# C-Reactive Protein and Prognosis in Diabetes: Getting to the Heart of the Matter

**Naveed Sattar[1] and Aroon D. Hingorani[2]**

C-reactive protein (CRP) is a liver-derived protein whose concentration increases manyfold during inflammation or infection, making it a useful diagnostic and treatment measure in diseases such as rheumatoid arthritis. However, in the last decade, CRP has garnered interest as a biomarker of vascular risk that has stimulated more studies than perhaps any other "novel" biomarker. In these studies, the much lower CRP values seen in healthy individuals free from overt infection or inflammation, detected by a new generation of sensitive assays, have been associated in study after study with the risk of a first cardiovascular event (rev. in 1). Yet, despite the consistency of this association, whether CRP is causally involved in atherogenesis or whether it helps in prediction of cardiovascular disease (CVD) events remains intensely controversial (2,3).

In light of this controversy, studies examining the association of CRP with vascular outcome and mortality in patient populations, such as those with diabetes, where prospective data remain relatively sparse are to be welcomed. In the current issue of *Diabetes*, Bruno et al. (4) report that although CRP was related to risk of all-cause and CVD mortality in their 5-year follow-up of the Casale Monferrato Study, the improvement in individual risk prediction beyond established risk markers, evaluated by a range of statistical tests, was marginal at best. The results from this helpful study, therefore, currently caution against routine measurement of CRP for risk prediction in diabetes patients.

Why should CRP not better predict risk in individuals, given its consistent association with CVD and mortality? Several issues contribute. The association of CRP with incident events is linear when both CRP values and risk are plotted on a log scale, with no threshold value of CRP above which risk is substantial and below which it is negligible. This means that individuals in a population with intermediate values of CRP are at moderate risk of events. Moreover, the distribution of CRP in a population is log (normal), such that most individuals have intermediate values of CRP. Thus, a large proportion of events would be expected among people with nearly average CRP values, which explains the wide overlap in the distribution of CRP values among those who remain disease free and those who later suffer events (whether fatal or nonfatal) (respectively 2.5 mg/l [95% CI 1.2–5.3] and 3.7 mg/l [1.6–9.1] in the study by Bruno et al. [4]). With the broad overlap, it is difficult to set CRP cut point values that adequately discriminate later cases from those remaining disease free, accounting for the modest C-statistic. Additionally, the modest incremental risk prediction of CRP also stems from the correlation of CRP with a range of established risk factors (e.g., lipids, BMI, blood pressure, and glycemia indexes), an observation confirmed by Bruno et al. (4).

In a recent systematic review of 31 prospective cohorts (1), CRP did not perform better than the established Framingham risk equation for discrimination. Moreover, improvement in risk stratification or reclassification from the addition of CRP was small and inconsistent (1). As such, the conclusion by Bruno et al. (4) regarding the marginal value of CRP in predicting mortality risk in diabetic patients should not be too surprising. The efforts of the Emerging Risk Factors Collaboration (5), which has established a central database of over 1.1 million participants from 104 prospective population-based studies, in which subsets have information on inflammatory markers as well as major cardiovascular morbidity and cause-specific mortality, will help define whether there are subgroups of risk in which CRP measurement will be more helpful.

Of course, CRP is not the only "new" risk factor being considered for a role in CVD risk prediction (6). Indeed, measures of obesity, socioeconomic status, and family history of premature CVD all in part capture inflammation signals, and all may be more easily obtained than CRP. A significant correlation to inflammation is also evident for the ankle-brachial index (7), a measure that appears to significantly enhance risk prediction beyond the Framingham risk score (8).

Irrespective of its use as a risk predictor (which does not require that CRP be causally involved in vascular disease), there is equal interest in whether CRP is causal and thus whether lowering it will reduce CVD risk. Established and proven causal risk factors such as blood pressure and cholesterol are individually poorly predictive of incident disease (9). This is again because of the log-linear association with risk and the normal distribution of these risk factors in populations, which again means that a major proportion of events occur among those with average blood pressure or cholesterol. Thus, a risk factor that is causally involved in atherosclerosis need not be a good predictive tool. Although some in vitro studies have suggested a causal role for CRP in atherogenesis, some of the effects may have been due to the contamination of commercial CRP preparations (10). Observational studies are also not able to assess unequivocally whether CRP is causally related to vascular disease because higher CRP values in people at higher risk of disease could simply mark other risk factors (confounding) or subclinical ath-

From the [1]British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, U.K.; and the [2]Department of Epidemiology and Public Health, University College London, London, U.K.
Corresponding author: Naveed Sattar, nsattar@clinmed.gla.ac.uk.
Received 23 December 2008 and accepted 3 January 2009.
DOI: 10.2337/db08-1788


**See accompanying original article, p. 926.**

erosclerosis (reverse causation). In the absence of a clinical trial of a specific CRP-lowering agent, genetic studies utilizing common variants in the CRP gene that affect its level can be used as a type of natural randomized trial (11). Genetic variants are allocated at random according to Mendel's Laws (Mendelian randomization), which means that factors that could confound the association of CRP itself with disease risk should distribute evenly among the genotypic groups (12). If CRP was causally involved in vascular disease, individuals with a high CRP genotype should have a greater degree of atherosclerosis and a higher risk of incident events. Such studies to date provide no strong evidence for a causal role for CRP in atherosclerosis or the risk of a first vascular event (13–15). A very-large-scale analysis using this approach is now in progress (16). Moreover, multiple observations demonstrating that CRP is as strongly linked to risk of noncardiovascular mortality (2) further argue against a causal role for CRP in CVD but suggest that the association might, in part, reflect reverse causation. Of interest, interleukin (IL)-6 may be linked more strongly to risk for CHD events in the general population than CRP (17), and there are more reasons to consider IL-6 as a potentially causal factor. However, such work is in its infancy, and no firm conclusions on IL-6 can currently be made.

Some commentators have argued that the results of the recent JUPITER (Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin) trial provide confirmation of the value of CRP in determining CVD risk (18). However, JUPITER was a randomized controlled trial of a statin in people with low LDL cholesterol but high CRP. Statins lower CRP but also lower LDL cholesterol, and so it can be difficult to distinguish whether reductions in risk observed were due to LDL lowering, CRP lowering, or some combination. This is the case even among people with low starting LDL cholesterol concentration because of the log-linear association of LDL cholesterol with vascular risk over the whole range of usual values (19), which suggests that a salutary effect of LDL cholesterol lowering might be expected irrespective of the starting LDL cholesterol value.

In summary, therefore, although CRP commands much interest as a CVD risk factor, higher-resolution observational epidemiology (such as that in the Emerging Risk Factors Collaboration [5]), continued genetic epidemiology, and eventually specific CRP inhibitors (20) are needed to help the vascular risk community make a more balanced judgment on any causal role and utility of CRP as a predictor of risk. Such efforts also need to be cognizant of a range of competing and overlapping risk factors, since some may have distinct benefits over CRP. Presently, therefore, the current focus in clinical practice should remain on established risk factors (e.g., smoking, lipids, and blood pressure), both in determining coronary heart disease risk and as targets for prevention.

**ACKNOWLEDGMENTS**

No potential conflicts of interest relevant to this article were reported.

**REFERENCES**

1. Shah T, Casas JP, Cooper JA, Tzoulaki I, Sofat R, McCormack V, Smeeth L, Deanfield JE, Lowe GD, Rumley A, Fowkes FG, Humphries SE, Hingorani AD: Critical appraisal of CRP measurement for the prediction of coronary heart disease events: new data and systematic review of 31 prospective cohorts. *Int J Epidemiol* 2008 [Epub ahead of print]
2. Lloyd-Jones DM, Liu K, Tian L, Greenland P: Narrative review: assessment of C-reactive protein in risk prediction for cardiovascular disease. *Ann Intern Med* 145:35–42, 2006
3. Lowe GD, Pepys MB: C-reactive protein and cardiovascular disease: weighing the evidence. *Curr Atheroscler Rep* 8:421–428, 2006
4. Bruno G, Fornengo P, Novelli G, Panero F, Perotto M, Segre O, Zucco C, Deambrogio P, Bargero G, Perin PC: C-reactive protein and 5-year survival in type 2 diabetes: the Casale Monferrato Study. *Diabetes* 58:926–933, 2009
5. Emerging Risk Factors Collaboration, Danesh J, Erqou S et al.: The Emerging Risk Factors Collaboration: analysis of individual data on lipid, inflammatory and other markers in over 1.1 million participants in 104 prospective studies of cardiovascular diseases. *Eur J Epidemiol* 22:839–869, 2007
6. Welsh P, Packard CJ, Sattar N: Novel antecedent plasma biomarkers of cardiovascular disease: improved evaluation methods and comparator benchmarks raise the bar. *Curr Opin Lipidol* 19:563–571, 2008
7. Elias-Smale SE, Kardys I, Oudkerk M, Hofman A, Witteman JC: C-reactive protein is related to extent and progression of coronary and extracoronary atherosclerosis: results from the Rotterdam study. *Atherosclerosis* 195:e195–e202, 2007
8. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD et al.: a meta-analysis. *JAMA* 300:197–208, 2008
9. Rose G: Sick individuals and sick populations. *Int J Epidemiol* 14:32–38, 1985
10. Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB: C-reactive protein and coronary heart disease: a critical review. *J Intern Med* 264:295–314, 2008
11. Hingorani A, Humphries S: Nature's randomised trials. *Lancet* 366:1906–8, 2005
12. Verzilli C, Shah T, Casas JP, Chapman J, Sandhu M, Debenham SL, Boekholdt MS, Khaw KT, Wareham NJ, Judson R, Benjamin EJ, Kathiresan S, Larson MG, Rong J, Sofat R, Humphries SE, Smeeth L, Cavalleri G, Whittaker JC, Hingorani AD: Bayesian meta-analysis of genetic association studies with different sets of markers. *Am J Hum Genet* 82:859–872, 2008
13. Casas JP, Shah T, Cooper J, Hawe E, McMahon AD, Gaffney D, Packard CJ, O'Reilly DS, Juhan-Vague I, Yudkin JS, Tremoli E, Margaglione M, Di Minno G, Hamsten A, Kooistra T, Stephens JW, Hurel SJ, Livingstone S, Colhoun HM, Miller GJ, Bautista LE, Meade T, Sattar N, Humphries SE, Hingorani AD: Insight into the nature of the CRP-coronary event association using Mendelian randomization. *Int J Epidemiol* 35:922–931, 2006
14. Lawlor DA, Harbord RM, Timpson NJ, Lowe GD, Rumley A, Gaunt TR, Baker I, Yarnell JW, Kivimäki M, Kumari M, Norman PE, Jamrozik K, Hankey GJ, Almeida OP, Flicker L, Warrington N, Marmot MG, Ben-Shlomo Y, Palmer LJ, Day IN, Ebrahim S, Smith GD: The association of C-reactive protein and CRP genotype with coronary heart disease: findings from five studies with 4,610 cases amongst 18,637 participants. *PLoS ONE* 3:e3011, 2008
15. Zacho J, Tybjaerg-Hansen A, Jensen JS, Grande P, Sillesen H, Nordestgaard BG: Genetically elevated C-reactive protein and ischemic vascular disease. *N Engl J Med* 359:1897–1908, 2008
16. CRP CHD Genetics Collaboration. Collaborative pooled analysis of data on C-reactive protein gene variants and coronary disease: judging causality by Mendelian randomisation. *Eur J Epidemiol* 23:531–540, 2008
17. Danesh J, Kaptoge S, Mann AG, Sarwar N, Wood A, Angleman SB, Wensley F, Higgins JP, Lennon L, Eiriksdottir G, Rumley A, Whincup PH, Lowe GD, Gudnason V: Long-term interleukin-6 levels and subsequent risk of coronary heart disease: two new prospective studies and a systematic review. *PLoS Med* 5:e78, 2008
18. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ, JUPITER Study Group: Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 359:2195–2207, 2008
19. Prospective Studies Collaboration, Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, Qizilbash N, Peto R, Collins R: Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. *Lancet* 370:1829–1839, 2007
20. Pepys MB, Hirschfield GM, Tennent GA, Gallimore JR, Kahan MC, Bellotti V, Hawkins PN, Myers RM, Smith MD, Polara A, Cobb AJ, Ley SV, Aquilina JA, Robinson CV, Sharif I, Gray GA, Sabin CA, Jenvey MC, Kolstoe SE, Thompson D, Wood SP: Targeting C-reactive protein for the treatment of cardiovascular disease. *Nature* 440:1217–1212, 2006