

Use of BNP and CRP as Biomarkers in Assessing Cardiovascular Disease: Diagnosis Versus Risk

Virginia M. Miller^{1,*}, Margaret M. Redfield² and Joseph P. McConnell³

Departments of Surgery, Physiology and Biomedical Engineering¹, Internal Medicine, Division of Cardiology² and Laboratory Medicine and Pathology³, Mayo Clinic Rochester, Rochester, MN 55905, USA

Abstract: Biomarkers are used in medicine to facilitate diagnosis, assess risk, direct therapy and determine efficacy of treatment. Sensitivity and specificity are essential in order for a biomarker to be useful. Brain natriuretic peptide (BNP) and C-reactive protein (CRP) are considered biomarkers of cardiovascular disease. However, they differ in function, sensitivity and specificity. BNP is released from the myocardium in response to myocardial stretch, a clear cause and effect relationship; therefore, it is useful in the diagnosis of heart failure when patients present with dyspnea of unknown origin and to assess treatment in high risk patients with diagnosed heart failure. Sex and age based reference ranges and partition values are established from clinical trials and from populations screened for the absence of cardiovascular disease. Highly sensitive and reproducible methods are also available to measure CRP. However, although CRP is associated with adverse cardiovascular events, unlike BNP, multiple stimuli increase production of CRP. Therefore, elevation in CRP is not specific to cardiovascular disease. Partition values for CRP and cardiovascular risk based on epidemiological studies predict risk for populations but may not always be useful when used alone to predict individual risk or to direct therapy. Given the non-specific stimuli which affect circulating concentrations of CRP, using CRP to monitor treatment to reduce cardiovascular risk may provide little benefit without understanding or targeting the underlying causes for its elevation.

Keywords: B-type natriuretic peptide, BNP, coronary artery disease, C-reactive protein, CRP, estrogen, heart failure, hormone replacement therapy.

INTRODUCTION

Biomarkers are measurable parameters that provide assessment of biological function. In clinical medicine, biomarkers are used to assess functional processes, assist in diagnosis, determine efficacy of treatment, and assess or predict risk of an adverse event so that therapy can be directed to reduce the risk. Biochemical assays, biophysical measurements, anatomical or immunohistochemical evaluations and gene expression can be used to assess biomarkers. Assays should be sensitive within defined ranges, specific so as not to cross-react with several molecules, easy to perform, readily available, reproducible and cost effective. Regardless of the technique, a biomarker should accurately assess a set of conditions at the exclusion of others; that is, it should demonstrate disease specificity. Reference ranges should be defined by sex, age and perhaps, ethnicity, although few studies have evaluated biomarkers in defined ethnic groups and perhaps in the future by genotype. Brain-type natriuretic peptide (BNP) and C-reactive protein (CRP) are used to aid in the diagnosis of heart failure and to assess risk for adverse cardiac events, respectively. This review will compare and contrast these biomarkers in regard to their disease specificity and their usefulness in general medical practice.

BNP AS A BIOMARKER FOR THE DIAGNOSIS AND TREATMENT OF HEART FAILURE

Heart failure is a clinical syndrome characterized by a constellation of symptoms and signs ascertained during the medical history and examination, by findings present on the chest radiograph and by the response to therapy. While heart failure is associated with altered systolic and/or diastolic function, it is not synonymous with ventricular dysfunction as patients can have significant ventricular dysfunction in the absence of clinical heart failure. Heart failure can be difficult to diagnose in elderly patients, obese and de-conditioned patients and patients with underlying lung disease. Echocardiography can be used to assist in the diagnosis of heart failure. However, this tool has limitations. Often it is not available in the acute care setting. Further, many echocardiography laboratories do not characterize diastolic function during the examination and thus the clinician may not be alerted to the presence of diastolic heart failure. Indeed, 50% of patients with the clinical syndrome of heart failure have normal systolic function and in these patients, an abnormality in the diastolic function of the heart is responsible for the heart failure [1]. Therefore, a reliable and inexpensive diagnostic test is desirable to detect physiologic properties common to both systolic and diastolic heart failure.

BNP, a member of the natriuretic peptide family, is a 32 amino acid polypeptide synthesized as pre-pro-BNP which is cleaved to pro-BNP₁₋₁₀₈, then cleaved by furin to subsequently be secreted as the biologically active BNP₇₇₋₁₀₈ and the inactive N-terminal BNP₁₋₇₆ [2]. BNP is released from cardiac myocytes in response to increased stretch resulting

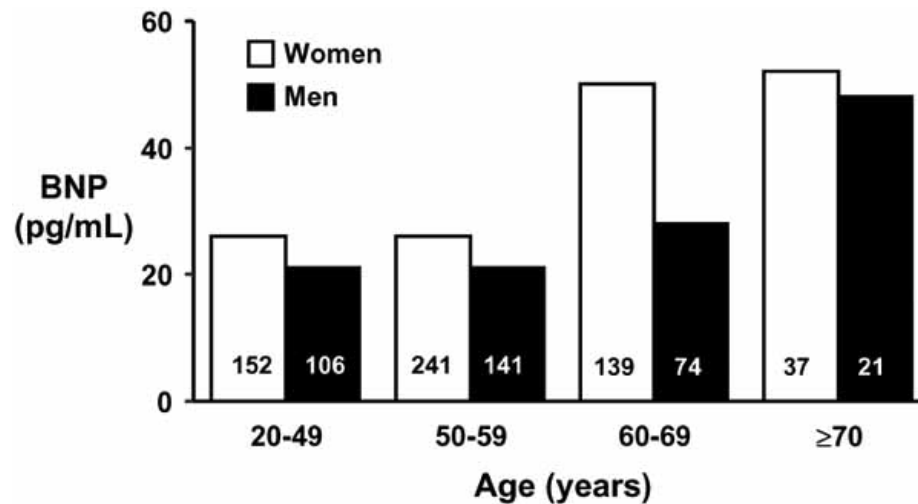
*Address correspondence to this author at the Medical Science Building 4-62, Mayo Clinic Rochester, 200 First Street, SW, Rochester, MN 55905, USA; Tel: 507-284-2290; Fax: 507-266-2233; E-mail: miller.virginia@mayo.edu

from high filling pressure, high arterial pressure or cardiac dilatation [3, 4]. Physiological actions of BNP act to reduce the adverse stimulus of stretch by causing both arterial and veno-dilatation and reduction in blood volume through natriuresis, and suppression of secretion of renin and aldosterone [5]. Therefore, the cause and effect relationship between stretch and release of BNP is established through basic science experiments and represents a classical physiological negative-feedback regulatory system. Although atrial natriuretic factor (ANP) is also released in response to atrial stretch, the biological half life of BNP (22 minutes) is longer than for ANP (2-5 minutes). Because synthesis of BNP requires activated gene transcription, concentrations of BNP may be stable in the blood for about 3 days. Therefore, the long half-life of BNP, the duration of the signal in the blood and established cause and effect relationship between stimulus and release of BNP make it an ideal candidate for a biomarker of heart failure. However, before BNP or any bio-

marker can be used clinically for indication of disease, it is necessary to establish reference values representative of individuals without the disease.

For reference, at the Mayo Clinic, individuals (n=767) were rigorously screened for the absence of cardiovascular, renal and pulmonary disease or diabetes (normal) by review of the medical records and Doppler echocardiography. Plasma concentrations of BNP increased with age (45-85 years) and both median and 95th percentiles were significantly higher in females compared to males [6]. In another healthy reference sample from the Framingham Heart Study (911 subjects, mean age 55 years with 62% women), plasma concentrations of BNP were also found to vary by age and sex [7] Fig. (1). Both of these independent studies support the need for both age and sex-based reference values for BNP used for clinical diagnosis. Similar data should be required in the development of other biomarkers as well and validated in relationship to ethnicity.

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1B)

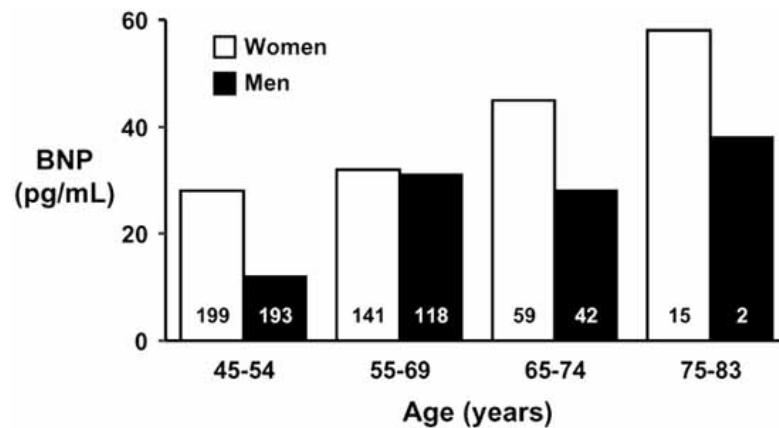


Fig. (1). Age and Sex-specific Reference values for plasma BNP (pg/ml) using the Shionogi Assay. Upper panel (1A). Data shown as 95th percentile upper limit for BNP in an offspring cohort of the Framingham study (derived from Table 4 of *Am J Cardiol* 2002; 90:254). Lower panel (1B). Data shown as median for BNP in a cohort of healthy residents of Olmsted County, MN (derived from Table 2 of *J Am Coll Cardiol* 2002; 40:976). Values inside of bars represent number of samples.

Numerous prospective clinical trials support that measurement of blood BNP aids in the diagnosis of heart failure in the acute care setting [8-10]. One definitive study, the Breathing Not Properly (BNP) study, was a prospective study of 1586 patients who presented in the emergency room with acute dyspnea [11]. BNP was measured in all of these patients. The accuracy of a diagnosis of heart failure made by an independent panel who had access to clinical and subsequent hospitalization data was compared to that of the admitting physician who did not have access to BNP data. BNP was significantly elevated in patients with congestive heart failure (Fig. (2)). Accuracy of the clinical diagnosis was 74% with 49% sensitivity and 95% specificity compared to an accuracy of 81% with 90% sensitivity and 73% specificity using BNP data with a partition (cut-off) value of 100 pg/ml [11]. Therefore, as a point of care assay for diagnosis of heart failure in patients presenting with dyspnea, suboptimal specificity reduced the overall accuracy of the test [12, 13]. In contrast, the clinical diagnosis by the emergency physician was specific but insensitive [11, 14].

Since BNP levels differ with age and sex in the reference population, the previously suggested partition value of 100 pg/ml, then, may not be suitable for all patients as the 95th percentile values for BNP in elderly females screened for the absence of heart failure exceeds 100 pg/ml [6, 7]. Further studies are needed to evaluate partition values relative to age and sex taking into account hormonal status [6] as BNP has not been routinely measured in postmenopausal women participating in any of the large hormone treatment trials [15, 16], nor has the impact of obesity been evaluated systematically. However, it has been argued that failing to treat cases

of heart failure in the acute setting is worse than treating negative cases and that in the acute care setting, BNP >100 pg/ml in a patient presenting with dyspnea may be appropriate regardless of age, sex, or ethnicity [17].

Extending the utility of BNP as a diagnostic marker to screen for asymptomatic or preclinical ventricular dysfunction (Stage B heart failure according to the ACC/AHA guidelines [18]) in the general population has not proved cost-effective as the prevalence of heart failure is low. However, if the test is used in patients stratified for risk using clinical criteria, BNP has proved useful to “rule out” ventricular dysfunction, thus eliminating the need for other more expensive diagnostic tests in this group [19]. Patients with diabetes may represent a sub-set of “at risk” individuals who might benefit from use of BNP as a screen for ventricular dysfunction [20]. In addition, in the outpatient setting, when added to the standard screening procedures for heart failure, knowledge of the BNP values significantly increased the accuracy for a diagnosis of heart failure by general practitioners [21], thus supporting the addition of BNP as a screening tool in the non-urgent care setting.

While it is not the purpose of this review to evaluate the technical aspects of the methodologies used in the detection of BNP, some comments are warranted. The rapid point of care assay (Triage BNP; Biosite Diagnostics, San Diego, CA) is an immunofluorescent assay using an antibody directed against the disulfide bond of the ring structure of BNP. Results of this assay are obtained quickly within about 15 minutes. Although most clinical studies have used this system, there is considerable intra- and interassay variability. In spite of these limitations, the system is convenient for use

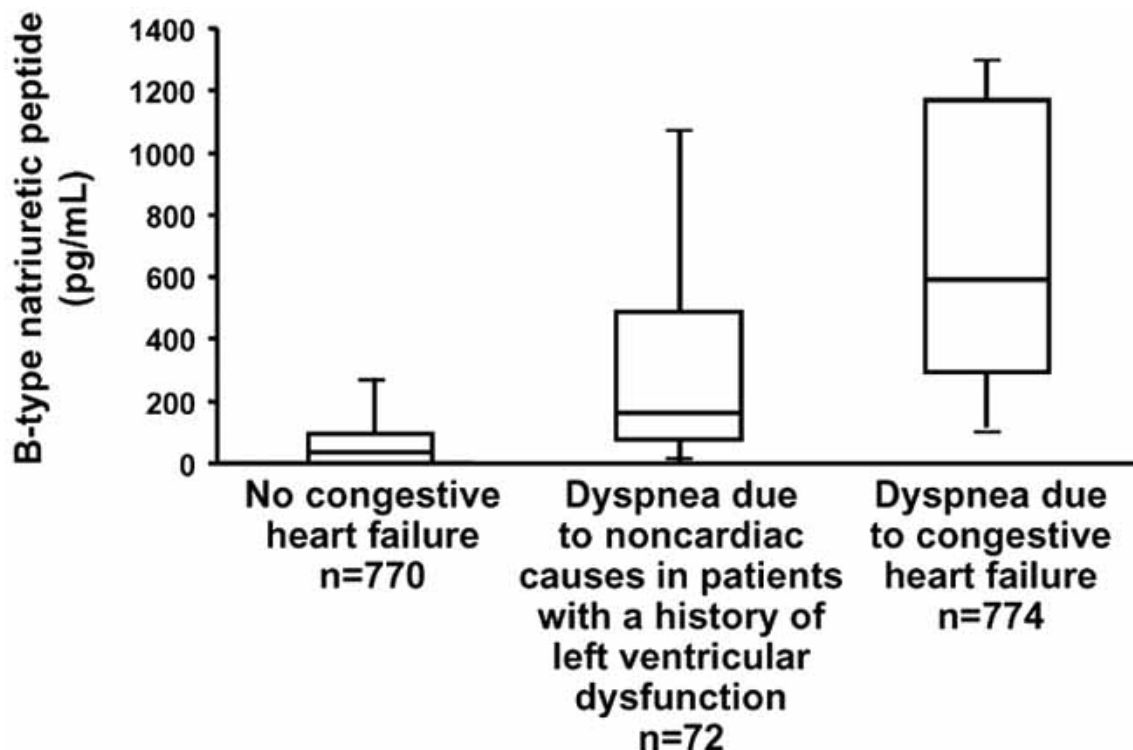


Fig. (2). Box plots showing median, interquartile range, minimum and maximum plasma BNP concentrations in patients without HF, with HF and with known systolic dysfunction but non-cardiac dyspnea in the Breathing Not Proper Trial from Maisel AS, *et al.* N Engl J Med 2002; 347:161.

in the general practice. However, automated systems (Shionogi BNP test, Bayer Diagnostics) which take up to 20 hours but carry the advantage of reduced variability may be more appropriate for clinical laboratories. Another automated test which quantifies the N-terminal fragment of BNP was approved by the FDA in 2002 (Roche Diagnostics). Because N-BNP is cleared in the kidneys, there is some concern that this test will be variable with renal dysfunction. However, this test offers the advantage of less inter- and intra-assay variability than the Biosite Triage BNP and the values correlate to unity with those of BNP and is a strong predictor of 1-year mortality for patients with heart failure [22-25].

BNP measured using the Triage BNP test increased with severity of heart failure based on the New York Heart Association Class [11]. Therefore, in addition to the use of BNP as a biomarker for diagnosis of heart failure in select populations, BNP may be useful in identifying pre-terminal (Stage D) heart failure and to direct care in that setting. For example, within 6 months of hospital discharge, 93% of patients with BNP values of >700 pg/ml (as evaluated with the Biosite Triage BNP test) were either readmitted to the hospital for treatment of heart failure or died [26]. Thus, this test could identify a group of patients with class II to IV symptoms in need of more intensive therapy. Indeed, when BNP was used to direct vasodilatation therapy, patients experienced significantly fewer adverse cardiovascular events than those in which BNP was not monitored [23, 25, 27].

Although there is a clear cause and effect relationship between BNP and heart failure, there are some pathophysiological conditions which may also influence BNP. These include renal failure, flash pulmonary edema, and non-cardiac dyspnea in patients with systolic dysfunction. And false-negative BNP may be associated with cardiac tamponade, hypertrophic cardiomyopathy, amyloid heart disease [2]. However, with these limitations in mind, BNP generally meets the criteria of a useful biomarker to diagnosis and direct treatment of heart failure in select populations when used in conjunction with clinical assessment (Table 1). The tests for the peptide show specificity, are easy to perform in the general clinical setting, and can be used in a cost effective manner to direct care.

CRP AS A BIOMARKER FOR ASSESSMENT OF CARDIOVASCULAR RISK

CRP is a highly conserved pentraxin protein (five noncovalently associated protomers arranged symmetrically around a central core) [28]. CRP is classified as an "acute phase" protein or first-line defense molecule against pathogenic organisms as it binds to phosphocholine of bacterial and fungal membranes and activates the complement system. CRP also stimulates phagocytic cells that remove apoptotic and necrotic cells thus contributing to healing of injured tissue. Production of CRP from the liver is stimulated by cytokines associated with non-specific tissue injury such as interleukin-1B, 6, and tumor necrotic factor [29, 30].

Although circulating concentrations of CRP are reported from several reference populations, these were from the general population or blood donors not screened for smoking or other cardiovascular risk factors. In these populations, CRP concentrations display a left-skewed distribution with most studies reporting 75-95th percent of values below 3 mg/L and median values ranging from 0.55 to 2.4 mg/L [31-37]. There is individual variability in CRP values over time, but within a 6-10 month period in healthy individuals, values range below 10 mg/L, the partition value used for identifying acute infection or inflammation [32, 34, 36].

Whether or not CRP values differ between males and females or increase with age is unresolved with some studies showing trends for increases with age [35, 37] and higher values in females than males [33, 35, 37] while a study of the Japanese population indicates that CRP values are higher in men compared to women (Fig. (3)) [38]. Oral conjugated equine estrogen but not estradiol patches or the selective estrogen receptor modulator raloxifene increases CRP [39-45]. Therefore, it might be expected that CRP in reference populations might be greater in women compared to men. Differences among studies between men and women probably reflect that hormonal status was not taken into account in the female participants. In addition, smoking status and obesity contribute to variability in CRP values [33]. Smoking status and body weight are not identified in all studies reporting reference values [35-37], thereby increasing variability that perhaps masks stronger age and sex differences.

Table 1. Reference Ranges and Partition Values for BNP^a

Range	Diagnosis	Action
<100 – 200 pg/ml	Normal ^b	Non-cardiac causes in patients presenting with dyspnea
200-400 pg/ml	Clinical judgment	Vary, depending upon practice populations and speed, quality and cost of available ancillary tests
400-700 pg/ml	Suspected heart failure	Other tests needed
>700 pg/ml	Pre-terminal stage of heart failure	Targeted aggressive therapy

^aValues reflect those developed from the Biosite Assay System and were derived from reference [2].

^bReferenced for age and sex.

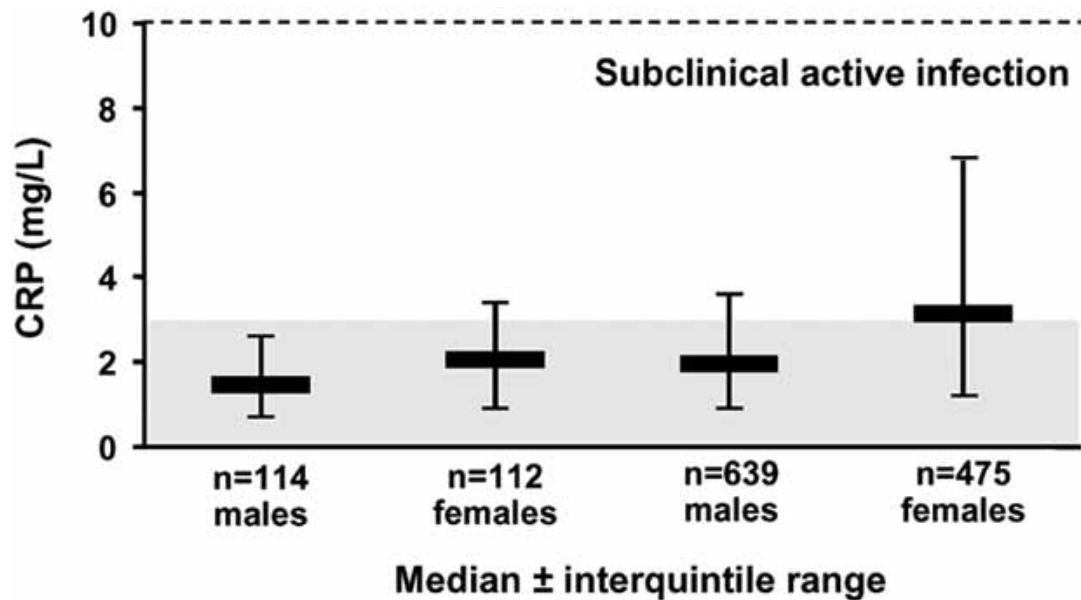


Fig. (3). CRP measured in sera of Mayo Clinic reference population using a Kamiya high sensitivity method. Samples were from 226 apparently healthy subjects without cardiovascular or liver disease and not receiving lipid lowering therapy (mean age 47.8, range 24-76 years) and 1114 individuals obtained through Mayo Medical Laboratories reference services (mean age 55.8 years, males and 57.7 years, females). Sex differences were independent of age. Data are derived from Clin Chem Lab Med 2002; 40:56 and are presented as median values with 1st and 5th quintiles ranges. Shaded area represents 3 mg/L a suggested risk stratification cut-point for CRP and representative of the 75-90th percentile in reference studies [31-37]; dotted line represents partition value for subclinical active infection.

Limited data suggest that normative ranges of CRP may differ among persons of different ethnicity [38, 46, 47]. However, no single study has evaluated reference values using a validated assay for CRP in various ethnic groups to include both men and women across decades of life defined by hormonal status or screened for existing inflammatory conditions including periodontal disease.

Initial tests to measure CRP were immunoassays (ELISA). These assays have been enhanced and automated using immunotubidimetric and immunoluminometric methods and are known as high sensitive assays (hs-CRP) [48] and have the sensitivity and reliability to be used to develop guidelines or reference standards as they might be applied to assess cardiovascular risk [48-50]. Unlike tests for BNP, high sensitivity assays for CRP, while available as point-of-care, do not have the adequate accuracy to be applied to epidemiological studies or have not been tested in the general practice to determine if they increase accuracy or specificity of diagnosis for cardiovascular disease [51, 52].

As a component of the "acute phase response" associated with infection, inflammation, and tissue damage, it is not surprising that in the general clinical setting CRP is used to diagnose new disease, monitor chronic inflammatory disease or screen for unknown infections and malignancies [53, 54]. In an evaluation of tests ordered in general practice, 27% of 1056 tests were ordered for screening purposes, and about 66% of the measured values of all tests were less than 10 mg/L, the partition value indicative of acute inflammation.

Based on large-scale epidemiological and prospective hormone treatment trials, baseline levels of CRP correlate positively to adverse cardiovascular events [33, 39-41, 44, 55-58]. Although CRP is being considered a "risk factor" for

cardiovascular disease, correlations based on statistical epidemiological evaluations do not establish cause and effect. Few experimental studies have demonstrated a direct cause and effect relationship between CRP and vascular remodeling as most studies in animals usually do not include measurement of CRP. In animals which genetically overexpress human CRP [59], arterial thrombosis increased which should be expected given that CRP is part of the acute phase response activating the coagulation cascade. However, local administration of CRP into a balloon-denuded area of carotid artery in rats increased development of neointima associated with the injury [60]. Although it is unclear whether the controls received an infusion of carrier and injection of gelling agarose around the injury, these results are suggestive that CRP may exacerbate a response to injury. In another model of vascular injury, turpentine-induced atherosclerosis was accelerated in apolipoprotein (apo)E⁻¹ mice, which expressed a transgene for human CRP [61]. More research is needed in order to determine if specifically inhibiting CRP would inhibit arterial disease processes. In another study of mice which overexpress human CRP, ovariectomy increased neointimal formation in response to ligation of the carotid artery, an effect reduced by subcutaneous estrogen treatment. This study supports the concept that estrogen may reduce adverse vascular remodeling and is consistent with observations in humans that it may be the mode of delivery of the estrogen (subcutaneous or transdermal compared to oral) which may affect production of CRP in the liver [45, 62].

Atherosclerosis was first described as an inflammatory disease in 1976 [63]. The inflammatory processes focused primarily on lipid peroxidation with production of cytokines in the damaged vascular tissue. These cytokines in turn

stimulate production of CRP. However, cytokines which stimulate production of CRP are also produced by adipose tissue [64]. So it could be expected that CRP would be elevated with metabolic syndromes and diabetes [65-67]. Because elevated lipids, metabolic syndrome and diabetes are known risk factors for atherosclerosis and adverse cardiac events, plasma CRP levels may represent a “risk marker” of diverse, ongoing inflammatory processes [50].

Considering CRP as a risk marker for cardiovascular disease, it is unclear how this information could be used to assess risk for an individual or to direct care in individuals with other established modifiable cardiovascular risk factors. For example, in men (ages 40-84) participating in the Physicians’ Health Study, baseline CRP levels were significantly greater in participants that subsequently developed a vascular event (myocardial infarction or stroke) than in age matched controls [68]. However, the median CRP value in controls was 1.13 mg/L, and in the group exhibiting events, CRP ranged from 1.36-1.51 mg/L (Fig. (4)). Using this study to establish risk and stratification of partition values can be criticized because newer assays for CRP have improved sensitivity and the cohort included only men and may not be applicable to women of varying hormone status. These values are well within the 75-95th percentile of CRP measured among “normal” reference individuals determined using high sensitive assays [32, 34, 36, 37].

In another population-based study, CRP was correlated with extent of graded coronary artery disease [69]. In individuals with advanced disease, the median CRP value was 5.4 mg/L with the 1st-3rd quartiles ranging from 2.6-14.1 mg/L (Fig. (4)). However, these values are also within the range for subacute clinical active infection. CRP may reflect ongoing infective processes or other risk factors that might contribute to adverse cardiovascular events rather than representing an independent risk factor for an adverse event. Therapies directed at defined risk factors such as lipid lowering drugs also lower CRP levels [65, 66, 70-72]. This result is expected if lipid peroxidation is causing the rise in CRP. However, even with CRP defined as an independent risk factor by statistical evaluations, there are no direct therapies targeted for CRP, nor are there any means to identify the underlying stimulus provoking changes in CRP production beyond traditional risk management [47]. Although CRP is activated by pathogens, pathogen screening is typically not routinely performed when assessing cardiovascular risk, even though some evidence supports an infectious etiology for some cardiovascular disease processes [58, 69, 73-75]. Since CRP binds to membranes of pathogens, it might be expected that CRP would be present in atheroma if a pathogen is causal [76]. When added to cultured endothelial cells, CRP increases adhesion of monocyte tissue factor, expression of adhesion molecules and production of monocyte chemoattractant protein-1 [77-80]. Expression of these

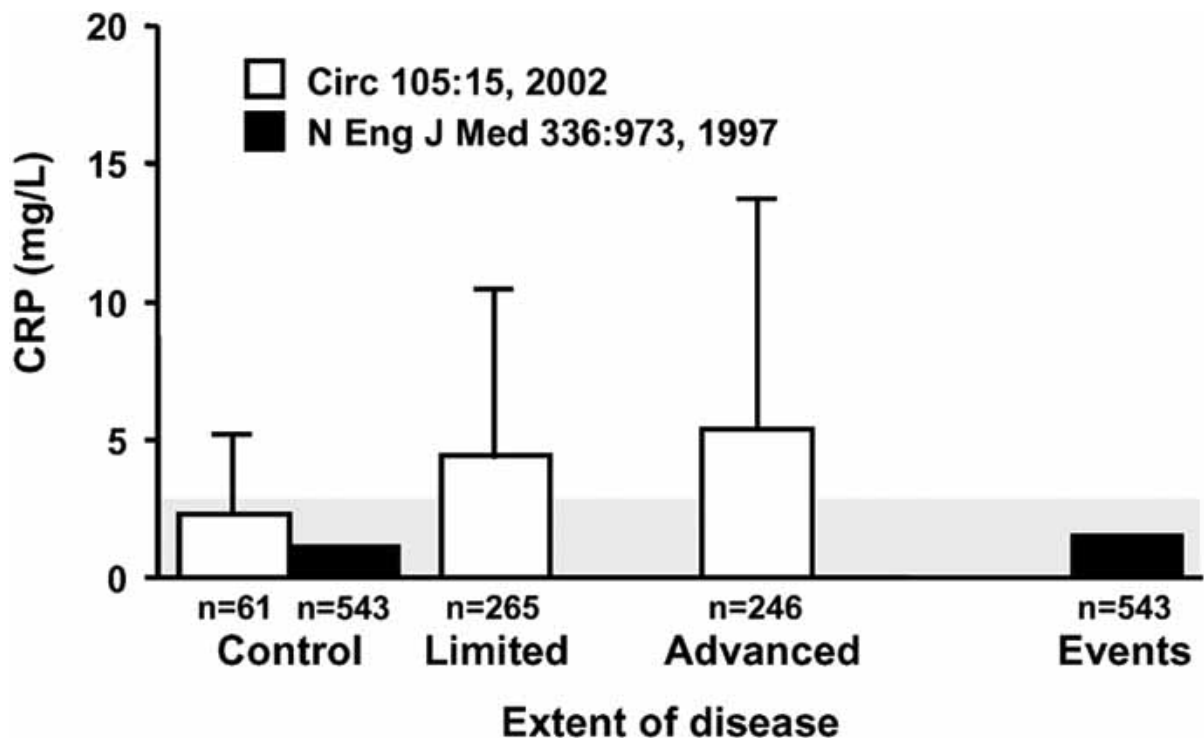


Fig. (4). CRP reported from population studies of risk assessment for cardiovascular disease. Clear bars represent median and 3rd quartile range of serum CRP from consecutive patients (men and women mean ages per group 60-65 years) admitted to the 2nd Medical Department of the University Clinic Mainz, Germany. Degree of cardiovascular disease was assessed by coronary angiography, carotid duplex sonography and peripheral Doppler flow velocity. Data are derived from Table 1 of Circ 2002; 105:15. Solid bars represent median baseline plasma CRP from participants of the Physicians Health Study who remained free of vascular disease and those who had a myocardial infarction or stroke (event). Data are derived from Table 2 of N Engl J Med 1997; 336:973. Shaded area represents suggested partition value for CRP in evaluation of cardiovascular risk [85] and the 90th percentile in referenced studies [31-37].

molecules defines an "inflammatory" endothelium which target monocytes to pathogens and may also change release of endothelium-derived factors which exacerbate vasoconstriction and platelet activation.

CRP has also been correlated to adverse cardiovascular events in post-menopausal women, with the suggestion that hormone therapy adversely increases CRP and, therefore, cardiovascular risk [39-41, 56, 57, 81]. However, measurements for CRP at baseline, before the initiation of hormonal therapies, show considerable variability (Fig. (5)). For example, in a study of effects of oral conjugated equine estrogen (CEE) on factors related to coagulation conducted by our group, one woman meeting the inclusion/exclusion criteria had a baseline CRP value of 28 mg/L even though she reported feeling well at the time of enrollment [43]. After 3 months, CRP in this individual (who had been randomly assigned to the placebo group) declined below the mean (3.3 mg/L, n=12) for the placebo group to 0.8 mg/L. Although it was possible to conclude that CRP had increased from baseline with CEE treatment (1.2 ± 0.8 to 3.5 ± 2.3 mg/L, n=13 mean \pm SD), mean levels of CRP did not differ between the placebo and treated groups at the end of the three month study but variance between control and treated groups did increase [43]. These data, from an albeit small prospective study [43], identify two important points of caution when using CRP as a "marker" of cardiovascular risk. First, CRP values may be elevated in individuals reporting to feel "well." Therefore, to obtain a representative CRP value for an individual, more than one measurement may be necessary. Secondly, even though some treatments may increase CRP levels, the increase may be within the 75-95th percentile of normal. Only in the tertiles with CRP greater than 3.8

mg/L were odds ratios increased for adverse cardiovascular events in both non-users and users of hormone treatment in women of the observational group of the Women's Health Initiative (WHI) (Fig. (6)) [56]. However, when odds ratios are examined per treatment group, the odds ratios for hormone users fall below those of non-users in ranges considered to be indicative of risk (Fig. (6)) [56].

Lower baseline CRP values were associated with fewer adverse cardiovascular events in women with hysterectomy randomized to using CEE in the estrogen only arm of the WHI [82] which may reflect the presence of fewer modifiable risk factors in those women at the beginning of the study. Alternatively, differences in baseline values could reflect genetic variances in the CRP gene, a consideration that warrants further investigation [83]. In menopausal women with four or five characteristics of metabolic syndrome and not using hormone treatment, CRP greater than 3.0 mg/L was associated with a lower eight-year survival rate compared to women with similar characteristics but CRP <3.0 mg/L [66]. In women with metabolic syndrome, CRP may add information to guide therapy to reduce risk. Whether this information applies to men needs to be confirmed although CRP (as well as interleukin-6 and tumor necrosis factors, stimuli for CRP) increased in both men and women with central adiposity [67].

So the question becomes, can measurements of CRP be used in general clinical practice to evaluate cardiovascular disease and improve outcomes in a cost effective manner? Assays for CRP are highly sensitive and show reasonable variation among assays [34, 36, 37]. But they may not be cost effective in terms of improving diagnosis as the test

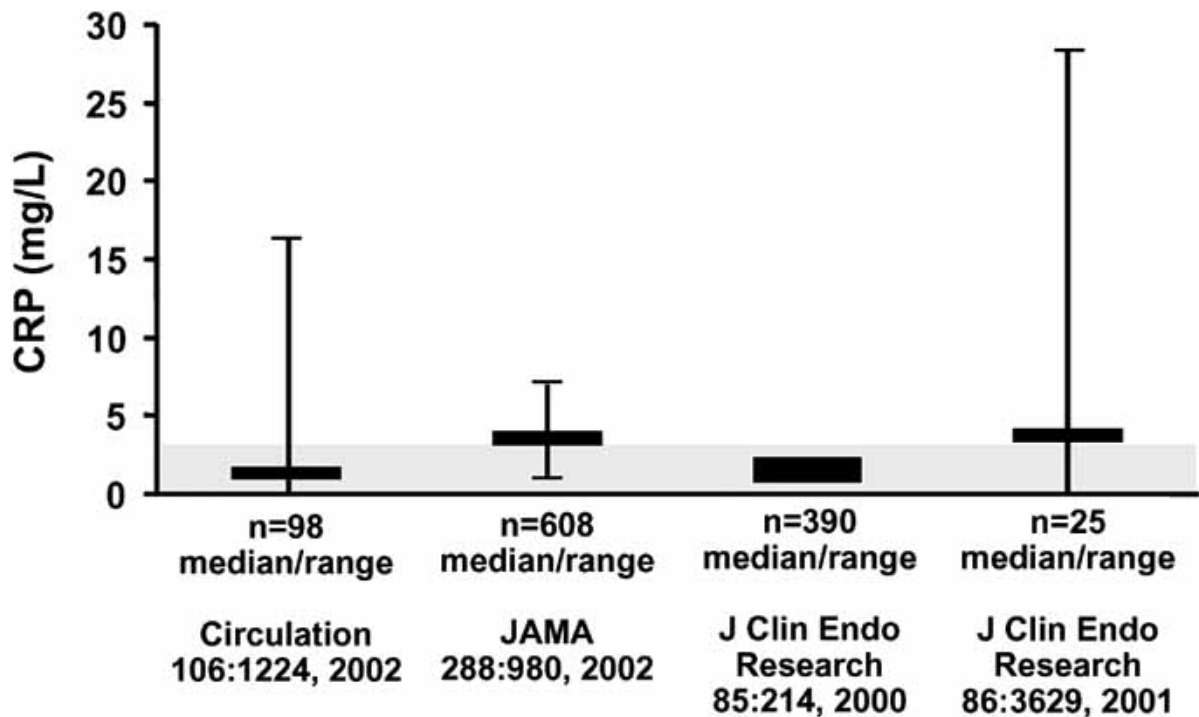


Fig. (5). Baseline CRP values measured in post-menopausal women enrolled in various hormone treatment trials. Data are shown as median and ranges reported derived from the stated references. Shaded area represents 3 mg/L representative of the 90th percentile in reference studies [31-37].

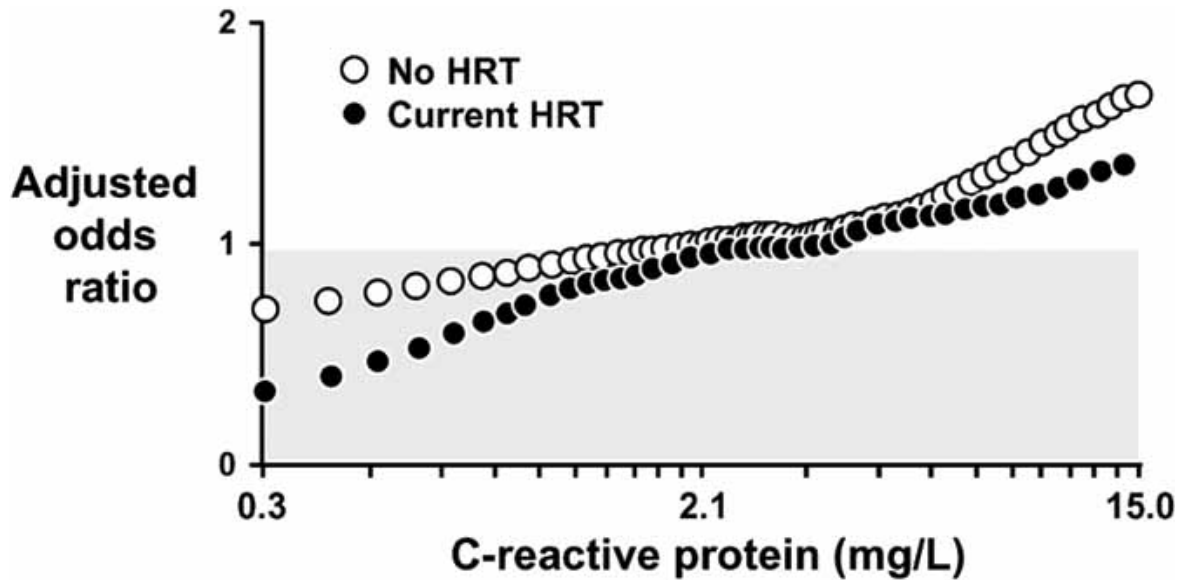


Fig. (6). Adjusted odds ratio for coronary heart disease (developed myocardial infarction) according to baseline C-reactive protein stratified by hormone therapy in post-menopausal women (age 50-79 years; mean 69 years) enrolled in the observational component of the Women's Health Initiative. In this study, 74% of current hormone users were taking oral conjugated equine estrogen (0.625 mg/day). Some were also taking estrogen with progestin, 87% of which was medroxyprogesterone acetate. Most individuals in the hormone user group had used hormones for more than 4 years. The estimated curves are adjusted for age, ethnicity, smoking and follow-up, lipoproteins, body mass index, history of hypertension, diabetes and family history of coronary disease. Redrawn from Fig. 2 of [56]. Shaded area represents decreased risk.

cannot help to target therapy as changes in CRP are non-specific, that is, concentrations increase following generalized tissue damage of multiple origin and infection [30]. Unlike BNP, in which clear cause and effect relationships are established between stimulus (stretch of the myocardium) and release of BNP, no such relationships exist for CRP as related to cardiovascular disease. Indeed, many of the established risk factors for cardiovascular disease like smoking, diabetes, hypertension and elevated lipids, are likely to increase release of CRP [33, 55, 84]. Therefore, CRP may not by itself be a risk factor but is elevated as a consequence of the presence of other risk factors as part of the natural physiological defense mechanism [47].

In the setting of general practice, CRP could be used to identify subclinical infection [58], which might increase risk for adverse cardiovascular events [76]. CRP values may be useful in individuals suspected of cardiovascular disease when the lipid profile is within the normal range [50] or to guide the intensity of therapy in patients with central adiposity and metabolic syndrome [65-67]. But the CRP values do not provide direction as how the therapy should be targeted. Alternatively, CRP values may be used to increase surveillance of some patients where multiple measurements (three at monthly intervals) of CRP may remain elevated above the 95th percentile of reference value [34], also supporting evaluation of active acute or chronic infection [69]. However, cost benefit analysis may dictate practicality of such repeat measurements in the general practice and may not add value of precision to the diagnosis or treatment [47, 50].

SUMMARY

Properties of an assay for a biomarker include reproducibility, simplicity, and cost. BNP is useful as a biomarker in

point of care diagnosis of heart failure and for evaluating effectiveness of treatment. The usefulness of BNP as a biomarker in diagnosis results from established cause and effect relationships for its production and release. Large-scale clinical trials have established receiver operator curves identifying selectivity and specificity of the value. In addition, age and sex specific data in a reference population free of disease aid in the interpretation of laboratory measures for individuals. Contrary to these findings with BNP, measurement of CRP alone is not a specific indicator of cardiovascular disease. Large-scale epidemiological trials point to correlations of CRP with adverse cardiovascular outcomes but cause and effect relationships have not been established. In addition, data are equivocal for interpretation relative to age and sex reference ranges, and partition values have not been identified or interpreted relative to those established for other clinical diseases or subacute infection. Large-scale clinical trials have not established receiver-operator curves that support improved accuracy or specificity of diagnosis or treatment beyond that of other modifiable factors known to lower cardiovascular risk. Until randomized trials are completed that clearly demonstrate that measurement of CRP enhances patient care, with clear evidence for selectivity and specificity, monitoring CRP as a general screening tool to assess risk for cardiovascular disease may be imprudent.

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