C-Reactive Protein as a Cardiovascular Risk Factor
More Than an Epiphenomenon?

Wim K. Lagrand, MD; Cees A. Visser, MD, PhD; Willem T. Hermens, PhD; Hans W.M. Niessen, MD, PhD; Freek W.A. Verheugt, MD, PhD; Gert-Jan Wolbink, MD, PhD; C. Erik Hack, MD, PhD

Background—Circulating levels of C-reactive protein (CRP) may constitute an independent risk factor for cardiovascular disease. How CRP as a risk factor is involved in cardiovascular disease is still unclear.

Methods and Results—By reviewing available studies, we discuss explanations for the associations between CRP and cardiovascular disease. CRP levels within the upper quartile/quintile of the normal range constitute an increased risk for cardiovascular events, both in apparently healthy persons and in persons with preexisting angina pectoris. High CRP responses after acute myocardial infarction indicate an unfavorable outcome, even after correction for other risk factors. This link between CRP and cardiovascular disease has been considered to reflect the response of the body to the inflammatory reactions in the atherosclerotic (coronary) vessels and adjacent myocardium. However, because CRP localizes in infarcted myocardium (with colocalization of activated complement), we hypothesize that CRP may directly interact with atherosclerotic vessels or ischemic myocardium by activation of the complement system, thereby promoting inflammation and thrombosis.

Conclusions—CRP constitutes an independent cardiovascular risk factor. Unraveling the molecular background of this association may provide new directions for prevention of cardiovascular events. (Circulation. 1999;100:96-102.)

Key Words: cardiovascular diseases □ myocardial infarction □ inflammation □ risk factors □ physiology

Recent studies provide evidence that inflammation plays a role in the pathogenesis of cardiovascular disease.1–3 Some inflammatory or hemostatic markers actually constitute cardiovascular risk factors. In this respect, the acute phase reactant C-reactive protein (CRP) is of special interest: Baseline levels of CRP in apparently healthy persons or patients with stable angina pectoris constitute an independent risk factor for cardiovascular events,4–8 whereas the rise in CRP after acute myocardial infarction (AMI)9–16 or during unstable angina pectoris 17–20 correlates with outcome.

The link between CRP and cardiovascular disease is thought to be indirect in that circulating CRP only reflects the extent of the acute phase reaction in response to nonspecific stimuli such as confounding risk factors, atherosclerosis, vascular injury, ischemia, and necrosis. However, several arguments are against this explanation that increased plasma levels of CRP are merely an epiphenomenon. First, chronic infections that cause a rise in circulating CRP also yield a higher risk for cardiovascular disease.21–24 Second, CRP is a cardiovascular risk factor even after correction for other risk factors.7 Finally, CRP can be found localized in inflamed tissues,25 including atherosclerotic vessels26 and infarcted myocardium.27,28 Here we review studies showing associations between CRP and cardiovascular disease and discuss possible explanations for these associations.

C-Reactive Protein

Acute phase responses are induced by cytokines released from the jeopardized tissue.29,30 These cytokines stimulate the liver to synthesize acute phase proteins including CRP.31 Plasma CRP increases markedly during acute phase reactions.32 The physiological role of CRP is yet unknown. In vitro, CRP displays both anti-inflammatory and proinflammatory effects.33,34 The latter includes the ability of ligand-bound CRP to activate the complement system.34

CRP and Cardiovascular Disease

Regarding associations between circulating CRP and cardiovascular disease (see Table 1), diseases without (atherosclerosis and stable and unstable angina) or with myocardial tissue damage (AMI) should be distinguished. In the latter situation the acute phase response is triggered, at least in part, by myocardial necrosis, and variations in postinfarct rise of circulating CRP are analyzed. In contrast, in the former the acute phase response is not triggered (at least not by myocardial necrosis) and baseline levels of circulating CRP are
TABLE 1. Studies Analyzing Associations Between CRP and Cardiovascular Disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of Study</th>
<th>Study Population (No. of Patients)</th>
<th>Follow-Up Time</th>
<th>CRP Assay Sensitivity, mg/dL*</th>
<th>Normal Range, mg/dL*</th>
<th>Correction for Risk Factors</th>
<th>Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Beer (1982)</td>
<td>Prospective</td>
<td>AMI (33) UAP (7) ACP (5)</td>
<td>10 d</td>
<td>0.001</td>
<td>90% &lt; 0.3, 99% &lt; 1.0</td>
<td>No</td>
<td>Post-AMI rise of CRP correlates with infarct size; persistently high levels associated with coronary events; CRP not correlated with clinical outcome in UAP</td>
</tr>
<tr>
<td>Pietilä (1987)</td>
<td>Prospective</td>
<td>(first) AMI (23)</td>
<td>14 d</td>
<td>1.0</td>
<td>&lt;1.0</td>
<td>No</td>
<td>Post-AMI rise of CRP correlates with infarct size; reperfusion reduces infarct-related CRP response</td>
</tr>
<tr>
<td>Berk (1990)</td>
<td>Prospective</td>
<td>UAP (37) CSAP (32) ACP (30)</td>
<td>8 d</td>
<td>0.6</td>
<td>&lt;0.6</td>
<td>No</td>
<td>CRP significantly higher in UAP than CSAP and ACP; CRP associated with occurrence of coronary events in UAP</td>
</tr>
<tr>
<td>Pietilä (1991)</td>
<td>Prospective</td>
<td>AMI (30)</td>
<td>10 d</td>
<td>1.0</td>
<td>&lt;1.0</td>
<td>No</td>
<td>Post-AMI rise of CRP in thrombolysis-treated AMI correlates with post-AMI heart failure but not with infarct size</td>
</tr>
<tr>
<td>Pietilä (1993)</td>
<td>Prospective</td>
<td>AMI (108)</td>
<td>4 d</td>
<td>1.0</td>
<td>&lt;1.0</td>
<td>No</td>
<td>Post-AMI rise of CRP correlates with infarct size; reperfusion reduces infarct-related CRP response</td>
</tr>
<tr>
<td>Liuzzo (1994)</td>
<td>Prospective</td>
<td>CSAP (32) UAP (31) ACP (29)</td>
<td>6 mo</td>
<td>0.005</td>
<td>90% &lt; 0.3, 99% &lt; 1.0</td>
<td>No</td>
<td>Elevated CRP (and SAA) on admission predicts coronary events in UAP</td>
</tr>
<tr>
<td>Casi (1995)</td>
<td>Prospective</td>
<td>AMI (40)</td>
<td>9 d</td>
<td>0.2</td>
<td>&lt;0.3</td>
<td>(mean of controls)</td>
<td>No</td>
</tr>
<tr>
<td>Thompson (1995)</td>
<td>Prospective</td>
<td>CSAP (1026) UAP (1346) ACP (411)</td>
<td>2 y</td>
<td>ND</td>
<td>ND</td>
<td>Yes</td>
<td>Association between CRP and coronary events independent of extent of CAD; adjusted for fibrinogen; association between CRP and coronary events no longer significant</td>
</tr>
<tr>
<td>Mendall (1996)</td>
<td>Population-based Cross-sectional</td>
<td>Random sample of middle-aged men (989)</td>
<td>NA</td>
<td>0.002</td>
<td>ND</td>
<td>Yes</td>
<td>CRP within normal range correlates with hemostatic, lipid, and infectious risk factors; higher levels associated with CVD</td>
</tr>
<tr>
<td>Kuller (1996)</td>
<td>Nested, case-control</td>
<td>High-risk men (256) Controls (491)</td>
<td>10–17 y</td>
<td>0.008</td>
<td>0.05–0.25</td>
<td>Yes</td>
<td>1st vs 4th CRP quartile: RR = 4.3 for CVD death, RR for nonfatal AMI not related to CRP</td>
</tr>
<tr>
<td>Pietilä (1996)</td>
<td>Prospective</td>
<td>AMI (188)</td>
<td>24 mo</td>
<td>1.0</td>
<td>&lt;1.0</td>
<td>Yes</td>
<td>Post-AMI rise of CRP higher in patients dying within 6 months after AMI; no correlation between CRP levels and infarct size</td>
</tr>
<tr>
<td>Ueda (1996)</td>
<td>Retrospective</td>
<td>AMI (37)</td>
<td>NA</td>
<td>ND</td>
<td>99% &lt; 0.02</td>
<td>No</td>
<td>Peak CRP $\geq$ 20 mg/dL is predictive for cardiac rupture, irrespective of infarct size</td>
</tr>
<tr>
<td>Haverkate (1997)</td>
<td>Prospective</td>
<td>CSAP (743) UAP (1030) ACP (226)</td>
<td>2 y</td>
<td>0.005</td>
<td>90% &lt; 0.3, 99% &lt; 1.0</td>
<td>Yes</td>
<td>Baseline CRP predictive for coronary events or ischemic stroke in UAP and CSAP</td>
</tr>
<tr>
<td>Toss (1997)</td>
<td>Prospective</td>
<td>UAP and non-Q-wave AMI (965)</td>
<td>5 mo</td>
<td>&lt;0.2</td>
<td>ND</td>
<td>No</td>
<td>Fibrinogen at inclusion associated with incidence of cardiac death and AMI; CRP associated with incidence of death</td>
</tr>
<tr>
<td>Ridker (1997)</td>
<td>Nested, case-control</td>
<td>Patients with CVD (543) Controls (543)</td>
<td>8 y</td>
<td>0.008</td>
<td>0.05–0.25</td>
<td>Yes</td>
<td>Baseline CRP predictive for coronary events or ischemic stroke; aspirin: significant risk reduction for AMI in highest CRP quartile</td>
</tr>
<tr>
<td>Anzai (1997)</td>
<td>Prospective</td>
<td>(First) AMI (220)</td>
<td>1 y</td>
<td>ND</td>
<td>ND</td>
<td>No</td>
<td>Early post-AMI rise of CRP associated with cardiac rupture, left ventricle aneurysm formation, and 1-year mortality</td>
</tr>
<tr>
<td>Tracy (1997)</td>
<td>Nested, case-control</td>
<td>Patients with CVD event (146) Controls (146) (Patients ≥65 years)</td>
<td>2.4 y</td>
<td>0.008</td>
<td>0.008–0.31</td>
<td>Yes</td>
<td>CRP associated with CVD events in the elderly; association most prominent in patients with subclinical disease at baseline</td>
</tr>
</tbody>
</table>

CSAP indicates chronic stable angina pectoris; UAP, unstable angina pectoris; ACP, atypical chest pain; CVD, cardiovascular disease; ND, no data; and NA, not applicable.

*As notified by authors.
studied. This explains why circulating CRP levels associated with increased risk or worse course vary from cutoff points of 0.3 mg/dL in unstable angina to 20 mg/dL in AMI.

In cardiovascular disease without myocardial necrosis, plasma CRP correlates with the extent and severity of atherosclerosis and with hemostatic, lipid, and infectious risk factors for cardiovascular disease. Even after correction for these risk factors, high-normal CRP levels still predict an increased risk for development of symptomatic peripheral arterial disease and the occurrence of coronary events in both stable and unstable angina pectoris and even in apparently healthy persons.

AMI triggers an acute phase response resulting in a rise of circulating CRP levels, which correlates with infarct size. Though infarct size is a major denominator for long-term prognosis after AMI, short-term prognosis, in particular mortality during the first 6 months, is associated with CRP responses in thrombolysis-treated patients independent of infarct size. Hence baseline levels of CRP constitute an independent risk factor for coronary events in healthy persons as well as in patients with stable or unstable angina pectoris. The postinfarct rise of circulating CRP is associated with short-term clinical outcome in patients with AMI. We will now discuss potential mechanisms explaining these associations (Table 2).

### Association Between CRP and Cardiovascular Disease: Possible Explanations

#### CRP Reflects Inflammation of (Coronary) Vessels by Pathogenic Agents

CRP may increase in cardiovascular disease in response to infectious (viral, bacterial) agents inducing inflammatory reactions in the (coronary) vessels. Although this possibility cannot be excluded definitely, infectious agents in coronary vessels or myocardium have not been demonstrated convincingly thus far. Notably, chronic infections elsewhere in the body are also associated with an increased risk for cardiovascular disease. Furthermore, the chronologic sequence of infection by pathogens and the initiation and progression of cardiovascular disease still remains to be elucidated. These infections likely are associated with raised CRP levels. Hence, chronic infections may be associated with cardiovascular disease by a coinciding rise of plasma CRP due to elicitation of an acute phase response.

#### CRP Reflects Inflammation Related to the Atherosclerotic Process

CRP levels have been considered to reflect the extent of inflammatory reactions in the atherosclerotic vessels. Thus, by virtue of its acute phase behavior, CRP is a marker for severity and progression of atherosclerotic processes in the vessels. However, many patients with stable and with unstable angina pectoris have normal levels of acute phase proteins, implying that coronary atherosclerosis itself does not induce a full-blown acute phase response. Moreover, levels of other acute phase reactants do not show similar associations as reported for CRP. Haverkate et al reported that baseline CRP levels predict subsequent coronary events in both stable and unstable angina, whereas levels of serum amyloid A peptide do not. Acute phase proteins such as α1-acid glycoprotein or α1-antichymotrypsin are also not associated with cardiovascular disease. Some studies report that CRP levels correlate with the incidence of coronary events only when not adjusted for fibrinogen. However, in one of these studies, a rather insensitive assay for CRP was used that was unable to differentiate levels within the normal range.

If baseline CRP reflects the extent of arteriosclerotic processes, levels would be expected to be higher in patients with angina pectoris than in apparently healthy persons, as was indeed found in a few small studies. However, median levels of CRP in the study of Mendall et al in apparently healthy individuals are remarkably similar to those reported by Haverkate et al in patients with stable angina pectoris (0.17 mg/dL). Finally, the possibility that CRP is linked to cardiovascular disease because it increases in response to clot formation superimposed on atherosclerotic lesions in the vessels is unlikely.

#### CRP Reflects Extent of (Myocardial) Ischemia

Myocardial ischemia without necrosis does not induce a rise of circulating CRP levels, as was demonstrated in patients with variant angina pectoris with documented episodes of myocardial ischemia. Hence the explanation that CRP simply reflects the extent of myocardial ischemia is not tenable.

#### CRP Reflects Extent of (Myocardial) Necrosis

Obviously, myocardial necrosis triggers a rise of circulating CRP. Thus the extent of necrosis in part determines the CRP response. In agreement herewith, CRP correlates with infarct size in conservatively treated patients with AMI. These correlations are less significant after early coronary recanalization in patients with AMI. Recanalization of an infarct-related coronary artery improves prognosis after AMI as it decreases infarct size. It also attenuates the CRP response, suggesting that successful reperfusion may limit inflammation in infarcted myocardium, though it also may induce reperfusion injury. Hence postinfarct CRP responses may simply reflect the extent of myocardial necrosis, although most studies do not correct for other possible confounders. However, this explanation does not fit with observations that CRP responses after AMI predict clinical outcome such as 6-month mortality, irrespective of infarct size. Thus CRP

### Table 2. CRP as an Indirect Cardiovascular Risk Factor: Possible Explanations

<table>
<thead>
<tr>
<th></th>
<th>CRP reflects inflammation of (coronary) vessels by pathogenic agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CRP reflects inflammation related to the extent and severity of atherosclerosis</td>
</tr>
<tr>
<td>2</td>
<td>CRP reflects inflammation related to the extent of myocardial ischemia (angina)</td>
</tr>
<tr>
<td>3</td>
<td>CRP reflects inflammation related to the extent of myocardial necrosis (AMI)</td>
</tr>
<tr>
<td>4</td>
<td>CRP reflects the amount and activity of circulating proinflammatory cytokines (eg, tumor necrosis factor-α, interleukin-1, interleukin-6).</td>
</tr>
</tbody>
</table>

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responses after AMI cannot simply reflect the extent of myocardial necrosis.

CRP Reflects Amount and Activity of Circulating Proinflammatory Cytokines

Local or circulating pro-inflammatory cytokines are detectable in atherosclerosis, unstable angina, or AMI and correlate with plasma CRP levels. Accordingly, cytokines may be the real risk factors, whereas plasma CRP reflects the release of these mediators. Although this possibility cannot be ruled out definitely, it does not explain the localization of CRP in inflamed tissues, including atherosclerotic vessels and infarcted myocardium. Rather, latter findings point to a contribution of CRP in the inflammatory processes ensuing in ischemic myocardium and atherosclerotic lesions.

Taken together, all explanations for the associations between CRP and cardiovascular disease, as discussed above, have in common that CRP levels are indirectly linked to the extent and severity of the atherosclerotic processes. None of these explanations consider that CRP may directly participate in the inflammatory reactions, contributing to tissue damage and clinical complications in cardiovascular disease.

CRP-Mediated Inflammation in Cardiovascular Disease: A Hypothesis

Recently, we observed colocalization of CRP and activated complement fragments in infarcted (but not in normal) myocardium of patients who had died after AMI. Furthermore, with the use of an assay that specifically detects CRP-induced complement activation, patients with AMI were found to have increasing plasma levels of CRP-induced complement activation fragments (W.K. Lagrand, MD, et al, unpublished observations, 1997). Thus, after AMI, CRP contributes to inflammation in ischemic myocardium by activating complement. Notably, CRP and activated complement have also been found in human atherosclerotic vessels. Thus CRP may constitute a cardiovascular risk factor because it localizes in ischemic myocardium and atherosclerotic lesions, thereby promoting local complement activation.

Local activation of the classic pathway of complement by ischemic myocardium has been observed in various animal models for AMI. Inhibition of this activation attenuates the infiltration of neutrophils into the jeopardized myocardium and reduces infarct size. Also in humans, complement is activated by ischemic myocardium. Activated complement fragments may mediate vascular and myocardial damage through various mechanisms: stimulation, aggregation and degranulation of neutrophils; enhancement of clotting by induction of tissue factor expression, and the formation of procoagulant microvesicles, or even direct damage of endothelial cells and cardiomyocytes by insertion of pores (C5b-9) into the cell membrane. Furthermore, activated complement may induce arrhythmia and provoke contractile dysfunction and vasoconstriction of the coronary vessels. Thus part of the hemodynamic alterations and myocardial dysfunction after myocardial ischemia and infarction may result from local complement activation.

Ligands for CRP in Cardiovascular Disease

Pivotal in CRP-mediated complement activation is binding of CRP to a ligand. Postulated ligands for CRP in atherosclerosis include lipoproteins. CRP can bind to phosphatidylcholine vesicles containing lysophosphatidylcholine. Lyosphopholipids are generated from phospholipids by phospholipase A2 (PLA2) enzymes and have been demonstrated in infarcted myocardium. Therefore we postulate that lysosphopholipids constitute the ligand for CRP in ischemic myocardium (see Figure).

PLA2 enzymes hydrolyze phospholipids to yield lysophospholipids and free fatty acid. Mammals have various PLA2 enzymes, including cytosolic (c)PLA2 and secretory (s)PLA2. Plasma concentrations of the latter markedly increase during acute phase reactions. The inner and outer leaflet of the cell membrane of normal cells differ in phospholipid composition, sphingomyelin and phosphatidylcholine being present in the outer leaflet and phosphatidylserine and phosphatidylethanolamine mainly in the inner. During apoptosis or ischemia this asymmetry is lost and the various phospholipids of outer and inner leaflets exchange (“flip-flop” of the membrane) (see Figure). Remarkably, sPLA2 cannot hydrolyze the phospholipids in the outer leaflet of normal cells but easily hydrolyzes those of a flip-flopped cell. Thus ligands for CRP may be generated on flip-flopped cells by sPLA2 (see Figure). Alternatively, lysosphopholipids in the outer leaflet of the cell membrane may result from hydrolysis of phospholipids in the inner leaflet via activation of cPLA2 followed by a flip-flop (see Figure). Finally, ischemic cells may generate microvesicles, which, on interaction with PLA2 enzymes, may also constitute binding sites for CRP. Ligand-bound CRP activates the classic pathway of complement, and this activation subsequently enhances inflammation and contributes to myocardial tissue damage or dysfunction (see Figure).

Implications

Our hypothesis predicts that high CRP responses after AMI will lead to more intense CRP depositions and inflammatory reactions and hence tissue damage in the jeopardized myocardium (see Table 1). It also explains why high-normal or slightly increased baseline levels of plasma CRP constitute and predict an increased risk for cardiovascular events since in these cases one condition for CRP-mediated complement activation (ie, available CRP in plasma) is then fulfilled. The other condition is the presence of lyosphopholipids and membrane flip-flop in the coronary vessels and affected ischemic myocardium (see Figure), which may result from short-term ischemic periods. Alternatively, variations in baseline plasma CRP of individuals may reflect differences in CRP responses elicited by appropriate stimuli, for example caused by genetic differences in the CRP gene yielding high and low responders, the former being at risk for cardiovascular disease.

Consequently, prevention of cardiovascular events in persons with high-normal or elevated plasma CRP levels may be achieved by anti-inflammatory agents like aspirin, reducing the synthesis of CRP (cytokine-antagonists?), preventing the binding of CRP to membranes (phosphorylcholine-like...
Model to explain the proinflammatory effect of CRP. Lysophospholipids in the outer leaflet of flip-flopped cells, generated by cPLA₂ or sPLA₂, constitute ligands for CRP. During ischemia, phospholipids and lysophospholipids of inner and outer leaflet of the cell membrane exchange ("flip-flop"), resulting in a more equal distribution of (lyso)phospholipids among either leaflet, compared with the asymmetrical localization in normal cells. Ligand-bound CRP activates complement, which leads to further tissue damage and hemodynamic effects. Binding of CRP to phospholipids may occur at cells but also at microvesicles derived from flip-flopped cells.

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References


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