hs-CRP), interleukin-6, tumor necrosis factor-a, interleukin-10, cardiac troponin (cTn), brain natriuretic peptide (BNP), Cystatin- C, and fibrinogen.

CRP

The initiation of the inflammatory process following a stimulus such as tissue injury or infection through the release of cytokines that in turn cause the increased production and release of acute phase protein reactants by the liver is the mechanism that results in high levels of CRP[4–5]. As a biomarker it has a position along the causal pathway to atherosclerosis and is the most frequently studied and cited inflammatory marker in cardiovascular disease. It has a long half life, no diurnal variation, and standardized methods for the high sensitivity assay making it easy to measure in the clinical setting. Multiple epidemiological studies of middle aged populations have consistently shown independent increased primary and secondary risk of cardiovascular events with elevated levels of CRP[6–7]

The American Heart Association stratifies cardiovascular risk into tertiles based on hs-CRP levels, i.e., low, average, and high-risk based on hs-CRP <1, 1 to 3, and >3 mg/L respectively. While an elevated level above 10 mg/L should initiate a search for a source of infection or inflammation.

There are far fewer studies that focus specifically on the predictive value of CRP in older adults. CRP measured in nested case control of participants in the Cardiovascular Health Study did not show statistically significant associations with incident cardiovascular disease across the whole group but did predict future events in women with CRP levels in the highest quartile with an odds ratio of 2.3 for all events and 4.5 for incident myocardial infarction [8]. Increased mortality in older women with levels of CRP >3.0 mg/L was also demonstrated in a case-cohort study within the Study of Osteoporotic fractures [9].

In a study of 3,045 individuals aged 70–79 from the Health ABC study, CRP exhibits only a weak association with CVD when compared to measured Il-6 and TNF-α [10]. Furthermore, there is no statistically significant increase in risk after adjusting for other CVD risk factors and no evidence of the previously shown gender interaction described in the Cardiovascular Health Study cohort. In another study of older men and women a single CRP measurement provides additive risk assessment for 10 year incidence of cardiovascular disease regardless of standard risk factors and may be beneficial for men that have an intermediate

Framingham risk score [11], whose risk increased from 10–20% to an observed incidence of 32% if the hs-CRP was measured over 3mg/L .Serial measurements over time and hence increasing or stable hs-CRP levels did not add any increased value to prediction as compared to a single value of hs-CRP. In the CHS All Stars study, a doubling of biomarker levels over a 9 year period, was associated with higher physical and cognitive impairment [12].

The utility of measuring hs-CRP in individual older adults is confounded by the fact that many non-cardiovascular factors also affect levels of CRP in this population. Chronic diseases (e.g., cancer and rheumatologic conditions) and medications (e.g., oral hormone replacement therapy[13]) can elevate levels of CRP. Lifestyle habits are also pertinent since increased physical activity can lower CRP levels[14]. The niche that hs-CRP may fulfill in clinical practice relates to its negative predictive value, i.e., prognostic implications of identifying individuals at reduced risk with very low levels of measured CRP (<0.5 mg/L)that have a markedly reduced risk of incident CVD over the full range of Framingham risk scores[15].

Il-6

The cytokine Il-6 is an important modulator of immune cells and is closely associated with CRP levels in cardiovascular disease. In older adults it is not only a marker of cardiovascular disease but to syndromes that preferentially affect the elderly such as anorexia, muscle wasting and anemia, and which are therefore confounders of cardiovascular outcomes.

Although Il-6 has not been assessed to the same magnitude as CRP, the relatively smaller body of literature suggests it may be a relatively better predictor of CVD. In the health ABC study individuals aged 70–79 with Il-6 levels in the highest tertile as compared to the lowest had an odds ratio of 1.58 for subclinical disease and 2.35 for clinical CVD. This association remained significant even when adjusted in the overall analysis in comparison to CRP [10]. The Women's Health and Aging Study also showed the predictive value of the highest tertile of Il-6 in women over the age of 65 with and odds ratio for cardiovascular mortality of 2.5 with levels over 3.1pg/ml[16]. The long term impact of Il-6 over time was examined in the Cardiovascular Health Study All Stars where a doubling in levels over time independently predicted CVD events [12]. Compared to CRP, Il-6 is not affected by oral hormone replacement therapy but can be acutely elevated following exercise.

However, in spite of its overall efficacy, standard laboratory techniques and range measurements for Il-6 are not well-defined, and despite much promise, it is still not a recommended tool.

Other markers

TNF-α is a central participant in the inflammatory cascade. It is chiefly produced by activated macrophages but can be produced by multiple cells and can bind to two different receptors. It is able to induce fever, apoptotic cell death, the sepsis response (through IL1 & IL6 production), cachexia and inflammation. As a biomarker for CVD it has been infrequently studied, however, it does tend to show a significant association between elevated levels and coronary artery disease [10]. In carotid artery atherosclerosis the

association between carotid plaque, TNF-α and its corresponding receptors 1 and 2 were found to be significant below the age of 70 years [17].

Fibrinogen although not technically an inflammatory biomarker is often found to elevated in response to stimuli of the inflammatory cascade and hence is often measured alongside other biomarkers where its levels can be considerably elevated. It shows similar correlation to cardiovascular disease as the previously mentioned biomarkers and tends to be highly sensitive albeit far less specific.

In addition to inflammatory biomarkers, chronic kidney disease also carries a substantial risk for cardiovascular morbidity and mortality. In the Cardiovascular Health Study renal insufficiency as defined as creatinine level over 1.5 mg/dl for men and 1.3 mg/dl for women was associated with a hazard ratio of 1.95 for CVD death in an adjusted model [18]. Cystatin-C is a low molecular weight protein that is removed from the blood stream by glomerular filtration and consequently as kidney function declines the levels blood levels increase. It is not as affected by age, sex, race and muscle mass and therefore is a more sensitive and precise test of kidney function that creatinine alone. Consistently, an analysis of Cystatin-C demonstrated its efficacy as a as a marker for disease. Analyzing 4663 elderly individuals without chronic kidney disease, those with cystatin-C concentrations over 1.0mg/l had a 4 fold risk for progressing to chronic kidney disease and a hazard ratio of 1.4 for cardiovascular death[19].

BNP and Troponin

Although brain natriuretic peptide (BNP) and cardiac troponin (cTN) are not in the same inflammatory realm as the previously discussed biomarkers, their use is prevalent in main stream clinical practice as a marker of myocardial stress and damage.

BNP and the N-amino terminal fragment of pro BNP (NT-proBNP) are released predominantly in response to left ventricular wall stress. Elevated plasma levels of these peptides are found during acute coronary syndromes and in acute and chronic heart failure and are a standard of care measurement in the inpatient and outpatient setting. In the acute setting BNP has shown to have prognostic value for left ventricular systolic function and long term survival following an acute MI[20]. In chronic heart failure BNP is an independent predictor of mortality and were found to be three times higher in non-survivors as compared to survivors[21]. There are fewer studies that have compared the predictive value of BNP in older adults. Circulating BNP was measured in a cohort of individuals over the age of 85 and was found to predict mortality in individuals with and without cardiovascular disease[22]. A second study assessed the prognostic value of NT-proBNP as compared to CRP and urinary albumin/creatinine ratio in nonhospitalized participants aged 50–89 years and was found to have a stronger association with first cardiovascular event, presence of cardiovascular disease and death than CRP and urinary albumin/creatinine ratio[23]. A more recent large meta-analysis looked at age stratified NT-proBNP levels and echocardiographic evidence of LV systolic dysfunction. Age groups were analyzed separately and the association between LV systolic function and NT-pro-BNP was found through all ages groups although sensitivity, specificity and receiver operator curve characteristics were reduced with

increasing age[24]. The study reported that the niche for NT-proBNP might lie in the high negative predictive value and could be a means to rule out LV systolic function in older adults.

Troponin is a three unit complex of proteins, troponin C (TnC), Troponin I (TnI) and Troponin T(TnT) that when activated by calcium play an integral role in contraction of the muscle. Cardiac TnC is indistinguishable from the skeletal isoform so is not used in the disgnosis of myocardial ischemia, whereas cardiac TnI (which has one isoform) and TnT (which has several isoforms) are highly specific for myocardial necrosis and damage. Elevated levels of circulating cardiac troponin (cTN) have been used as a diagnostic biomarker for myocardial damage and are central to the definition of acute myocardial infarction [25]. Plasma levels of troponin have been found to be associated with renal failure, left ventricular hypertrophy, myocarditis and mortality on acute and chronic heart failure. The prognostic value of an elevated troponin level has even been shown to predict first hospitalization for cardiovascular disease and death for apparently healthy older adults in a community cohort[26]. Further analysis of this same cohort revealed that males aged 70 that were followed for approximately 11 years had a hazard ratio of 5.25 for first hospitalization for heart failure in a multivariate analysis if their cTN was found to be > or = 0.03 mcg/L as compared to < 0.03mcg/L[27].

The combined biomarker

The majority of studies have generally evaluated the value of each biomarker singly and its role in predicting cardiovascular disease. Just as individual traditional risk factors may play unequal parts in their pathway to pathological disease development in each patient, individual biomarkers may also contribute to the heterogeneity of disease; the biomarker that predicts risk in one patient may not be the same as in another patient. Data collected from 4,900 adults in the National Health and Nutrition Examination Survey (NHANES) evaluated the combination of CRP, homocysteine and insulin sensitivity (homeostatic model assessment (HOMA) fasting insulin) and CVD. The study found that concomitant elevated levels of CRP, homocysteine and HOMA revealed a more significant relationship with disease than individual biomarkers alone. Pooling 3 biomarkers CRP, Il-6 and TNF-α as compared to individual inflammatory markers at baseline revealed a significant trend for the additive value of predicting incident heart failure in older adults with HR 1.26, 1.65 and 1.76 for each additional elevated biomarker from 1,2 and 3 respectively[28].

Biomarkers for biological age

The interest in using a biomarker of biological age rather than using chronological age for risk assessment and prediction has been hotly pursued in the cardiovascular field where risk assessment scores discriminate poorly between older adults and therefore provide little perspective on significant differences in prognosis. This has direct bearing on management choices, since it misses an important opportunity to tailor therapy relative to the needs of individual patients.

Biomarkers may, for example, provide a robust way to characterize and quantify pertinent aspects of frailty. Frailty is a phenotype defined by the investigators of the Cardiovascular Health Study which is highly prevalent in the aging population and which confers an increased risk of hospitalization, institutionalization and mortality [293031]. It describes increased vulnerability to stressors that create a downward spiral of disability, morbidity and mortality. Interest in frailty has broadened beyond geriatrics to many aspects of cardiovascular care, including surgery. Frailty has been used to make pre-operative identifications of high risk older patients undergoing general [32–33] and cardiac surgical procedures [34] . The syndrome of frailty appears to be associated with a pro-inflammatory, catabolic and sarcopenic state.

In community-dwelling older adults increased levels of catabolic cytokines such as Il-6 and TNF-α along with increased sarcopenia are linked to increased mortality whereas circulating levels of IG-F 1 has the opposite effect [35–36]. Individuals that meet criteria for frailty have been shown to have elevated levels of CRP, Il-6 and TNF-α in cross-sectional analysis [28, 37] Leptin, a hormone produced in adipose tissue and in high circulating levels, has been found to be associated with obesity. Conversely, in frail individuals low leptin levels are common in conjunction with high Il-6, CRP and low albumin [38]. Nonetheless, the role of biomarkers for predicting frailty among individuals with cardiovascular disease has not been established and routine measurement is not recommended.

Another marker of biological age that has been used recently in epidemiological studies is telomere length. Telomeres are highly conserved tandem repeats found at the end of chromosomes that allow cells to divide without the loss of DNA sequences during cell division. There is a balance over time between creation of these lengths of nucleotides by telomerases and by shortening through replication and cellular damage. Over time, telomeres eventually reach critically short levels and at this point cells are unable to replicate without losing critical information and the cell becomes senescent. An individuals telomere length is influenced by genetics[39], gender, oxidative stress (smoking, cytokines, obesity, radiation, diabetes) and age itself[40–43], all of which also have an influence on cardiovascular risk. Telomere length has been shown to be associated with hypertension [43], atherosclerosis [44], heart failure [44] and aortic valve stenosis[45]. Nonetheless, many limitations to telomeres as biomarkers have been described, the many different techniques for measuring telomere length and telomerase activity are each either only able to provide comparative values or only measure a discrete range. Furthermore, assessments relying on peripheral blood leukocytes may not represent telomere length in other cell types elsewhere in the body. Other limitations relate to error inherent in assessment of cross-sectional measurements for what is a long term longitudinal biologic process; a variety of factors typically confound sampling and measurement [46–47].

Cellular senescence has also been characterized in other ways, with the hope that markers other than telomeres may be discovered and applied clinically. Many cells have the intrinsic capacity of secreting of cytokines, growth factors, proteases and other proteins that are used to limit tumors during youth, but which may accumulate abnormally as a function of age. Markers such as p21, p19, Pai1, p16INK4a, TGF-β, Senβ-gal have been measured in

different cell types and are being investigated as markers or even the determinants of cellular aging dysfunction[48].

AHA/ACC Guidelines

The clinical utilization of these novel inflammatory biomarkers for evaluation of cardiovascular disease risk increased as commercial assays became available and the number of peer reviewed papers depicting their predictive value expanded. As a consequence of this the Center for Disease Control (CDC) and the American Heart Association (AHA) in 2002 convened a workshop to discuss how these markers should be measured and used in clinical practice. In 2003, the AHA published the scientific statement on consensus guidelines to support the use of these studies in addition to other established risk assessment tools. However, in the absence of robust data, there were no Class I guidelines to support the use of inflammatory markers. The consensus statement is that there is a Class IIb indication to use hs-CRP to assist in evaluating intermediate risk patients. This recommendation likely stems from the presence of the large body of data to support the use of this biomarker compared to the others.

There are many studies in middle aged populations that identify high risk individuals as well as using biomarkers to risk stratify those that will benefit from interventions. Specifically, CRP has been identified in large population based studies to be associated with increased risk of cardiovascular disease. The finding was first described in the Physicians' Health Study which showed an association with elevation in baseline hs-CRP and risk of myocardial infarction (MI) or stroke in men [49]. Similar findings were reported in women with baseline CRP as well as IL-6, SAA, and sICAM-1 in the Women's Health Initiative [13] Both short and long term follow-up in the Honolulu Heart Study also revealed increased risk of MI with elevated CRP[50].

While CRP was identified as a marker for increased risk of cardiovascular events, it was still unclear whether elevated CRP still identified risk among adults that lacked traditional risk factors. The Justification for the use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) addressed this question. Men over the age of 50 and women over the age of 60 without a history of cardiovascular disease and with an LDL < 130 and elevated CRP were randomized to either rosuvastatin or placebo. The trial was stopped early as an apparent benefit in reduction in LDL and CRP as well as a decreased rate of first major cardiovascular event, the combined primary endpoint of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure, confirmed death from cardiovascular causes was established. These findings suggested there was an additional benefit to rosuvastatin, and potentially a class effect of all statins, in reducing inflammation and in turn reducing cardiovascular events. Nonetheless, its also not entirely clear if beneficial effects of rosuvastatin were from changes in inflammation or from its potent LDL-lowering effects. Furthermore, Jupiter excluded adults with diabetes and other common comorbidities; generalizability of these results to more typical older adults (among whom inflammation may be exacerbated by comorbidity) also remains uncertain.

Conclusions

While current literature substantiates value of biomarkers in addition to traditional risk assessment tools in younger and middle aged adults, their utility for older adults is not as clear. An association between inflammatory markers and cardiovascular disease is often present but with poor specificity. However, the rapid growth of an older population that is inherently at risk for cardiovascular disease essentially mandates further research in this area. Biomarkers loom as a potential means to better risk stratify risk among the heterogeneous population of elderly, and to thereby guide therapy in manner that is both optimally safe, effective, efficient, and valued.

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