

## C-reactive protein and prognosis after percutaneous coronary intervention

See doi:10.1053/euhj.2001.2988 for the article to which this Editorial refers

Based on evidence from vascular biology and clinical research, it is now evident that inflammatory mechanisms play a key role in the pathogenesis of atherosclerosis and its complications<sup>[1]</sup>. In this regard, C-reactive protein (CRP), a sensitive marker of low-grade vascular inflammation, has been the subject of extensive investigation, and has been shown to aid cardiovascular risk prediction in a variety of clinical settings. The report by de Winter *et al.* in the current issue provides further insight into the potential role of CRP to help assess prognosis among those at risk for cardiovascular events<sup>[2]</sup>. These workers studied the association between baseline levels of CRP and future cardiovascular risk among 501 patients with stable coronary artery disease who underwent elective percutaneous transluminal coronary angioplasty (PTCA). Over a 2-year follow-up, levels of CRP were significantly higher among those who subsequently reached the composite end-point of death, myocardial infarction, urgent revascularization or admission for unstable angina, than among those who remained free of cardiovascular events. In adjusted analyses, increased CRP levels ( $>3 \text{ mg} \cdot \text{l}^{-1}$ ) were a strong independent predictor of future cardiovascular events with a relative risk of 2.5 ( $P=0.0014$ ); indeed CRP was a stronger predictor than other well-established risk factors such as diabetes, hypertension, and ACC/AHA lesion class.

The finding that normal CRP levels were more common among those on statin treatment is consistent with evidence that statins have potent anti-inflammatory effects<sup>[3–5]</sup> and that statins lower CRP levels<sup>[6–9]</sup>. The lower risk observed among those with low CRP levels, however, cannot be solely attributed to concomitant statin therapy, as CRP remained a strong predictor of future risk in adjusted analyses which controlled for statin use. Further, changes in CRP and lipid levels with statin therapy have not been found to correlate to any significant degree<sup>[9–11]</sup>.

As acknowledged by the authors, the generalizability of the current data are somewhat limited due to the low rate of use of stents and glycoprotein IIb/IIIa inhibitors. However, data in this regard are available from several other studies<sup>[12,13]</sup> including a very recent report by Chew *et al.* showing that CRP predicts the risk of death or myocardial infarction at

30 days among 727 patients undergoing percutaneous coronary intervention<sup>[14]</sup>. The use of stents and glycoprotein IIb/IIIa inhibitors in this cohort was high, reflecting current practice. The adjusted relative risk for the highest quartile of CRP compared to the lowest quartile was 3.68 ( $P=0.004$ ). Moreover these workers reported that the risk associated with elevated CRP is independent of, but additive to, the effect of increased ACC/AHA lesion score.

These studies are important additions to the growing body of data showing that CRP levels may help guide prognosis for patients with a wide variety of clinical presentations of coronary artery disease. The current study by de Winter and colleagues suggests that CRP levels predict risk at 2 years among patients with stable coronary artery disease undergoing PTCA. In this regard, CRP levels have also been found to predict risk of death, myocardial infarction, and restenosis at 6 months among those with unstable coronary syndromes undergoing percutaneous coronary intervention<sup>[15]</sup>, while other workers have found that CRP levels predict coronary outcomes as far as 4 years into the future following admission for unstable angina and acute coronary syndromes<sup>[16–18]</sup>.

In order to assess the potential clinical utility of testing for CRP levels among patients with acute coronary syndromes, it is necessary to evaluate the predictive value of CRP in relation to biochemical markers of myocardial ischaemia. Data from the FRISC, CAPTURE and TIMI investigators suggest that both troponin T and CRP are independent predictors of risk in patients with acute coronary syndromes, and that their predictive value is additive. Even among those with negative troponin T, an elevated CRP level is predictive of future risk. The TIMI group have shown that the increased risk associated with elevated CRP levels may be evident as early as 14 days<sup>[17]</sup>. In the CAPTURE study, only troponin T was predictive of early risk in the initial 72 h period after presentation with an acute coronary syndrome, while both CRP and troponin T were independent predictors of risk at 6 months<sup>[15]</sup>. The FRISC group found that the difference in risk between those with and without elevated CRP levels at the time of the index event continues to increase for several years<sup>[18]</sup>. It is of note that in these cohorts, the predictive value of CRP was independent of that of troponin T. Indeed Chew and colleagues have reported that the addition of CRP testing to

clinical, and angiographic features provides excellent prognostic usefulness for patients undergoing percutaneous coronary intervention<sup>[14]</sup>.

Nonetheless, before embracing CRP testing as a risk stratification tool among those presenting with acute coronary syndromes or undergoing percutaneous coronary intervention, more data is required regarding the appropriate cut point used to define 'high' CRP levels. Unlike primary prevention cohorts in which the range of CRP levels is relatively consistent<sup>[10,11,19]</sup>, the thresholds used to define abnormal CRP in the above reports among patients with documented coronary artery disease has varied from  $>3 \text{ mg} \cdot \text{l}^{-1}$ <sup>[2,14]</sup> to  $>15.5 \text{ mg} \cdot \text{l}^{-1}$ <sup>[17]</sup>. The CAPTURE workers found that a threshold of  $10 \text{ mg} \cdot \text{l}^{-1}$  maximized the predictive value of CRP using receiver operating curve analysis<sup>[15]</sup>. In concert with data from primary prevention, it is thus likely that a gradient for CRP levels exists, with the lowest range among the healthy general population, an intermediate range among those with stable documented coronary artery disease, and a higher range among those with acute coronary syndromes. Thus the appropriate threshold above which CRP levels confer increased risk may vary according to the population studied.

The precise source of elevated CRP levels remains unclear. Intriguing data from workers in Rome indicate that CRP levels do not change after PTCA in patients with stable and unstable angina who have normal levels pre-procedure, but increase after PTCA in unstable patients with elevated CRP levels at baseline<sup>[20]</sup>. These data suggest that plaque rupture per se may not be the source of elevated CRP levels among patients with unstable angina, but rather that elevated CRP levels may be a marker of hyper-responsiveness of the inflammatory system to even small stimuli. Indeed among patients with elevated CRP levels at baseline even diagnostic angiography without subsequent intervention caused an increase in CRP levels<sup>[20]</sup>.

What should be done for individuals identified as high risk by CRP levels? CRP levels are higher among smokers, diabetics and obese subjects. Recent data indicate that elevated levels of CRP and interleukin-6 (IL-6) are potent predictors of the risk of future development of type II diabetes<sup>[21]</sup>. Indeed, adipose tissue is an important source of IL-6, which is the main stimulus for hepatic production of CRP. Thus intensification of lifestyle modification and regular exercise would seem appropriate. Further data suggests that the benefit of aspirin and statins may be greatest among those with elevated CRP levels<sup>[11,19,22]</sup>. Several recent studies have demonstrated that statin therapy lowers CRP levels<sup>[6-9]</sup>, and statins appear to be protective against coronary occlusion

even in the absence of hyperlipidaemia. Data regarding the effect of aspirin on CRP levels is more controversial<sup>[23,24]</sup>. Kennon *et al.* have reported that CRP levels are a strong predictor of risk among patients with unstable angina not pre-treated with aspirin, but among those pre-treated with aspirin the predictive value of CRP is attenuated<sup>[25]</sup>. This finding is consistent with results from the Physicians' Health Study which demonstrated that the benefit of aspirin therapy for preventing future myocardial infarction is greatest among those with the highest CRP levels<sup>[11]</sup>.

In sum, the current data from de Winter *et al.* provides further evidence that CRP may be useful for risk stratification among patients with stable coronary artery disease undergoing percutaneous coronary intervention. These data add to a growing body of evidence from prospective studies that CRP levels are a strong independent predictor of cardiovascular risk among apparently healthy men and women<sup>[10,11,26-31]</sup>, patients with documented coronary artery disease<sup>[32]</sup>, patients with unstable coronary syndromes<sup>[15,17,18,25,33]</sup>, patients undergoing percutaneous coronary intervention or coronary artery bypass grafting<sup>[12,13,34]</sup>, and patients in the stable phase post myocardial infarction<sup>[22]</sup>. Although questions remain regarding the appropriate cut points to define elevated levels of CRP among patients with different clinical presentations, risk stratification based on a combination of clinical and/or angiographic features, lipid parameters, troponin levels, and inflammatory markers such as CRP may help identify those presenting with coronary artery disease who are at highest risk and who may therefore benefit most from intensification of both interventional and medical therapy.

**G. J. BLAKE**  
**P. M. RIDKER**

*Center for Cardiovascular Disease Prevention,  
Brigham and Women's Hospital,  
Boston, Massachusetts, U.S.A.*

## References

- [1] Ross R. Atherosclerosis — an inflammatory disease. *N Engl J Med* 1999; 340: 115–26.
- [2] de Winter RJ, Heyde GS, Koch KT *et al.* The prognostic value of pre-procedural plasma C-reactive protein in patients undergoing elective coronary angioplasty. *Eur Heart J* 2002; 23: 960–6.
- [3] Bustos C, Hernandez-Presa MA, Ortego M *et al.* HMG-CoA reductase inhibition by atorvastatin reduces neointimal inflammation in a rabbit model of atherosclerosis. *J Am Coll Cardiol* 1998; 32: 2057–64.
- [4] Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. *Circulation* 2001; 103: 926–33.

- [5] Fukumoto Y, Libby P, Rabkin E *et al.* Statins alter smooth muscle cell accumulation and collagen content in established atheroma of watanabe heritable hyperlipidemic rabbits. *Circulation* 2001; 103: 993–9.
- [6] Ridker PM, Rifai N, Pfeffer MA, Sacks F, Braunwald E. Long-term effects of pravastatin on plasma concentration of C-reactive protein. The Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1999; 100: 230–5.
- [7] Ridker PM, Rifai N, Lowenthal SP. Rapid reduction in C-reactive protein with cerivastatin among 785 patients with primary hypercholesterolemia. *Circulation* 2001; 103: 1191–3.
- [8] Jialal I, Stein D, Balis D, Grundy SM, Adams-Huet B, Devaraj S. Effect of hydroxymethyl glutaryl coenzyme a reductase inhibitor therapy on high sensitive c-reactive protein levels. *Circulation* 2001; 103: 1933–5.
- [9] Albert M, Danielson E, Rifai N, Ridker PM. Effect of statin therapy on C-reactive protein levels. The Pravastatin Inflammation/CRP Evaluation (PRINCE): a randomized trial and cohort study. *JAMA* 2001; 286: 64–70.
- [10] Ridker PM, Hennekens CH, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med* 2000; 342: 836–43.
- [11] Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med* 1997; 336: 973–9.
- [12] 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: 515–8.
- [13] Gottsauner-Wolf M, Zasmata G, Hornykewycz S *et al.* Plasma levels of C-reactive protein after coronary stent implantation. *Eur Heart J* 2000; 21: 1152–8.
- [14] Chew DP, Bhatt DL, Robbins MA *et al.* Incremental prognostic value of elevated baseline C-reactive protein among established markers of risk in percutaneous coronary intervention. *Circulation* 2001; 104: 992–7.
- [15] Heeschen C, Hamm CW, Brummer J, Simoons ML. Predictive value of C-reactive protein and troponin T in patients with unstable angina: a comparative analysis CAPTURE Investigators. Chimeric c7E3 AntiPlatelet Therapy in Unstable angina REfractory to standard treatment trial. *J Am Coll Cardiol* 2000; 35: 1535–42.
- [16] Toss H, Lindahl B, Siegbahn A, Wallentin L. Prognostic influence of increased fibrinogen and C-reactive protein levels in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *Circulation* 1997; 96: 4204–10.
- [17] 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: 1460–5.
- [18] Lindahl B, Toss H, Siegbahn A, Venge P, Wallentin L. Markers of myocardial damage and inflammation in relation to long-term mortality in unstable coronary artery disease. FRISC Study Group. Fragmin during Instability in Coronary Artery Disease. *N Engl J Med* 2000; 343: 1139–47.
- [19] Ridker PM, Rifai N, Clearfield M *et al.* Measurement of C-reactive protein for the targeting of statin therapy in the primary prevention of acute coronary events. *N Engl J Med* 2001; 344: 1959–65.
- [20] Liuzzo G, Buffon A, Biasucci LM *et al.* Enhanced inflammatory response to coronary angioplasty in patients with severe unstable angina. *Circulation* 1998; 98: 2370–6.
- [21] Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001; 286: 327–34.
- [22] Ridker PM, Rifai N, Pfeffer MA *et al.* Inflammation, pravastatin, and the risk of coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events (CARE) Investigators. *Circulation* 1998; 98: 839–44.
- [23] Ikonomidis I, Andreotti F, Economou E, Stefanadis C, Toutouzas P, Nihoyannopoulos P. Increased proinflammatory cytokines in patients with chronic stable angina and their reduction by aspirin. *Circulation* 1999; 100: 793–8.
- [24] Feldman M, Jialal I, Devaraj S, Cryer B. Effects of low-dose aspirin on serum C-reactive protein and thromboxane B2 concentrations: a placebo-controlled study using a highly sensitive C-reactive protein assay. *J Am Coll Cardiol* 2001; 37: 2036–41.
- [25] Kennon S, Price CP, Mills PG *et al.* The effect of aspirin on C-reactive protein as a marker of risk in unstable angina. *J Am Coll Cardiol* 2001; 37: 1266–70.
- [26] Danesh J, Whincup P, Walker M *et al.* Low grade inflammation and coronary heart disease: prospective study and updated meta-analyses. *BMJ* 2000; 321 (7255): 199–204.
- [27] Harris TB, Ferrucci L, Tracy RP *et al.* Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med* 1999; 106: 506–12.
- [28] Koenig W, Sund M, Frohlich M *et al.* C-Reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg Cohort Study, 1984 to 1992. *Circulation* 1999; 99: 237–42.
- [29] Kuller LH, Tracy RP, Shaten J, Meilahn EN. Relation of C-reactive protein and coronary heart disease in the MRFIT nested case-control study. Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1996; 144: 537–47.
- [30] Ridker PM, Buring JE, Shih J, Matais M, Hennekens CH. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. *Circulation* 1998; 98: 731–3.
- [31] Tracy RP, Lemaitre RN, Psaty BM *et al.* Relationship of C-reactive protein to risk of cardiovascular disease in the elderly. Results from the Cardiovascular Health Study and the Rural Health Promotion Project. *Arterioscler Thromb Vasc Biol* 1997; 17: 1121–7.
- [32] Anderson JL, Muhlestein JB, Horne BD *et al.* Plasma homocysteine predicts mortality independently of traditional risk factors and C-reactive protein in patients with angiographically defined coronary artery disease. *Circulation* 2000; 102: 1227–32.
- [33] Liuzzo G, Biasucci LM, Gallimore JR *et al.* The prognostic value of C-reactive protein and serum amyloid A protein in severe unstable angina. *N Engl J Med* 1994; 331: 417–24.
- [34] Milazzo D, Biasucci LM, Luciani N *et al.* Elevated levels of C-reactive protein before coronary artery bypass grafting predict recurrence of ischemic events. *Am J Cardiol* 1999; 84: 459–61.