money is exhausted, the right-wing religious elements in Pakistan will once again move in to provide much needed aid, resulting in their gaining popularity among the affected.

It is incumbent upon the world to step up and provide immediate humanitarian aid to the internally displaced people of the Swat Valley. I declare that I have no conflicts of interest.

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Rosuvastatin, C-reactive protein, LDL cholesterol, and the JUPITER trial

In the JUPITER trial (April 4, p 1175),1 Paul Ridker and colleagues enrolled apparently healthy men and women who were regarded as being at increased vascular risk because of raised concentrations of C reactive protein (CRP). However, the assumption they make in associating elevated CRP concentrations with an enhanced inflammatory profile could be misleading in some patients. One study showed that certain polymorphisms in the CRP gene, although associated with substantial increases in CRP concentrations, are not in themselves associated with an increased risk of ischaemic vascular disease.

Accordingly, it has been suggested that CRP per se might not have a causal role in vascular diseases, but represent a confounding factor or reverse causation.4 In line with this, drug therapy given on a massive scale on the basis of surrogate markers that might not be uniformly linked to an elevated vascular risk could expose some patients to undesired adverse effects without health benefits. In my opinion, it seems more judicious to treat modifiable risk factors for which a causal role is well established in vascular diseases—eg, smoking, diabetes, high blood pressure, and dyslipidaemia—reinforcing the importance of lifestyle modifications in addition to drug therapy as appropriate.

I declare that I have no conflicts of interest.

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In JUPITER,1 Paul Ridker and colleagues found that, in people with normal LDL cholesterol concentrations and elevated high-sensitivity C-reactive protein (hsCRP), rosuvastatin gave substantial benefit with regard to cardiovascular endpoints. Concentrations of hsCRP increase with inflammation of any cause, including the accumulation of modified LDL cholesterol within the arterial wall. The amount of LDL cholesterol accumulating within the intima depends on the cholesterol entering the arterial wall (LDL) and the cholesterol being removed from the arterial wall by reverse cholesterol transport (HDL).

Since we know that people who sustain atherothrombotic events despite a normal cholesterol concentration tend to do so in association with a low HDL concentration,2 I submit that, in JUPITER,1 the elevated hsCRP concentration is simply a surrogate for low HDL cholesterol and that patients who benefitted from rosuvastatin were those whose LDL:HDL ratio favoured atherogenesis, which was substantially improved by rosuvastatin. The use of HDL cholesterol instead of hsCRP is on much firmer grounds pathophysiologically and I suspect that use of the LDL:HDL ratio would obviate the need to use hsCRP.

I have consulted for AstraZeneca in the past.

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The data presented by Paul Ridker and colleagues1 on the benefit of combined reduction of LDL cholesterol and high-sensitivity C-reactive protein (hsCRP) with rosuvastatin are another piece in the puzzle of the effects of statins on cardiovascular prevention. From a public health point of view, however, a major question is whether the benefit of rosuvastatin is limited to patients with increased hsCRP (those included in JUPITER) or if similar results would have been found (at least in terms of relative risk reduction) whatever the initial level of hsCRP.

Even after several major JUPITER publications, the investigators have never presented the primary outcomes according to baseline hsCRP levels. Careful reading of the current paper, however, gives an indication that the benefit of rosuvastatin was, if anything, larger in the patients who initially had lower hsCRP levels: indeed, patients who had the greatest reduction in cardiovascular events were those who had an on-treatment hsCRP level of less than 2 mg/L, but they were also those who had the lowest initial values of hsCRP (2.2 mg/L in those who achieved a target CRP of <2 mg/L, compared with 5.4 mg/L for those who did not).
Rather than having the reader try to interpret fragments of data, it would be better if the investigators at last reported their findings according to initial hsCRP levels. That would help the reader (and health authorities) make their minds up about the appropriateness of using hsCRP as a screening tool in the general population.

I declare that I have no conflicts of interest.

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Paul Ridker and colleagues conclude that reductions of LDL cholesterol and high-sensitivity C-reactive protein (hsCRP) are indicators of successful treatment with rosuvastatin. However, the JUPITER trial did not target specific concentrations of hsCRP or LDL cholesterol by means of a strategy of titration of rosuvastatin. Rather, it assessed a single dose versus placebo.

No evidence was presented to suggest that adjusting statin doses to reach a particular concentration of hsCRP (or LDL cholesterol) would improve outcomes.

We were also concerned with the finding (figure 2) that an hsCRP concentration of less than 1 mg/L with an LDL cholesterol concentration of at least 1.8 mmol/L did not significantly reduce the risk of the primary outcome (although there seemed to be a favourable trend), yet the hazard for hsCRP concentrations of less than 2 mg/L (irrespective of LDL cholesterol concentration) revealed a significant improvement in favour of rosuvastatin. This inconsistency raises concerns about the usefulness of hsCRP in the assessment of treatment in the lower-risk population targeted by JUPITER.

Perhaps if the trial had not been prematurely halted this trend could have been more completely assessed with longer follow-up and greater numbers of events. Additionally, early cessation of a clinical trial for benefit could lead to overestimation of treatment effects. Although the recommendation to stop the trial was made according to predefined criteria by an independent data and safety monitoring board, the decision to start a low-risk patient on statins on the basis of hsCRP remains controversial.

We declare that we have no conflicts of interest.

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The clinical implications of the JUPITER study are substantial. Therefore an understanding of the methods matters even more than usual.

First, the participants were divided into four mutually exclusive groups on the basis of an arbitrary cutpoint for C-reactive protein (CRP) and for LDL cholesterol. This approach can produce larger differences than the more conventional one of continuous analysis. Were there significant independent continuous relations between LDL cholesterol and risk versus CRP and risk?

Second, the treatment group with high LDL cholesterol and high CRP received no benefit from rosuvastatin, whereas in the group with low LDL cholesterol and low CRP, risk was reduced by 65%. Outcome after therapy is the product of the initial as well as the final risk. Accordingly, what were the initial and final levels of LDL cholesterol, apolipoprotein B, and CRP in the four groups?

Finally, what was the prevalence in the placebo group of those who had a CRP of less than 2 mg/L at any time during the trial? The earlier the evidence of an independent effect of CRP, the more rapid will be the clinical application of these results.

I declare that I have no conflicts of interest.

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Although I laud Paul Ridker and colleagues for demonstrating the vascular anti-inflammatory benefits of rosuvastatin, we should consider the less expensive anti-inflammatory option: aspirin.

Aspirin was used by only 16–6% of participants in the placebo and rosuvastatin groups, despite their elevated cardiovascular risk and thus indication for aspirin (42–31% in the placebo group and 38–3% in the rosuvastatin group had metabolic syndrome). Why aspirin use was not enforced is unclear, since its use is indicated (in the absence of specific contraindications) by age, diabetes, and hypertension individually, let alone when in combination. Ironically, a previous article by Ridker supports aspirin use to lessen myocardial infarction risk through reduction of high-sensitivity C-reactive protein (hsCRP). Meanwhile we must consider that if we do treat patients on the basis of their hsCRP concentration, most...