

# The *impact* of *C-Reactive Protein*:

## A Look at the Most Recent Studies and Trials

By Davinder S. Jassal, MD, FRCPC; and  
Blair O'Neill, MD, FRCPC, FACC

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Ischemic heart disease is the world's leading killer, but new insights involving inflammatory markers could lead to quicker and more precise diagnosis of its cause.

Ischemic heart disease is the leading cause of death worldwide. It is associated with high patient morbidity and mortality. Approximately half of all individuals who present with an acute coronary event do not have any of the conventional risk factors, such as smoking, diabetes, and hypertension.<sup>1</sup> In recent years, new insights have revolutionised our understanding of potential inflammatory markers as risk factors for underlying cardiovascular disease.<sup>2-5</sup> In particular, C-reactive protein (CRP) has received great attention as one of these novel atherogenic markers.<sup>2-5</sup>

### What is CRP?

Inflammation plays a pivotal role in the development and evolution of atherosclerosis.<sup>6-8</sup> It has been recently recognised that both local and systemic inflammation exists in patients with coronary artery disease, whether stable or unstable. A number of acute phase inflammatory markers have been linked to the development of the acute plaque. CRP is an acute phase reactant produced by the liver in response to cytokine production, such as interleukins and tumour necrosis factor, during acute inflammation. Specifically, CRP is present in the vessel wall of coronary arteries

that binds to plasma membranes of damaged cells and activates complement via the classic pathway, leading to thrombus formation. In addition, CRP facilitates thrombogenesis by stimulating macrophages to overproduce tissue factor, contributing to the development of an acute coronary syndrome.<sup>6-8</sup>

### How to measure CRP

Standard CRP tests determine levels, which are increased up to 1000-fold in response to tissue inflammation, but cannot adequately determine the normal range. The development of high sensitivity assays for CRP (hs-CRP), that serve as important indicators of microinflammation, has become the standard.<sup>6-8</sup>

### CRP in healthy individuals?

There has been an increasing body of evidence to support the theory that serum concentration of CRP is an independent predictor of risk for a myocardial infarction (MI) and stroke among healthy individuals. Three studies, the Womens' Health Study, the Physicians' Health Study, and the MONICA-Ausburg cohort, suggest that

higher levels of CRP are predictive of future events in asymptomatic individuals (Table 1).<sup>5,9-11</sup>

The Womens' Health Study is an ongoing prospective trial investigating the use of acetylsalicylic acid (ASA) and vitamin E in the primary prevention of cardiovascular disease and cancer. Using the hs-CRP assay in the Womens' Health Study, mild elevations in this inflammatory marker, in particular in those patients in the highest quartile, were three times more likely to experience an adverse cardiovascular event as compared to those women in the lowest quartile (Figure 1).<sup>5,9</sup>

In the Physicians' Health Study, CRP levels were examined in 543 healthy males in whom a MI venous thrombosis, or cerebrovascular event developed subsequently. These men were compared to 543 men in whom vascular disease did not develop.<sup>10</sup> Baseline CRP levels were higher in males who subsequently developed a MI. There also appeared to be a dose-response rela-

lowest quartile (Figure 1). Finally, CRP levels were also predictive of an increased predisposition to peripheral vascular disease in the Physicians' Health Study.<sup>12</sup>

The MONICA-Ausburg Cohort study provides further support demonstrating the importance of CRP as a powerful independent risk factor for a coronary event in a European population.<sup>11</sup> The study evaluated the association of CRP with the incidence of a first major coronary event in 936 middle-aged males followed for eight years. There was a positive relationship between CRP values and subsequent development of an adverse coronary event.<sup>11</sup>

### CRP in acute coronary syndromes

CRP is also predictive of an increased risk of a future cardiac event for those with pre-existing ischemic heart disease. In the European Concerted Action on Thrombosis and Disabilities (ECAT) study, baseline CRP levels were identified in 2,021 patients with stable angina. Individuals with serum levels of CRP > 3.6 mg/L had a twofold increased risk of a subsequent coronary event.<sup>13</sup> Along the spectrum of acute coronary syndromes, Liuzzo et al. identified that patients with unstable angina with serum levels of CRP > 3 mg/L were also associated with an increased rate of recurrent ischemic episodes, need for revascularisation, and progression to an acute MI infarction compared with patients with lower CRP levels.<sup>14</sup>

A number of trials illustrate the potential prognostic importance of serum CRP in patients with unstable angina. CRP levels

*In the Physicians' Health Study, CRP levels were predictive of increased predisposition to peripheral vascular disease.*

relationship, such that males in the quartile with the highest CRP levels were three times more likely to develop an infarct and two times more likely to suffer a stroke compared to males in the

#### About the author...

Dr. Jassal is associate chief cardiology resident, Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, Nova Scotia.

Dr. O'Neill is chief of cardiology and professor of medicine, Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, Nova Scotia.

Table 1

### Studies involving CRP

1. Womens' Health Study
2. Physicians' Health Study
3. MONICA-Ausberg Cohort
4. European Concerted Action on Thrombosis and Disabilities study (ECAT)
5. Fragmin during Instability in Coronary Artery (FRISC) trial
6. Thrombolysis in Myocardial Infarction (TIMI) 11A trial
7. Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCaps)
8. Cholesterol and Recurrent Events (CARE) study

were determined in 965 patients with an acute coronary syndrome in the Fragmin during Instability in Coronary Artery (FRISC) trial. In the FRISC trial, the probabilities of MI or death at five months were 2.2%, 3.6%, and 7.5% respectively, for patients stratified by CRP tertiles at enrolment ( $< 0.2$ ,  $0.2-1.0$  and  $> 1.0$  mg/dL respectively) (Figure 2).<sup>15</sup> The influence of CRP on prognosis was independent of, and in addition to, the prognostic influence of serum troponin T concentrations.<sup>15</sup>

The Thrombolysis in Myocardial Infarction (TIMI) 11A trial evaluated the important prognostic value of combined CRP and troponin T measurement in acute coronary syndrome. An elevated mean hs-CRP  $> 15.5$  mg/L more than six hours after symptom onset predicted an increased two-week mortality. Patients with an elevated troponin T and CRP had the highest mortality rate of 9.1% compared to those patients with only an elevated CRP or

troponin T, whose mortality rate was 4.7%. Individuals with both negative troponin and low levels of CRP were at the lowest risk of a subsequent adverse cardiovascular event of 0.4%.<sup>16</sup>

## CRP and disease-modifying treatments

A number of disease modifying drugs can alter the process of inflammation and CRP, hence, affecting the chance of an adverse coronary event. Such interventions include the use of ASA, hormone replacement therapy (HRT), and lipid lowering agents.

The Physicians' Health Study involved 1,086 males over an eight-year period, where baseline plasma CRP levels were measured.<sup>17</sup> The use of ASA (325 mg per day) was associated with an overall 44% risk reduction of a first MI. Although this apparent risk was reduced by 56% in individuals in the highest quartile of CRP, ASA use had a non-significant effect of 14% on those patients in the lowest quartile of CRP.<sup>17</sup> This observation suggests that the cardiovascular benefit associated with ASA may be mediated by its combined antiplatelet and anti-inflammatory activities.

Ridker et al. evaluated the relationship between CRP and HRT in 493 postmenopausal women from the Womens' Health Study.<sup>18</sup> The median CRP levels in women using estrogen alone, or estrogen plus progesterone, was twice as high as in those women not taking HRT.<sup>18</sup> Similarly in the Postmenopausal Estrogen/Progesterone Investigation (PEPI) trial, serum CRP concentrations were measured in 365 women at baseline, with followups at one year and three years.<sup>19</sup> Compared to placebo, all preparations of HRT were associated with an

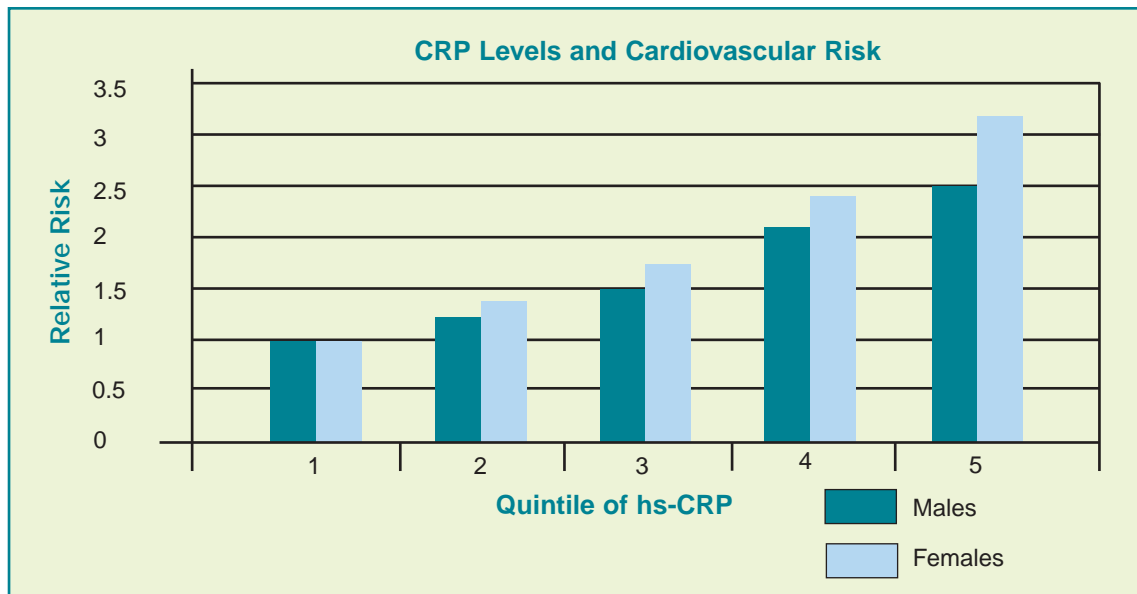


Figure 1. The predictive power of CRP for an adverse cardiovascular event.

increased serum CRP, which occurred primarily during the first year of treatment.<sup>19</sup> In light of the recent findings from the Women's Health Initiative study demonstrating the adverse effects of HRT on the risk of developing a MI, it is plausible that CRP levels were higher in this cohort, serving as a potential indicator of a future adverse cardiovascular event.

Aside from ASA and HRT, statins also have an impact on CRP in primary and secondary prevention. The Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) evaluated the use of lovastatin in 5,742 individuals for the primary prevention of reducing cardiovascular risk.<sup>20,21</sup> Treatment with the HMG coenzyme A reductase inhibitor reduced serum CRP by approximately 15% in the entire cohort. Out of those individuals with a total cholesterol/high-density lipoprotein ratio below the median, with a high serum CRP, 43 patients needed treatment for five years to prevent one event.<sup>20,21</sup> The observation that

lovastatin reduces serum CRP independent of its effects on serum cholesterol suggests that the measurement of CRP may improve risk stratification for the primary prevention of coronary disease, although this needs to be confirmed in randomised trials.

The Cholesterol and Recurrent Events (CARE) study evaluated the use of pravastatin as a secondary prevention method of reducing cardiovascular risk.<sup>20-24</sup> CRP was measured at baseline and at five years in 472 individuals who remained free of recurrent coronary events. The relative risk reduction with pravastatin was 54% in those patients in the highest quartile of CRP.<sup>22-24</sup>

## CRP or LDL: Which should we measure?

Recent data by Ridker et al. raise the question of whether routine use of CRP will become stan-

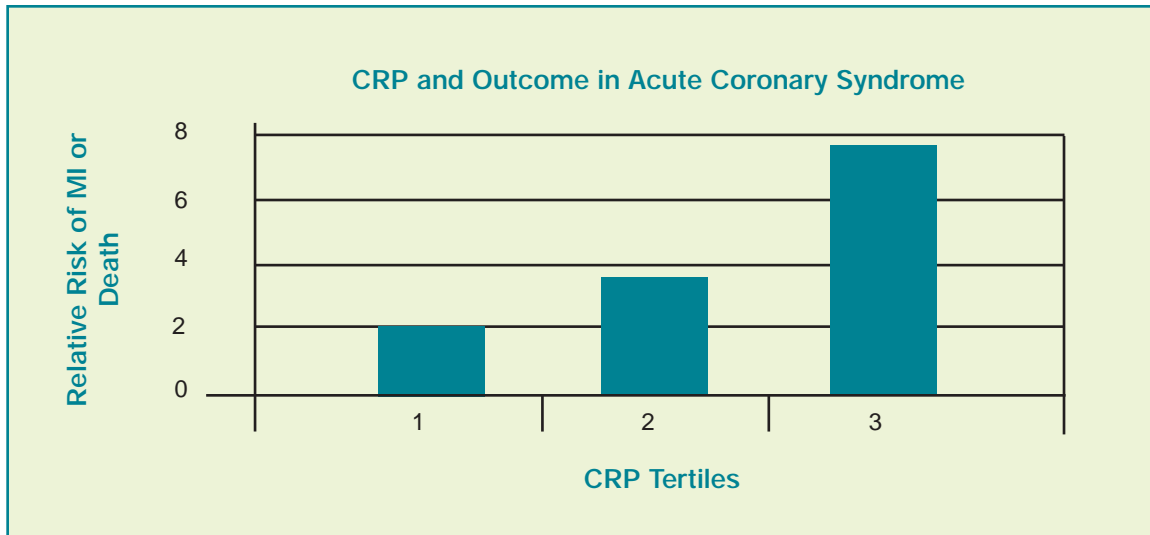


Figure 2. CRP and outcomes in NonST-elevation myocardial infarction.

*Individuals with high levels of CRP and low levels of LDL may be at significantly higher risk of adverse coronary events compared with patients with high levels of LDL and low levels of CRP.*

dard for predicting a future adverse cardiovascular event. Using data collected from the Women's Health Study, Ridker et al. compared CRP and low-density lipoprotein (LDL) cholesterol levels in 27,939 women to determine which was the more powerful predictor of increased cardiovascular risk.<sup>25</sup> They found a linear relationship, whereby higher levels of each marker correlated to a higher degree of coronary risk after adjustment for age, smoking status, blood pressure, diabetes, and the use of HRT. Specifically, individuals with high levels of CRP and LDL were at the highest risk,

whereas those patients with low levels of both markers were at a lower risk (Figure 3). Of interest however, were those individuals with high levels of CRP and low levels of LDL, who

were at a significantly higher risk of an adverse coronary event compared with those patients with high levels of LDL and low levels of CRP. A large scale trial designed to evaluate statin therapy in individuals with low levels of LDL and high levels of CRP is the forthcoming JUPITER trial. It is a double-blind study that will randomise 15,000 individuals with high levels of CRP and low levels of LDL (< 130 mg/dL) to either placebo or rosuvastatin at a dose of 20 mg/day. The objective of this megatrial is to determine whether statin therapy will have a primary preventive role in reducing CRP levels and hence decrease an

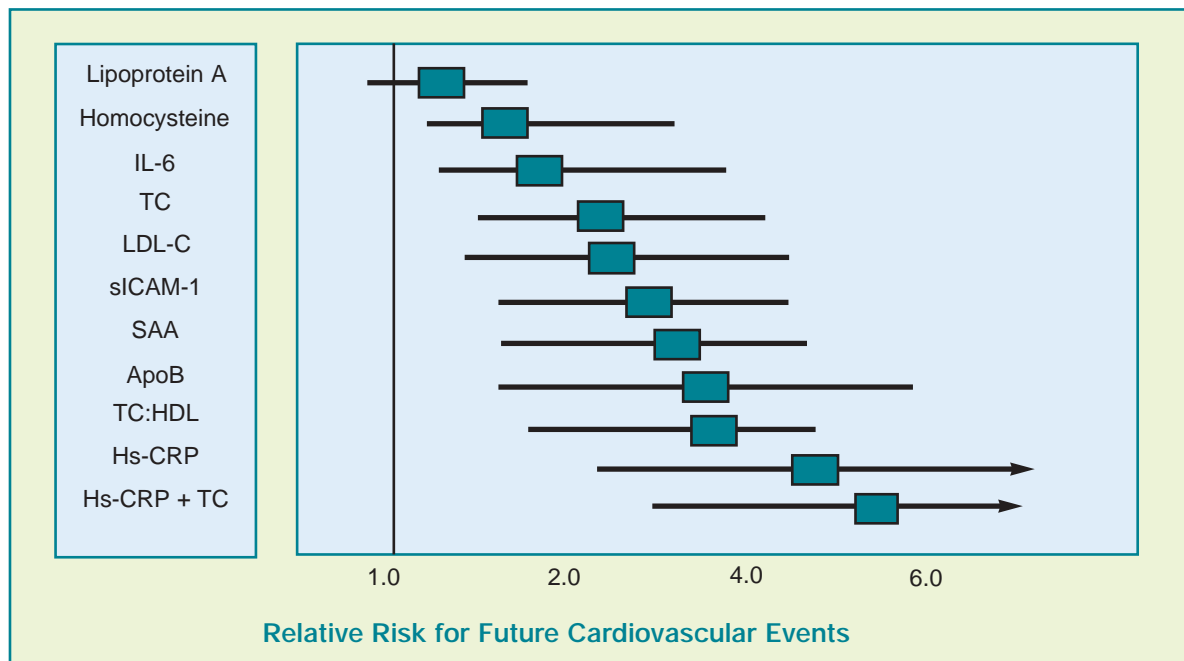



Figure 3. Risk factors for future cardiovascular events.

adverse cardiovascular event in this patient population.

*It is likely that future guidelines for therapy of cardiovascular events will incorporate CRP as an additional risk factor.*

### Future Outlook

The recognition of atherosclerosis as an inflammatory disease has created an intriguing area of research, particularly on the use of CRP as a marker of an adverse coronary event. As illustrated by the multitude of prospective studies presented, high-sensitivity CRP is able to predict an increased risk of initial cardiovascular event and increased risk for recurrent events in patients with pre-exist-

ing acute coronary syndromes. Furthermore, the well-established benefit of ASA in the primary prevention of ischemic heart disease, and perhaps the role of statin therapy in reducing CRP, will be validated in future trials. It is likely that future guidelines for lipid lowering therapy will incorporate CRP as an additional risk factor to guide initiation of therapy. 

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