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C-reactive protein comes of age

Subodh Verma*, Paul E Szmitko and Paul M Ridker

SUMMARY

Cardiovascular disease remains a leading cause of death throughout the world despite advances in its detection and treatment. Commonly used risk algorithms, such as the Framingham Risk Score fail to identify all affected individuals. Novel cardiovascular risk factors that identify these missed individuals would greatly improve overall care of patients. C-reactive protein (CRP), an inflammatory biomarker, has emerged as a leading candidate to fulfill this role. Based on the results of several prospective epidemiologic studies, CRP has emerged as one of the most powerful predictors of cardiovascular disease. This marker provides valuable information to clinicians in various clinical settings, ranging from overt cardiovascular disease, stable angina, presenting acute coronary syndromes and peripheral vascular disease, to the metabolic syndrome. Furthermore, CRP has been demonstrated to actively contribute to all stages of atherogenesis, participating in endothelial dysfunction, atherosclerotic-plaque formation, plaque maturation, plaque destabilization and eventual rupture. Thus, it might also serve as a therapeutic target. It is our contention that the future will see much wider use of CRP and CRP-driven therapies in clinical medicine, improving our ability to identify and manage cardiovascular disease.

REVIEW CRITERIA

MEDLINE was searched for papers published from 1996 to October 2004, using the keywords "C-reactive protein", "cardiovascular disease", "atherosclerosis", "endothelium", "endothelium and epidemiology" and "epidemiology". Full-text original research and review articles from peer-reviewed journals were selected. Only articles printed in English were reviewed. The reference lists from retrieved articles were also scanned.

CME

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INTRODUCTION

In the past century, our understanding of the underpinnings of atherosclerosis and cardiovascular disease has evolved significantly. Since atherosclerosis is now widely believed to represent a process of vascular inflammation, extensive research has been done into the utility of inflammatory biomarkers in clinical medicine. Accumulating evidence suggests that one such inflammatory biomarker, C-reactive protein (CRP), plays a critical role in the pathogenesis and prognostication of cardiometabolic risk.

Cardiovascular disease represents the leading cause of death throughout the Western world. Despite advances in its treatment and detection, current cardiovascular risk prediction algorithms, such as the Framingham Risk Score, fail to identify all susceptible individuals. A fifth of all cardiovascular events occur in individuals who have no identifiable traditional risk factors,[1] namely hypertension, smoking, hyperlipidemia, diabetes or family history, and most vascular events tend to occur in patients without very high cholesterol levels.[2] Thus, novel cardiovascular risk factors would greatly improve primary prevention strategies. The advent of high-sensitivity CRP (hsCRP) assays might help to improve CRP's candidacy to fulfill this role.

C-REACTIVE PROTEIN'S ROLE IN RISK ASSESSMENT

On the basis of results from several prospective epidemiologic studies, circulating hsCRP has emerged as one of the most powerful independent predictors of cardiovascular disease risk and cardiovascular death.[3] Elevated hsCRP concentrations predict cardiovascular risk in various subgroups of patients, including men and women without overt cardiovascular disease,[4] patients with stable angina or those with acute coronary syndromes,[5] after

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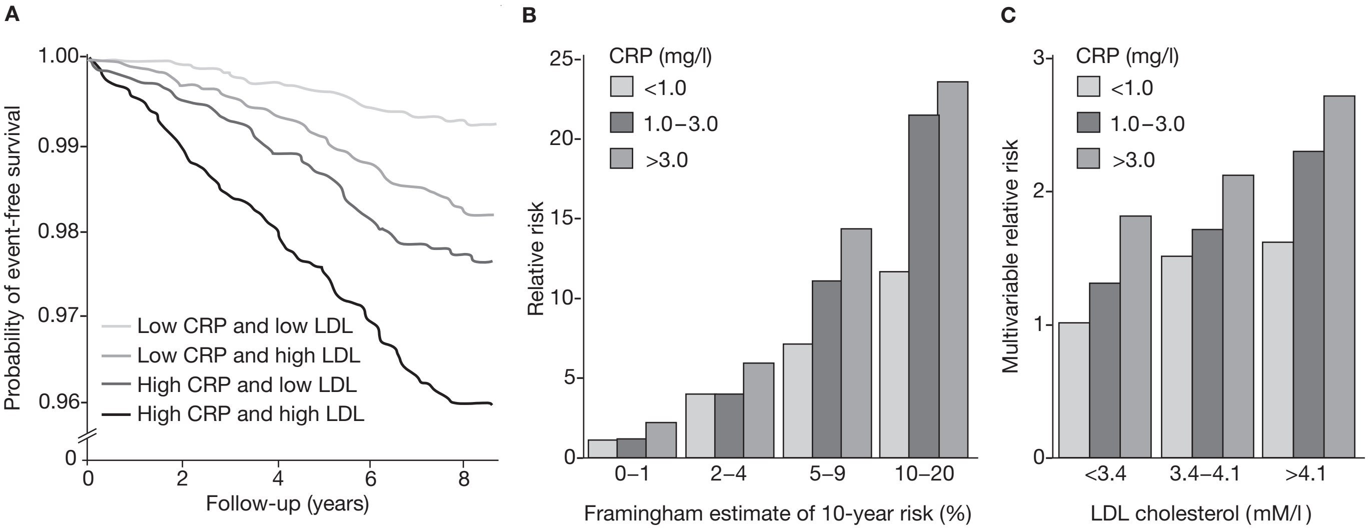

Figure 1 Predictive value of high-sensitivity C-reactive protein. (**A**) Cardiovascular event-free survival among apparently healthy individuals based on high-sensitivity CRP and LDL-cholesterol levels. (**B**) High-sensitivity CRP compared with all levels of Framingham Risk Score. (**C**) High-sensitivity CRP compared with all levels of LDL cholesterol. Copyright © 2002 Massachusetts Medical Society; adapted, with permission, from: Ridker PM *et al.* (2002) Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* **347:** 1557–1565.

myocardial infarction[6] and in those with the metabolic syndrome.[7] Furthermore, hsCRP predicts incident myocardial infarction and risk of ischemic stroke,[8] sudden cardiac death,[9] incident peripheral artery disease[10] and restenosis after percutaneous coronary intervention.[11] In primary prevention, CRP confers additional prognostic value at all levels of the Framingham Risk Score, metabolic syndrome and blood pressure.[2,12]

In head-to-head comparisons with LDL cholesterol, CRP was at least as strong a predictor of incident cardiovascular events. In the Women's Health Study,[2] 27,939 US women with no history of cardiovascular disease underwent Framingham risk assessment, hsCRP evaluation and a full lipid screen. Baseline concentrations of LDL cholesterol and hsCRP were compared for their ability to predict first myocardial infarction, ischemic stroke, coronary revascularization or cardiovascular death. Mean follow-up was 8.3 years. The relative risks for a future vascular event for increasing quintiles of hsCRP at baseline were 1.0, 1.8, 2.3, 3.2 and 4.5 ($P<0.001$). After adjustment for age, smoking status, diabetes, blood pressure and the use of hormone-replacement therapy, the relative risk in the top hsCRP quintile was 2.3 (95% CI 1.6–3.4). Risk of a first vascular event increased with increasing quintile for both LDL cholesterol and hsCRP (each $P<0.001$). Of all the vascular events that occurred in the study population, 46% occurred in participants whose baseline LDL-cholesterol levels were below current LDL-cholesterol goals. Importantly, LDL cholesterol and hsCRP levels correlated poorly ($r=0.08$), suggesting that these biomarkers predicted events in different risk groups. Assessment of LDL cholesterol and hsCRP levels combined provided an improvement in the prediction of survival free from cardiovascular events (Figure 1). The predictive power of hsCRP remained significant after adjustment for the Framingham Risk Score, a result reproduced in other studies.[13–15] Recent evidence also suggests that the prognostic potential of CRP extends beyond endothelial function testing.[16]

The Reykjavik Study[17] was a prospective cohort study of 18,569 middle-aged men and women with no history of myocardial infarction. After adjustment for typical Framingham covariates and additional control for diabetes, triglycerides, BMI and pulmonary function, the odds ratio for coronary heart disease among the participants with baseline CRP levels in the top 33% was 1.45 (95% CI 1.25–1.68). The odds ratio was lower than those reported in previous studies after Framingham adjustment (generally 1.7–1.8). This predictive value was, however, very close to those observed for hypertension and smoking. The fully adjusted odds ratio for

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hsCRP during the initial 10 years of follow-up was 1.84, reinforcing its status as a strong, independent predictor of heart disease risk.

The Centers for Disease Control and Prevention and the American Heart Association have made recommendations on the application of hsCRP for the assessment of cardiovascular risk.[18] They recognize that hsCRP retains an independent association with incident coronary events after adjustment for age, total cholesterol, HDL cholesterol, smoking, BMI, diabetes, hypertension, exercise level and family history of cardiovascular disease, and thus adds to the predictive capacity of established risk factors. In secondary prevention, hsCRP is a good predictor for poorer outcomes following acute coronary syndromes, percutaneous transluminal interventions or stroke. On the basis of the current clinical data available, the recommendation is to use hsCRP as a routine part of global cardiovascular risk assessment in patients at intermediate risk according to global risk assessment (10–20% risk of cardiovascular disease per 10 years) and for the estimation of prognosis in patients with stable coronary disease or acute coronary syndromes who need secondary preventive care.

CRP levels exhibit no circadian variability and, unlike cholesterol testing, measurement requires no fasting blood sample; therefore, testing may be done at any time of day. The population distribution of hsCRP seems to be consistent across sex and ethnic groups. Classifications of <1, 1–3 and >3 mg/l to differentiate low, moderate and high risk has been generally adopted clinically.[19] Although some investigators initially suggested that very high levels of hsCRP (>10 mg/l) were due to the acute-phase response and thus might represent false-positive findings, later data showed that this is not the case. Rather, individuals with persistent elevations of hsCRP >10 mg/l are at the highest risk. By contrast, the very lowest levels (<0.5 mg/l) represent exceptionally low risk, irrespective of other risk factors.[20] Regardless, the AHA suggests that if the hsCRP level is >10 mg/l, the test should be repeated and the patient should be examined for sources of infection or inflammation.[18]

DIABETES AND METABOLIC SYNDROME

It seems that hsCRP is useful for identifying patients with, or who are at risk of developing, diabetes and the metabolic syndrome.[21] The components of the metabolic syndrome are midline obesity, elevated triglycerides, decreased HDL cholesterol, hypertension and glucose intolerance. Levels of hsCRP correlate with these individual components and provide additional prognostic information regarding disease severity.[22] In the West of Scotland Coronary Prevention Study,[23] a randomized intervention trial of pravastatin in 6,447 middle-aged men over a 5-year period, baseline hsCRP levels above and below 3 mg/l were highly predictive of incident vascular events after stratification of patients by the presence or absence of the metabolic syndrome. The observed relative risks of future coronary events were as follows: 1.0 (reference) for low CRP and metabolic syndrome absent; 1.6 for high CRP and metabolic syndrome absent; 1.6 for low CRP and metabolic syndrome present; and 2.8 for high CRP and metabolic syndrome present (each $P<0.05$). Similar results from other studies support the relationship between inflammation and the metabolic syndrome.[21,24–27] Thus, it seems hsCRP should be a clinical criterion for the metabolic syndrome.

DOES C-REACTIVE PROTEIN INCITE ATHEROSCLEROSIS?

Atherosclerosis is regarded as a dynamic and progressive disease arising from the combination of endothelial dysfunction and inflammation.[28] The maintenance of vascular homeostasis depends on a balance between endothelium-derived relaxing and contracting factors. With disruption of this balance, the vasculature becomes susceptible to atheroma formation. Endothelial dysfunction, which implies the diminished production or availability of nitric oxide (NO), an increase in endothelium-derived contracting factors, such as endothelin-1, angiotensin or both, sets the stage for inflammation and atherogenesis. CRP appears to serve not only as a marker of this pathologic inflammatory process but also as an active partaker in all stages of atherogenesis, since it is present in atherosclerotic lesions but not in the normal vessel wall.[29]

Laboratory data from our group and others suggests that human recombinant CRP, at concentrations known to predict vascular disease, elicits a multitude of effects on endothelial biology favoring a proinflammatory and proatherosclerotic phenotype. CRP potently downregulates endothelial NO synthase transcription and destabilizes endothelial NO

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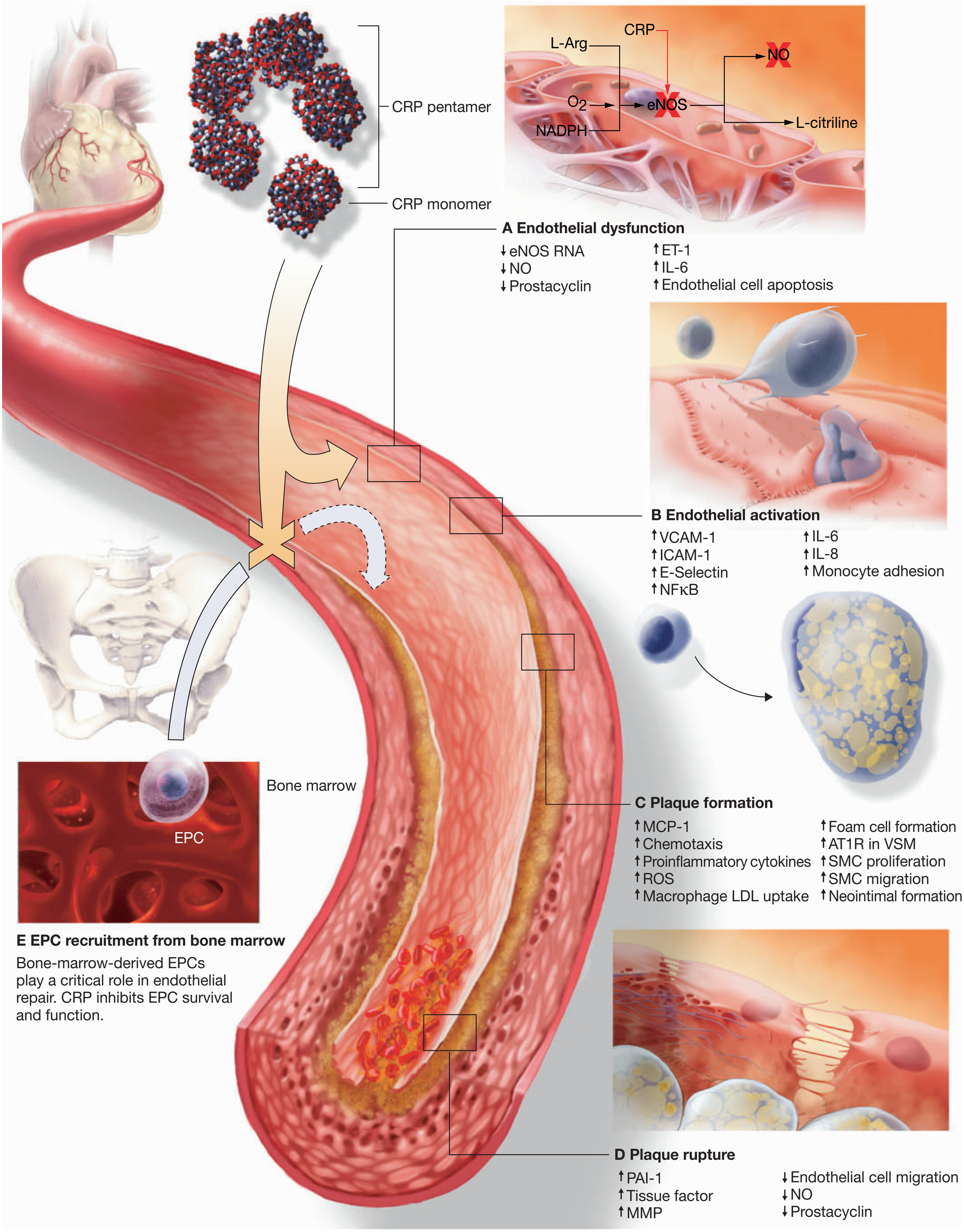

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Figure 2 The role of C-reactive protein in atherogenesis. (**A**) Endothelial dysfunction. (**B**) Endothelial cell activation. (**C**) Plaque formation. (**D**) Plaque rupture. (**E**) Inhibition of EPC survival and function. AT1R, angiotensin type I receptor; CRP, C-reactive protein; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cells; ET-1, endothelin-1; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin 6; IL-8, interleukin 8; MCP, monocyte chemotactic protein-1; MMP, matrix metalloproteinase; NADPH, nicotinamide adenine dinucleotidase phosphate; NFκB, nuclear factor κB; NO, nitric oxide; PAI-1, plasminogen activator inhibitor type I; ROS, reactive oxygen species; SMC, smooth-muscle cells; VCAM-1, vascular cell adhesion molecule-1; VSM, vascular smooth muscle.

synthase mRNA *in vitro*, resulting in decreased basal and lowered release of stimulated NO, a key endothelium-derived relaxing factor.[30] In a synchronous fashion, CRP stimulates endothelin-1 and interleukin 6 release from endothelial cells,[31] and decreases the production of the potent vasodilator prostacyclin,[32] shifting the balance towards endothelial dysfunction. Furthermore, CRP facilitates endothelial cell apoptosis and blocks angiogenesis by inhibiting NO production,[30] and inhibits bone-marrow-derived endothelial progenitor cell survival and differentiation.[33] Endothelial progenitor cells are thought to play an important part in postnatal neovascularization, and the ability of CRP to inhibit progenitor cells could be an important mechanism inhibiting compensatory angiogenesis in chronic ischemia.[34] For CRP to promote this proinflammatory phenotype, native pentametric CRP has been suggested to undergo structural modification, forming monomeric subunits.[35] By promoting endothelial dysfunction, CRP sets the stage for subsequent endothelial activation and plaque formation.

Endothelial activation is marked by the expression of adhesion molecules on the surface of endothelial cells. CRP potently upregulates nuclear factor κB,[36] a key proatherosclerotic nuclear transcription factor, and stimulates the expression of adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and E-selectin, which recruit monocytes to the vascular surface. Furthermore, expression of interleukin 8, induced by CRP, promotes monocyte–endothelial cell adhesion and arrest. Transmigration of monocytes into the arterial wall, stimulated by CRP-induced monocyte chemotactic protein-1, promotes inflammatory response by tumor necrosis factor α and interleukin 1, which promote lipid oxidation. This oxidation perpetuates this cycle, leading to atherosclerotic-plaque formation. CRP also has direct proatherogenic effects by directly upregulating angiotensin type 1 receptors in vascular smooth-muscle cells, stimulating vascular smooth-muscle migration, proliferation and neointimal formation.[37]

CRP plays a role in the destabilization of the atheroma's fibrous cap by stimulating matrix metalloproteinase 1 release, which degrades collagen and other matrix scaffolding proteins.[38] Platelet adherence and activation is enhanced by CRP-stimulated release of tissue factor from monocytes, and from decreases in NO and prostacyclin release. Furthermore, CRP impairs fibrinolysis by promoting the synthesis of plasminogen activator inhibitor type 1.

Expression of human CRP in mice actively promotes adverse cardiovascular processes. First, human CRP creates a prothrombotic phenotype, as evidenced by higher rates of thrombotic occlusion following arterial injury.[39] Second, by crossing CRP-transgenic mice with the atherosclerosis-prone apolipoprotein E knockout mice, CRP was shown to be active in atherogenesis *in vivo*.[40] The CRP transgenic apolipoprotein E knockout mice displayed accelerated aortic atherosclerosis, which was associated with increased complement deposition and elevated expression of angiotensin type I receptor, vascular cell adhesion molecule 1 and collagen within the lesions. CRP also, however, upregulates complement inhibitory proteins and protects endothelial cells from complement-mediated cell injury,[41] which suggests that a balance of proatherogenic and antiatherogenic effects of CRP on the vessel wall might be important in the development of atherosclerosis. The direct proatherogenic effects of CRP are depicted in Figure 2.

GENOTYPE–PHENOTYPE CORRELATION

Baseline levels of CRP show a clear heritability of approximately 40% in family studies. Currently, three polymorphisms in the CRP gene, which maps to chromosome 1, associated with changes in CRP level have been documented.[42–44] The first polymorphism, the 1059 C/G allele in exon 2, revealed that men with the 1059 C allele had a 36% lower median CRP level than those with the 1059 G allele.[42]

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Szalai *et al.*[43] showed that the length of an intron GT repeat influenced the level of CRP by approximately a factor of two. Finally, Brull *et al.*[44] demonstrated a two-fold difference in basal and stimulated CRP levels among individuals with the CRP gene +1444C>T allele. Although not yet established, such genotype-specific risk categories might identify individuals at risk of future cardiovascular events before CRP levels increase, or people who have low serum CRP levels but display an enhanced proinflammatory phenotype.

C-REACTIVE-PROTEIN-DRIVEN THERAPY

When hsCRP values are raised (>3 mg/l), what does the clinician have to offer his patient? First, the possible increased risk of developing vascular disease or for having their current condition worsen should be explained. Furthermore, the patient should be counseled that the best ways to lower CRP levels are already well-established methods for improving cardiovascular health; smoking cessation, exercise, blood-pressure control and cholesterol lowering with statins can all lower CRP levels. Strategies to increase HDL cholesterol might also counteract the harmful effects of CRP; HDL can prevent CRP-induced upregulation of inflammatory adhesion molecules via its oxidized phospholipid components.[45] Statin therapy in particular appears to be highly effective at lowering CRP levels. Results from several large-scale, randomized, controlled trials of statin therapy, including the Cholesterol and Recurrent Events (CARE) trial,[46] the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS),[15] the Pravastatin Inflammation CRP Evaluation (PRINCE) trial,[47] the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL)[48] and the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial,[49] suggest that 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) reduce CRP levels in addition to their cholesterol-lowering effect. Thus, the beneficial effect of statins on reducing adverse cardiovascular outcomes might be due to their ability to reduce inflammatory mediators, such as CRP, which fuel atherogenesis. In an effort to determine whether isolated, elevated CRP warrants medical treatment, the Justification of the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial[50] has been started.

This trial will prospectively address the relationship between statins, inflammation, CRP and incident vascular events to investigate whether long-term rosuvastatin 20 mg daily will reduce the rate of first major cardiovascular events (cardiovascular death, stroke, myocardial infarction, hospitalization for unstable angina or coronary revascularization) among individuals with LDL-cholesterol levels less than 3.36 mM/l (129 mg/dl) but who are at elevated risk because of hsCRP levels greater than 2.0 mg/l.

The critical link between CRP lowering and cardiovascular events has been demonstrated in analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy (TIMI 22; PROVE IT-TIMI 22) study,[51] in which patients who achieved low levels of CRP had better clinical outcomes at all levels of achieved LDL cholesterol. The best clinical outcomes were obtained among statin-treated patients who achieve the "dual goals" of LDL cholesterol <1.8 mM/l (<70 mg/dl) and CRP levels <2.0 mg/l. As such, achieving a dual target of low levels of LDL cholesterol and CRP were of greater importance for subsequent event-free survival than the specific allocation to either aggressive or moderate statin therapy.

CONCLUSION

The CRP-atherosclerosis relationship is still being elucidated. Epidemiologic and biologic evidence suggest that CRP is a powerful biomarker of and partaker in vascular disease. As our understanding of the molecular mechanisms involved in atherogenesis expands, new therapeutic targets will emerge. Further studies, in particular those assessing treatment strategies for patients with elevated CRP levels and no other modifiable cardiovascular risk factors, are required to provide us with evidence to appropriately manage these patients. Given CRP's proven status as a powerful predictor for cardiometabolic risk, we believe the future will see much wider use of CRP and CRP-driven therapies and improved ability to identify and treat the epidemic of cardiovascular disease.

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Competing interests
PR declared competing interests; go to the article online for details. VS and PES declared they have no competing interests.

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