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# C-reactive protein: A 'golden marker' for inflammation and coronary artery disease

## ABSTRACT

Numerous studies have shown that elevated levels of C-reactive protein (CRP) are associated with increased cardiovascular risk. We advocate greater use of CRP measurements in clinical practice to identify patients at high risk in a variety of situations.

## KEY POINTS

The development of an atherosclerotic plaque involves a complex interaction between the endothelium, inflammatory cytokines, and numerous blood elements. Inflammation plays a key role.

Elevations of CRP predict cardiovascular risk in apparently healthy persons, patients presenting with acute coronary syndromes, and patients undergoing coronary revascularization.

Normal values for CRP are not well defined. From the data available, people should be considered at increased risk if they have values greater than 0.3 mg/dL during an acute coronary syndrome, 0.3 mg/dL before undergoing coronary revascularization, 0.5 mg/dL at 72 to 96 hours after revascularization, or 0.38 mg/dL for healthy postmenopausal women or 0.15 mg/dL for healthy men.

Persons at high risk should receive aggressive risk-lowering therapy. Some conventional therapies (ie, aspirin, statin drugs, and angiotensin-converting enzyme inhibitors) may owe some of their benefit to intrinsic anti-inflammatory properties.

**C**-REACTIVE PROTEIN (CRP) is finding new uses these days as a marker of coronary artery disease. Long used in rheumatology to monitor the activity of rheumatoid arthritis, this acute phase protein has been shown in recent years to be a risk factor for cardiovascular events and death in a variety of populations: apparently healthy people, patients presenting with acute coronary syndromes, and those undergoing percutaneous or surgical revascularization.

These findings coincide with a paradigm shift in our understanding of the events leading to acute coronary syndromes, with a focus on the role of inflammation in plaque formation, progression, rupture, and thrombosis.

*See related editorials, pages 535–540*

In this paper we:

- Review the role of inflammation in the pathogenesis of acute coronary syndromes
- Summarize the studies that established a correlation between CRP levels and cardiovascular risk
- Offer our recommendations on how to use CRP measurements in clinical practice.

## NEEDED: BETTER MARKERS OF RISK

Coronary atherosclerosis remains the leading cause of death in the United States and other Western countries despite growing public awareness of the disease and major advances in its treatment.

Thanks to epidemiologic studies, we know about many risk factors for cardiovascular dis-

ease, such as hypertension, cigarette smoking, diabetes mellitus, family history of premature coronary artery disease, obesity, male gender, and hypercholesterolemia.<sup>1</sup> Moreover, some of these factors can be modified or treated to reduce cardiovascular morbidity and mortality. In particular, trials in apparently healthy people and in patients with coronary artery disease showed that lipid-lowering therapy for hyperlipidemia significantly reduces ischemic cardiac events.<sup>2-4</sup>

However, many patients who present with acute coronary syndromes have no apparent clinical risk factors. For example, the Framingham Study showed that 35% of cases of coronary artery disease were in people with normal total cholesterol levels (ie, < 200 mg/dL).<sup>5</sup> These findings point out the need for markers that better predict cardiovascular risk.

#### ■ OTHER MARKERS

Other markers that predict cardiac events include homocysteine, lipoprotein(a), plasminogen activator inhibitor-1, and fibrinogen. These are often assessed in patients with premature coronary artery disease or coronary disease without associated traditional risk factors.<sup>6,7</sup>

Markers of inflammation are also being investigated as predictors of coronary ischemic events, following studies suggesting the key role of inflammation in the progression of atherosclerosis.<sup>8</sup> These markers include CRP, interleukin-1 (IL-1), interleukin-6 (IL-6), serum amyloid A (SAA), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ).

#### ■ HOW ATHEROSCLEROSIS DEVELOPS

The development of an atherosclerotic plaque involves a complex interaction between the endothelium, inflammatory cytokines, and numerous blood elements (FIGURE 1). Therefore, physicians need a detailed understanding of the central role of inflammation in atherosclerosis, how to stratify patients at risk on the basis of inflammatory markers, and the impact of current and future therapeutic interventions to provide state-of-the-art medical care.

The process starts with various triggers that injure and activate endothelial cells. These triggers include oxidized low-density lipoprotein (LDL), shear stress on the vessel wall, free radicals, infection, and hyperglycemia.

The activated endothelial cells increase their production of two types of molecules: chemokines and adhesion molecules. Chemokines (monocyte chemotactic protein-1, interleukin-8, macrophage colony-stimulating factor, and macrophage antigen-1) attract (recruit) mononuclear cells (T lymphocytes and monocyte-derived macrophages).<sup>9-15</sup> Adhesion molecules (vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and selectins) help these mononuclear cells migrate into the subendothelium.

In the subendothelium, the mononuclear cells produce inflammatory cytokines (IL-1, IL-6, and TNF- $\alpha$ ) that further augment the expression of adhesion molecules. They also promote plaque growth by expressing matrix metalloproteinases (which promote smooth-muscle cell proliferation) and, in the case of macrophages, by taking up low-density lipoprotein and transforming themselves into foam cells.<sup>16</sup>

Hence, endothelial injury sets in motion a self-perpetuating cycle that further drives atherogenesis.

#### From fatty streak to ruptured plaque

The incipient lesion, called a fatty streak, may never become a problem. Maturation of a fatty streak depends on the balance between synthetic and proteolytic factors. Plaques grow when inflammatory cytokines and mitogens such as fibroblast growth factor and platelet-derived growth factor promote smooth-muscle cell proliferation. The muscle cells, in turn, secrete collagen, which forms a stable fibrous cap.<sup>17,18</sup>

In contrast, other inflammatory cytokines weaken the fibrous cap: interferon- $\gamma$  (by decreasing collagen production) and IL-1 and TNF- $\alpha$  (by promoting collagen degradation via matrix metalloproteinases).<sup>19</sup> The thinning makes the fibrous cap vulnerable to fissure or rupture, which exposes the procoagulant atheromatous core to circulating blood elements.

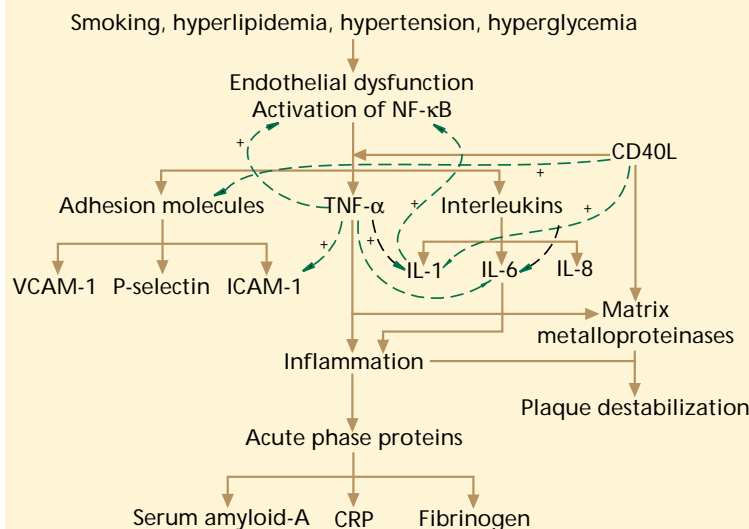
Endothelial injury sets in motion a self-perpetuating cycle



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**FIGURE 1**

## How inflammatory cytokines lead to release of acute phase proteins



**FIGURE 2.** Schematic representation of the complex interplay between various inflammatory cytokines. Secretion of these cytokines by direct stimulation or positive feedback results in inflammation and production of acute phase proteins.

### From plaque rupture to thrombosis

On pathologic evaluation, ruptured plaques often show a predominance of inflammatory cells (macrophages, T lymphocytes) and a paucity of smooth-muscle cells.<sup>20</sup> The exposure of highly procoagulant substances such as collagen and thromboxane A<sub>2</sub> leads to activation of platelets and the coagulation cascade, with resultant coronary thrombosis.

While coagulation factors play a pivotal role in the evolution of thrombus formation, inflammatory cytokines further accentuate the process by inducing expression of P-selectin and CD40 ligand on the platelet surface. These molecules promote platelet adherence to other platelets, the endothelium, and leukocytes.

Inflammation is therefore vital in plaque destabilization, and sets in motion a self-perpetuating cycle of platelet activation and thrombus formation.

### MARKERS OF INFLAMMATION IN CORONARY ARTERY DISEASE

Several novel markers of inflammation have been identified in the past decade, and many of these are present or up-regulated in patients with acute coronary syndromes.<sup>21</sup>

**Nuclear factor kappa-B (NF-κB)**, a transcription factor, is present in its inactive form in the cytoplasm of monocytes, endothelial cells, and smooth muscle cells. It is activated by factors such as hypercholesterolemia, hyperglycemia, oxidized LDL, and elevated levels of angiotensin II—some of the same triggers that also cause endothelial dysfunction. Once activated, NF-κB transcriptionally activates interleukins, interferons, TNF-α, and adhesion molecules. NF-κB, as measured by electromobility shift assays, is shown to be specifically activated in acute coronary syndromes before the clinical event and mechanistically may be involved in plaque rupture.<sup>22</sup>

**TNF-α**, a pivotal cytokine high in the inflammatory cascade, promotes induction of IL-1 and IL-6, expression of adhesion molecules (ICAM-1), and production of acute phase proteins (SAA, fibrinogen, and CRP).<sup>23</sup> IL-6 decreases plasma lipoprotein lipase activity with a resultant increase in macrophage uptake of lipids, and is a powerful inducer of the hepatic acute phase response.<sup>24</sup> Both IL-1 and IL-6 are up-regulated in patients with coronary artery disease.<sup>25</sup>

**CD40 ligand (CD40L)**, a transmembrane protein structurally related to TNF-α, binds to CD40 and activates macrophages and T lymphocytes. Both CD40 and CD40L are expressed prominently in the “shoulder” regions of the atherosclerotic plaque—a vulnerable site for plaque rupture.<sup>26</sup> Furthermore, CD40 ligation induces expression of other inflammatory cytokines and release of matrix metalloproteinases (MMP-1, MMP-3, and MMP-9)—all contributing to development of acute coronary syndromes.<sup>27</sup> Enhanced activity and high levels of soluble and membrane-bound forms of CD40L are present in patients with unstable angina.<sup>28</sup>

Elevated levels of **soluble intercellular adhesion molecule-1 (sICAM-1)** are associated with increased risk of future myocardial infarction.<sup>29</sup>



**P-selectin** expression is significantly greater in coronary arterectomy specimens from patients with unstable angina than from patients with stable angina.<sup>30</sup>

**Acute phase proteins** (SAA, fibrinogen, and CRP) are systemic markers and can be easily measured. They can therefore serve as more comprehensive markers of inflammation, and hence clinical predictors of future cardiovascular risk. SAA and fibrinogen levels have been shown to be elevated in patients with acute coronary syndromes and are associated with adverse cardiovascular outcome; however, CRP has been more extensively studied than either SAA or fibrinogen.<sup>31-33</sup>

The remainder of this paper deals with CRP.

**The inflammatory markers are interrelated.** The various individual inflammatory molecules, independently as well as via complex feedback mechanisms, contribute to liver-induced release of acute phase proteins (FIGURE 2).

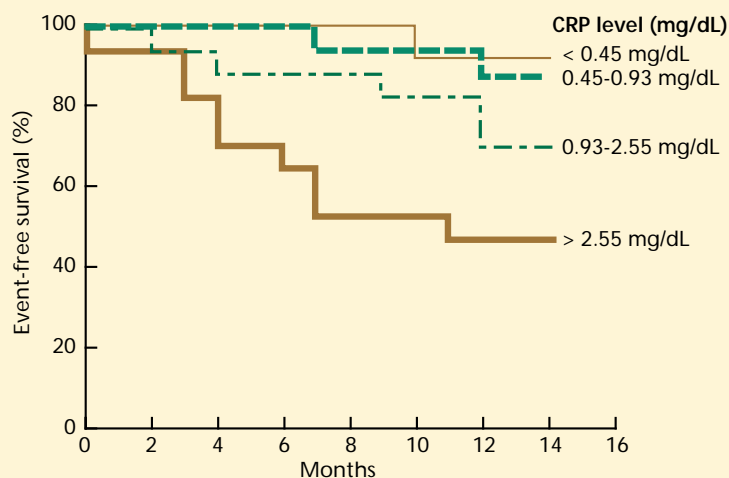
For the most part, the up-regulation or expression of various cytokines such as IL-1, IL-6, TNF- $\alpha$ , adhesion molecules, and matrix metalloproteinases occurs in a site-specific manner as these chemokines are produced locally by activated macrophages. However, “shedding” of some of these molecules (IL-6, TNF- $\alpha$ ) or soluble forms of adhesion molecules (sICAM-1) or selectins (P-selectin) may be considered systemic since they are present in the circulation.

#### ■ CRP: THE ‘GOLDEN MARKER’ FOR INFLAMMATION

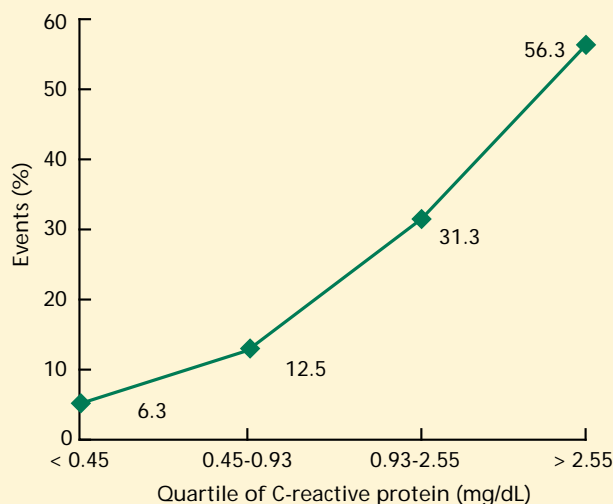
C-reactive protein, a pentameric protein produced by the liver, has emerged as the “golden marker” for inflammation. It has been evaluated in many phases of coronary disease and has proven to be a reliable predictor of cardiovascular risk.

Recent evidence lends support to the concept that CRP plays a direct role in promoting inflammation and is not merely a response to it.<sup>34</sup> In addition, SAA and fibrinogen both have additive effects when combined with CRP in risk stratification of patients with acute coronary syndromes.

### After an MI, higher CRP levels correlate with lower event-free survival rates



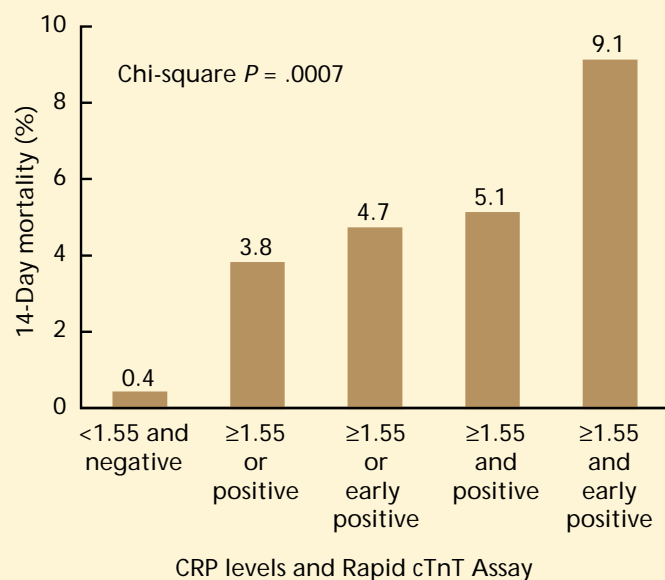
### ...and higher cardiac event rates



**FIGURE 3.** Event-free survival curves stratified by quartiles of CRP concentration in MI patients. **Top**, patients in the highest quartile of CRP had a significantly lower event-free survival rate. **Bottom**, the cardiac event rate increased with rising CRP concentration.

FROM TOMMASI S, CARLUCCIO E, BENTIVOGLIO M, ET AL. C-REACTIVE PROTEIN AS A MARKER FOR CARDIAC ISCHEMIC EVENTS IN THE YEAR AFTER A FIRST, UNCOMPLICATED MYOCARDIAL INFARCTION. AM J CARDIOL 1999; 83:1595-1599. REPRODUCED WITH PERMISSION.

### Cardiac troponin T and CRP predict mortality in acute coronary syndromes



**FIGURE 4.** Risk stratification based on CRP and early positivity (within 10 minutes) of cardiac troponin T (cTnT) in patients with acute coronary syndromes. CRP elevation and cTnT positivity independently and additively predicted 14-day mortality.

FROM MORROW DA, RIFAI N, ANTMAN EM, ET AL. C-REACTIVE PROTEIN IS A POTENT PREDICTOR OF MORTALITY INDEPENDENTLY OF AND IN COMBINATION WITH TROPONIN T IN ACUTE CORONARY SYNDROMES: A TIMI 11A SUBSTUDY. THROMBOLYSIS IN MYOCARDIAL INFARCTION. J AM COLL CARDIOL 1998; 31:1460-1465. REPRODUCED WITH PERMISSION.

Several properties make CRP a good marker. It does not break down between sample collection and processing in the lab. It is present in the blood only when it is produced de novo in the liver in the presence of a stimulus. Furthermore, new, highly sensitive assays for CRP (hsCRP assays) can measure levels within the “normal” range (0.0–0.5 mg/dL, depending on the assay), thus enabling careful evaluation of underlying systemic inflammation in apparently healthy people as well as those with established coronary artery disease.

#### ■ CRP IN ACUTE CORONARY SYNDROMES

##### CRP in ST-elevation MI

In ST-elevation MI, CRP levels reach a peak 2 to 4 days after the initial event and thereafter often decline. Whether the rise in CRP

is a cause or effect of myocardial necrosis is extensively debated.<sup>35</sup>

Several groups of investigators found that CRP levels predict the risk of subsequent events in patients with ST-elevation MI.

Pietila et al,<sup>36</sup> in a study of patients who received fibrinolytic therapy, found that peak CRP levels correlated with the risk of mortality at 6-month follow-up. In contrast, the levels of total creatine kinase or creatine kinase MB fraction did not. CRP levels dropped more rapidly or were lower when the patency of infarct-related artery was restored.<sup>37</sup>

Anzai et al<sup>38</sup> found that peak CRP levels were higher in patients who suffered severe post-MI complications such as cardiogenic shock, cardiac rupture, or death within 1 year of follow-up.

Tommasi et al<sup>39</sup> found that elevated CRP (especially > 2.55 mg/dL) at admission during an uncomplicated MI (without residual ischemia and with normal left ventricular function) was associated with a higher rate of ischemic events (death, recurrent angina, MI) and a lower 1-year event-free survival rate (FIGURE 3).

##### CRP in non-ST-elevation MI and unstable angina

Elevated CRP levels at admission, independently or in conjunction with abnormal troponins, have been shown to be associated with adverse outcome in unstable angina or non-ST-elevation MI.<sup>40–42</sup>

The European Concerted Action on Thrombosis and Disabilities Angina Pectoris (ECAT) study<sup>41</sup> found that patients with stable angina and CRP elevation (> 0.36 mg/dL) at admission had a twofold increase in risk of coronary events at 2-year follow-up.

The Thrombolysis in Myocardial Infarction (TIMI) 11A study<sup>43</sup> found that early detection of troponin T and elevation in CRP was associated with twofold increase in mortality (FIGURE 4).<sup>43</sup> Importantly, elevated CRP levels retained their predictive value even in patients with negative rapid troponin T, thus eliminating the contribution of myocardial necrosis from its prognostic strength.

Biasucci et al<sup>44</sup> confirmed these observations, evaluating the prognostic power of CRP levels at discharge in the setting of unstable





angina without myonecrosis. At discharge, CRP was elevated ( $> 0.3$  mg/dL) in 49% of patients; of these, 42% had elevated levels at admission and at 3-month follow-up. Recurrent instability or new MIs occurred in 69% of patients with elevated discharge CRP. At 1-year follow-up, event-free survival was significantly lower in those with elevated discharge CRP (FIGURE 5).

#### In acute coronary syndromes, risk is elevated with CRP $> 0.3$ mg/dL

There is no one absolute CRP value that precisely predicts risk of subsequent cardiac events for any given clinical presentation. However, from the data available, a value greater than 0.3 mg/dL either upon admission or at discharge appears to identify patients at increased risk for subsequent ischemic cardiac events for the entire spectrum of acute coronary syndromes.

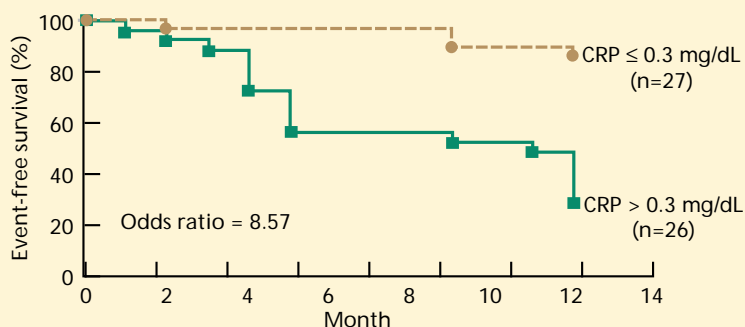
#### ■ CRP AND REVASCULARIZATION

The traditional clinical risk factors, while helpful in identifying patients at risk for coronary artery disease, are of little help in risk stratification of patients undergoing either percutaneous or surgical coronary revascularization.

Interestingly, biochemical markers may be rather useful in this patient population. In fact, evidence of inflammation (ie, elevated CRP or SAA levels) after a percutaneous coronary intervention appears to portend adverse outcomes in patients with unstable angina.<sup>45</sup> Furthermore, persistent elevation of CRP ( $> 0.5$  mg/dL at 72 hours) following coronary artery stenting in patients with stable angina was associated with lower event-free survival at 1-year follow-up (FIGURE 6).<sup>46</sup> Another study reported a higher restenosis rate in patients with persistent elevation of CRP at 96 hours following coronary artery stenting.<sup>47</sup>

Even *preprocedural* CRP elevation ( $> 0.3$  mg/dL) in patients undergoing coronary angioplasty predicted early complications and late clinical restenosis.<sup>48</sup> Similarly, elevated CRP ( $> 0.3$  mg/dL) prior to coronary artery bypass surgery was associated with a fivefold increase in new ischemic cardiac events.<sup>49</sup>

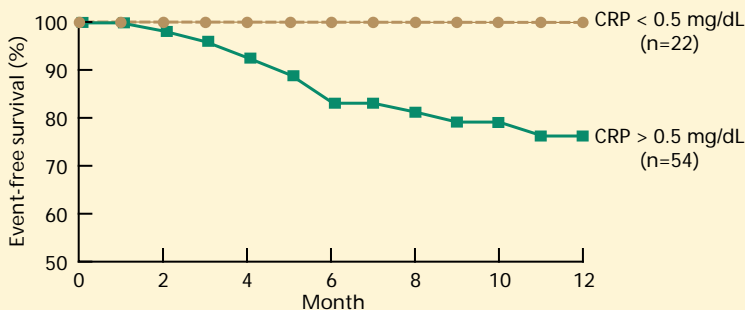
#### In unstable angina, CRP values $> 0.3$ mg/dL predict future events



**FIGURE 5.** One-year survival curves with freedom from myocardial infarction or recurrent instability according to CRP concentration at discharge. Patients with elevated CRP ( $> 0.3$  mg/dL) had a significantly lower survival rate.

FROM BIASUCCI LM, LIUZZO G, GRILLO KL, ET AL. ELEVATED LEVELS OF C-REACTIVE PROTEIN AT DISCHARGE IN PATIENTS WITH UNSTABLE ANGINA PREDICT RECURRENT INSTABILITY. CIRCULATION 1999; 99:855–860. REPRODUCED WITH PERMISSION.

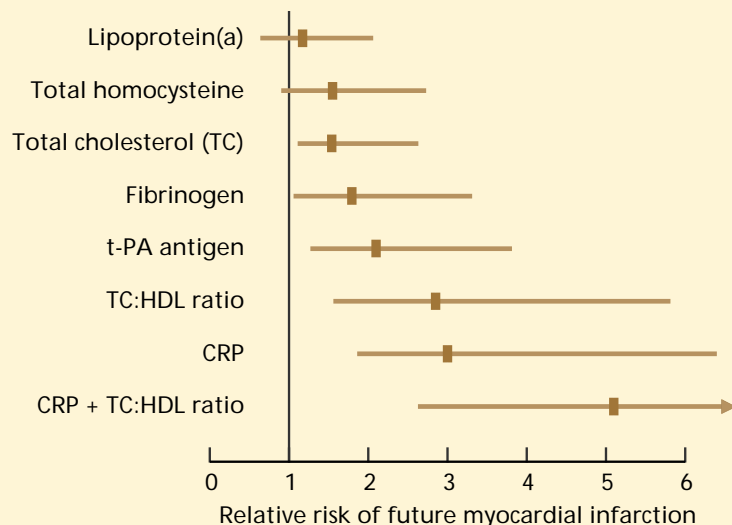
#### After coronary stenting for stable angina, CRP levels $> 0.5$ mg/dL predict future events



**FIGURE 6.** One-year event-free survival according to CRP levels 72 hours after coronary artery stenting. Patients with persistently elevated CRP ( $> 0.5$  mg/dL) after stenting had a significantly lower survival rate, and those without CRP elevation had remarkably no events during the 1-year follow-up.

FROM GASPARDONE A, CREA F, VERSACI F, ET AL. PREDICTIVE VALUE OF C-REACTIVE PROTEIN AFTER SUCCESSFUL CORONARY-ARTERY STENTING IN PATIENTS WITH STABLE ANGINA. AM J CARDIOL 1998; 82:515–518. REPRODUCED WITH PERMISSION.

### How CRP compares with other markers of risk



**FIGURE 7.** Risk of future myocardial infarction according to baseline levels of various biochemical markers in apparently healthy men in the Physicians' Health Study. CRP elevation and abnormal total cholesterol to HDL ratio (TC:HDL) independently and additively proved to be powerful prognostic indicators.

FROM RIDKER PM. EVALUATING NOVEL CARDIOVASCULAR RISK FACTORS: CAN WE BETTER PREDICT HEART ATTACKS? ANN INTERN MED 1999; 130:933-937. REPRODUCED WITH PERMISSION.

These observations have now been extended to patients undergoing cardiac transplantation.<sup>50</sup> Independent of other predictors of allograft failure, a twofold increase in CRP level resulted in a 32% increased risk of graft failure resulting in death or retransplantation.

In general, patients with stable or unstable angina and CRP levels greater than 0.3 mg/dL before undergoing coronary angioplasty or bypass surgery should be considered at high risk for ischemic complications. Furthermore, in patients with significant CRP elevation immediately after coronary intervention, an attempt should be made to measure CRP approximately 72 hours after the procedure to identify an even higher-risk group. Those with postprocedural CRP levels greater than 0.5 mg/dL should be followed closely for future ischemic events and restenosis.

### CRP AND HEALTHY INDIVIDUALS

The availability of hsCRP assays has advanced the field of preventive cardiovascular medicine by allowing detection of CRP at very low levels. These assays can detect small changes in CRP levels within the normal range, and hence low-grade inflammation in healthy persons.

Several studies demonstrated that small increases in CRP within the normal range (established for the surveillance of chronic arthritis and measured as tertiles or quartiles) in apparently healthy persons without established coronary artery disease reliably predict the risk of future cardiovascular events.

The Multiple Risk Factor Intervention Trial (MRFIT)<sup>51</sup> reported a nearly threefold increase in cardiac mortality among healthy men (primarily smokers) in the highest quartile of CRP.

The Physicians' Health Study<sup>52</sup> reported a higher incidence of MI in men in the highest CRP quartile, irrespective of smoking history.

The Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study<sup>53</sup> reported similar findings: the risk of future MIs increased by nearly 50% with an increase in CRP of 1 standard deviation.<sup>53</sup> This remarkable prognostic power was sustained even after adjusting for several important clinical risk factors for coronary artery disease.

### Women have higher CRP levels

The clinical significance of CRP is not gender-specific. However, women appear to have higher plasma CRP levels than men do. In the Women's Health Study,<sup>54</sup> women who subsequently had a cardiac event had a median CRP level of 0.42 mg/dL, compared with 0.28 mg/dL in those who remained event-free. In contrast, in the Physicians' Health Study, the median CRP in men with cardiac events was 0.15 mg/dL, vs 0.11 in those who were event-free.<sup>52</sup>

Furthermore, postmenopausal women who take hormone replacement therapy have approximately twofold higher CRP values than those who are not on hormone replacement therapy.<sup>55</sup> Interestingly, a recent study of postmenopausal women reported no correla-





tion between CRP levels and coronary calcium score by electron beam computed tomography for coronary artery disease screening.<sup>56</sup> In the Women's Health Study,<sup>57</sup> healthy women in the highest CRP quartile ( $> 0.73$  mg/dL) had a fivefold higher risk of any vascular event and a sevenfold higher risk for MI or stroke compared with those in the lowest CRP quartile.

### CRP in patients with diabetes or hyperlipidemia

Additional support for use of CRP measurements comes from studies that specifically evaluated its role in other medical conditions such as diabetes mellitus and hyperlipidemia. In an overall healthy population, advancing age, higher body mass index, and rising glycohemoglobin concentration have been shown to be associated with increasing CRP levels.<sup>58</sup> In people with diabetes, CRP levels in the highest tertile ( $> 0.28$  mg/dL) were associated with a twofold increase in cardiovascular mortality after adjusting for age, sex, and glucose tolerance status.<sup>59</sup>

Hypercholesterolemia, defined as an elevated ratio of total cholesterol to HDL (TC:HDL), is a known major modifiable risk factor for coronary artery disease. (A ratio greater than 5 is considered abnormal or elevated.) It appears that elevated CRP is just as potent a predictive risk indicator as an elevated TC:HDL ratio, and the combination of the CRP level and the TC:HDL ratio may be the best overall predictor of future MI (FIGURE 7).<sup>60</sup>

These important studies highlight the significance of incorporating CRP assessment in screening healthy persons at risk for future cardiovascular events. Especially in patients with diabetes or hyperlipidemia or both, hs-CRP assays provide strong additive prognostic value and should be considered as a routine part of screening examination.

### Risk elevated with CRP $> 0.38$ mg/dL for healthy women, $> 0.15$ for healthy men

It appears from the data available thus far that a CRP value greater than 0.38 mg/dL for otherwise healthy women and 0.15 mg/dL for healthy men identifies individuals who may benefit from aggressive risk-factor modification and close medical follow-up.

## ■ THERAPY TO REDUCE INFLAMMATION

The complexity of the inflammatory cascade would suggest that one specific therapy may not halt the process of atherogenesis. While this is probably true, certain commonly used preventive therapies hold a particular promise in slowing atherosclerosis.

**Aspirin.** In the Physicians' Health Study, men who regularly used aspirin had a 44% lower incidence of first MIs.<sup>52,61</sup> Importantly, the magnitude of the benefit was lowest in men in the lowest quartile of CRP level, and highest in the highest CRP quartile. Thus, the anti-inflammatory properties of aspirin may contribute to its efficacy in preventing cardiovascular disease.

**Statins** are known to reduce ischemic cardiac events by lowering LDL levels, but they may also have immune-modulating and anti-inflammatory properties.

The Cholesterol and Recurrent Events (CARE) trial<sup>62</sup> showed a 24% reduction in the rate of death or MI in patients receiving pravastatin compared with placebo. Recently, Ridker et al<sup>62</sup> reported a direct relationship between the degree of risk reduction and baseline levels of CRP in the CARE trial. In fact, pravastatin resulted in a dramatic 54% relative risk reduction of coronary artery disease in patients with active inflammation (defined as elevated serum amyloid-A and CRP) compared to a 25% reduction in those without inflammation despite nearly identical baseline lipid profiles in both groups. Furthermore, over a 5-year follow-up, pravastatin-treated patients had a significant 38% reduction in mean CRP values compared to placebo, which was independent of changes in lipid profile.<sup>63</sup>

**Angiotensin-converting enzyme (ACE) inhibitors** continue to impress clinicians in their broad spectrum of efficacy in patients with or without heart failure as well as those with or without established coronary atherosclerosis.

Recent data from the Heart Outcomes Prevention Evaluation (HOPE) study showed a remarkably consistent 21% relative reduction in death, MI, or stroke in patients with normal left ventricular function and either established coronary artery disease or diabetes without established coronary artery disease

In ST-elevation MI, CRP levels reach a peak in 2 to 4 days

who received an ACE inhibitor compared with placebo.<sup>64</sup> This observation lends support to previous studies that found that ACE inhibitors have antiproliferative properties.

#### **Trials support CRP measurement**

Collectively, data from these trials of readily available therapies provide strong evidence for implementing high-sensitivity CRP measurements in routine clinical practice, and using them not only in screening for coronary disease but also in assessing the success of therapeutic interventions.

#### **■ FUTURE STRATEGIES TO REDUCE INFLAMMATION**

Although the emphasis at present is on acute phase proteins, the ultimate goal would be to halt atherosclerosis upstream in the complex inflammatory cascade. In this quest, inhibition of cytokines such as TNF- $\alpha$ , IL-6, CD40 ligand, and transcription factor NF- $\kappa$ B hold promise.

**Anti-TNF- $\alpha$  antibody.** Preliminary data suggest that giving anti-TNF- $\alpha$  antibody (infliximab) reduces other inflammatory cytokines such as IL-6 and thus production of acute phase proteins.<sup>65</sup> Anti-TNF- $\alpha$  therapy may hold potential in prevention of coronary artery disease as well as restenosis following percutaneous coronary intervention.

**Anti-CD40L antibody.** Similarly, giving anti-CD40L antibody to hyperlipidemic mice led to a dramatic 59% reduction in atherosclerotic lesion size and a 79% reduction in lipid content.<sup>66</sup> Therefore, anti-CD40L antibody may prove to be invaluable in atherosclerosis regression and plaque stabilization.

**Flavonoids and gallates** (phenolic compounds present in red wine and plants) have been shown to inhibit activation of NF- $\kappa$ B in experimental studies.<sup>67,68</sup>

**Aspirin** has also been shown to inhibit NF- $\kappa$ B activity.<sup>69</sup> Given the pivotal role of NF- $\kappa$ B in the inflammatory cascade (FIGURE 2), a therapy that inhibits this trigger of inflammation without causing significant adverse effects would contribute tremendously to halting atherosclerosis.

**Cyclo-oxygenase 2 (COX-2) inhibitors.** Inhibition of COX-2, a promoter of inflamma-

tory prostanoids and prominently expressed in atherosclerotic tissue, can potentially provide additive benefit to other known COX-1 inhibitors such as aspirin or nonsteroidal anti-inflammatory drugs. While COX-2 inhibitors have been shown to be effective in inflammatory conditions such as rheumatoid arthritis and osteoarthritis, their efficacy in coronary atherosclerosis prevention is not well known. One concern with selective COX-2 inhibition is its lack of antiplatelet activity, which may negate its anti-inflammatory benefit.

#### **■ CONCLUSION AND RECOMMENDATIONS**

In general, it appears that for a given clinical scenario, the higher the CRP level, the greater the risk of future events. Thus, for healthy persons at risk for coronary artery disease, CRP even within the normal range should not be disregarded. Instead, a high-sensitivity assay should be used in persons with clinical risk factors (smoking, diabetes, hyperlipidemia), and those with CRP in the upper range of normal should be considered for aggressive risk-factor modification and early therapeutic intervention.

Intense research is going on, targeting novel therapies aimed at various inflammatory cytokines in the inflammatory cascade. The results of these investigations will likely provide new directions in therapy for atherosclerosis. However, the greater challenge will still be to appropriately incorporate these findings into clinical practice.

#### **General guidelines**

Highly sensitive assays for CRP are commercially available from several vendors (eg, Dade Behring, Abbott Laboratories, Roche Laboratories) for inpatient and outpatient screening evaluation and can be ordered like other routine laboratory tests. Clinicians should ask their local laboratories for additional information about the locally available assay and the normal reference values.

An hsCRP assay should be ordered for risk stratification in patients with MIs or unstable angina, those undergoing coronary revascularization, or healthy persons who smoke or have diabetes mellitus or hyperlipidemia, based on available evidence thus far.

In acute MI,  
we recommend  
measuring CRP  
on admission



- **In patients with acute MI**, an hsCRP assay should be ordered on admission. A level greater than 2.55 mg/dL identifies patients at high risk. Coronary revascularization should be performed as indicated; however, its influence on CRP levels in acute MI requires further investigation.

- **In patients with unstable angina**, an hsCRP assay should be drawn upon admission or at discharge. Those with CRP levels greater than 0.3 mg/dL should be considered at higher risk for future ischemic events and managed aggressively in achieving therapeutic goals. Appropriate medical therapy (statins, aspirin, ACE inhibitors) should be started, preferably in the hospital or at hospital discharge. Aggressive management may include coronary revascularization if indicated.

- **In patients undergoing coronary revascularization**, those with CRP levels greater than 0.3 mg/dL before the procedure or

greater than 0.5 mg/dL at 72 to 96 hours after the procedure should be followed closely for ischemic complications and late restenosis.

- **In persons without documented coronary artery disease**, especially those who smoke or have diabetes mellitus or hyperlipidemia, an hsCRP assay should be considered as a screening tool for early detection of subclinical inflammation. Other causes of inflammation should be ruled out before ordering this assay as a screening tool. CRP levels in the upper tertile or quartile of the normal reference range have been associated with future ischemic events. In general, a level of 0.38 mg/dL or greater for healthy postmenopausal women and 0.15 mg/dL or greater for men may be considered as thresholds for future risk. In these persons, therapy with aspirin and statins has been shown to reduce future risk of ischemic events.<sup>52,62</sup>



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