The role of C-reactive protein (CRP) in cardiovascular disease risk remains controversial, and several interrelated questions are unresolved. Although it is clear that higher circulating CRP levels are associated with coronary heart disease (CHD) incidence and mortality rates in prospective studies, the magnitude of this association has been downgraded in recent years (1). It is also clear that CRP levels are strongly related to many potential confounding factors that influence CHD incidence and mortality rates. In predictive models that appropriately account for these confounders, the magnitude of the association between CRP levels and CHD outcomes is considerably attenuated toward the null (2). Whether CRP is a marker of cardiovascular disease risk or is causally related to cardiovascular disease is uncertain. Nonetheless, some authors have recently claimed that CRP itself is indeed a promoter of atherosclerosis and increased CHD risk (3, 4). If this is true, CRP would become a clear and explicit target for therapeutic intervention.

In this issue, 2 articles (5, 6) express widely divergent views regarding the role of CRP in cardiovascular disease risk stratification. Because individuals at greatest risk for disease have the most to gain from medical interventions (7), correctly specifying level of risk is an important clinical task. Both Cook and colleagues (5) and Lloyd-Jones and coworkers (6) investigate whether adding CRP to predictive models could usefully improve the ability of clinicians to target interventions. Lloyd-Jones and coworkers (6), who review the published evidence, show that adding CRP to predictive models containing conventional cardiovascular risk factors leads to minor improvement in measures of discrimination (receiver-operator characteristic curve properties or c-statistics). This finding is in line with the findings of the most recent study on this issue (8). Cook and colleagues (5) argue that these measures of discrimination are not appropriate for evaluating the utility of adding single variables to predictive models. Indeed, their data show that adding CRP did not greatly improve these statistics, but they point out that neither did adding total, low-density lipoprotein, or high-density lipoprotein cholesterol to models lacking these predictors. Although they reach different conclusions, these 2 papers (5, 6) actually discuss similar data, and the discrepancy between them relates to their assessment of the value of the small improvement in risk prediction provided by CRP.

Improvement in risk prediction is important, but if it were the main aim, it would be much easier, quicker, and cheaper to ask patients about their lifetime socioeconomic circumstances, which, like CRP, generally predict CHD mortality rates even after adjustment for a wide range of conventional risk factors (9). Established approaches reduce CHD risk by the same proportion regardless of which combination of risk factors generated the risk. For example, through their influence on cholesterol levels, statins lower CHD risk to about the same relative extent independent of age, sex, presence of established CHD, baseline cholesterol level, blood pressure, or history of diabetes (10). People who experience the greatest absolute risk reduction are those at the highest level of CHD risk (7). Identifying a patient at high risk by using inexpensive methods, such as asking about general ill health (8), family history, or socioeconomic position (9), all of which are strong predictors of CHD risk, will enable the physician to target treatment to people who will experience the most benefit and therefore the most favorable ratio of benefit to side effects. If the use of such simple measures can perform this classificatory task as well as CRP measurement can, then the advantages of including CRP in risk assessment are far from clear.

When Cook and colleagues favorably compare the inclusion of CRP to the inclusion of cholesterol in a predictive model, they appear to make a compelling case for the importance of CRP. But why is using cholesterol as an example so compelling? The reason, of course, is that cholesterol levels are causally related to CHD. Lowering a person’s very high cholesterol level will reduce CHD risk even if other CHD risk factors are absent. If CRP is not a causal factor for CHD, lowering it would not alter CHD risk, and we would have no particular reason to identify the risk ascribed to CRP, especially if we could gain a similar level of improved risk prediction through the inexpensive, convenient elicitation of health status, family history, or socioeconomic data.

It is, therefore, important to ask whether CRP is causally related to cardiovascular disease risk. Many commentators have pointed to epidemiologic evidence that CRP is a cause of CHD, not just a consequence of it or a marker of other causes (3, 4). C-reactive protein enjoys its status as an “independent” risk factor for CHD because adjusting for classic confounders leaves a residual elevated risk associated with higher CRP levels. Others, however, remain skeptical on whether CRP is causally related to cardiovascular outcomes (11). They point out that observational studies provide relatively weak evidence for proving causation. Relying on observational evidence to argue for interventions to lower CRP levels is like advocating taking vitamin E supplements, since taking these supplements was an “independent” predictor of reduced CHD risk in observational studies. In randomized trials, vitamin E supplements did not reduce CHD risk, indicating that observational data and data from randomized, controlled trials on precisely the same exposure could lead to different conclusions (12). Furthermore, an observational study that ap-
plied stringent adjustment for confounding found no “independent” association of CRP with CHD in older women (2).

A more stringent test of causality within observational studies is to apply the principles of Mendelian randomization (13, 14), in which genetic variants serve as unconfounded markers of exposures and allow better delineation of causality. Genetic variants in the CRP gene influence circulating CRP levels (15). The genetic variants are not, however, related to any of the factors that confound conventional observational studies of CRP and CHD risk, such as smoking, obesity, or socioeconomic position (15). Furthermore, the existence of early stages of cardiovascular disease cannot alter inherited genetic variants, and thus reverse causation, where coronary artery disease influences CRP level rather than vice versa, is not an issue. Groups defined on the basis of CRP genotype have long-term differences in average CRP levels, and these should translate into differences in CHD risk if CRP were causally related to CHD (Figure). Current evidence from studies using this paradigm suggests that inherited genotypes that produce different CRP levels do not alter the cardiovascular risk factors that CRP has been thought to influence (hypertension and insulin resistance) or the risk for CHD itself (15–17). In other words, the weight of current evidence suggests that CRP does not cause CHD. We will need larger studies before we can draw definitive conclusions from this line of evidence, however.

Randomized, controlled trials of CRP lowering will provide the strongest evidence as to whether CRP causes CHD. To be truly informative, these studies must pick an intervention that targets only CRP. Some agents (for example, statins) that lower CRP also lower other established risk factors, so it is difficult to separate their effects on CRP from effects on cholesterol, for example. Lloyd-Jones and coworkers are surely right when they state that the analyses of statin influences on both CRP and CHD outcomes in the PROVE-IT (Pravastatin Or atorVastatin Evaluation and Infection Therapy) trial (18) do not add new information to this debate.

The place of CRP in the cardiovascular disease prevention pantheon remains uncertain. Recent evidence suggests that inhibition of the effects of very high levels of human CRP administered to rats undergoing coronary artery ligation–induced myocardial infarction reduces infarct size (19). Although this observation does not directly address the issue of the causal effects of postinfarct levels of CRP in humans, it does suggest that further investigation of the postinfarct role of CRP may be warranted. It does not inform debates about the role of CRP in predicting or preventing incident CHD, however.

Evidence that CRP may not cause CHD does not mean that inflammation plays no role in atherosclerosis. The focus on CRP rather than some other mediator of inflammation may have been largely pragmatic. Of the many inflammatory markers, CRP is one of the most easily and inexpensively measured (20), and the particular focus on this protein rather than others may reflect its convenience for large-scale investigation rather than compelling biological reasoning about its possible unique role. Its low cost could also be seen as a reason to promote its value in prediction models. However, there are many reasons for skepticism about the role of CRP as a predictor of CHD: CRP may not be causally related to CHD; it remains more expensive than asking patients about their health, lifestyle, and socioeconomic background; and it adds only modest additional predictive ability over conventional risk factors, even in Cook and colleagues’ study. Evidence against a causal effect of CRP doesn’t alter the probability that other components of these inflammatory pathways do have a causal role. The direction of research on inflammatory markers and CHD risk should be driven by the level of evidence, as provided by a combination of clinical, genetic, and epidemiologic studies.

George Davey Smith, MD, DSc
Nic Timpson, MSc
Debbie A. Lawlor, MB, PhD
University of Bristol
Bristol BS8 2PR, United Kingdom

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: George Davey Smith, DSc, Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, United Kingdom.

Current author addresses are available at www.annals.org.

References


11. Scirica BM, Morrow DA. Is C-reactive protein an innocent bystander or proatherogenic culprit? The verdict is still out. Circulation. 2006;113:2128-34. [PMID: 16651484]


© 2006 American College of Physicians
Current Author Addresses: Drs. Davey Smith, Timpson, and Lawlor: Department of Social Medicine, University of Bristol, Canynge Hall, Whiteladies Road, Bristol BS8 2PR, United Kingdom.