Prognostic Utility of ApoB/AI, Total Cholesterol/HDL, Non-HDL Cholesterol, or hs-CRP as Predictors of Clinical Risk in Patients Receiving Statin Therapy After Acute Coronary Syndromes

Results From PROVE IT–TIMI 22

Kausik K. Ray, Christopher P. Cannon, Richard Cairns, David A. Morrow, Paul M. Ridker, Eugene Braunwald

Objectives—The purpose of this study was to compare the prognostic utility of apoB/AI, total cholesterol/HDL (TC/HDL) ratio, non-HDL cholesterol (non–HDL-C), or hs-CRP as predictors of clinical risk among patients receiving statin therapy after acute coronary syndromes (ACS).

Methods and Results—Patients with ACS were randomized in the PROVE IT–TIMI 22 trial to either pravastatin 40 mg or atorvastatin 80 mg. Cox regression models adjusting for confounders were used to assess the relationship between on-treatment lipids or hs-CRP and risk of death or acute coronary events. At 4 months a 1 SD increment in apoB/AI (HR 1.10, 95% CI 1.01 to 1.20), TC/HDL (HR 1.12, 95% CI 1.01 to 1.24), and non–HDL-C (HR 1.20, 95% CI 1.07 to 1.35) predicted events to a similar extent as LDL-C (HR 1.20, 95% CI 1.07 to 1.35) with neither apoB/AI, TC/HDL, nor non–HDL-C improving risk prediction models which included LDL-C. In contrast, the addition of hs-CRP significantly improved risk prediction models irrespective of the lipid parameters included, with a 29% to 30% increased risk observed per 1 SD increment in log CRP.

Conclusion—In the present study of ACS patients receiving statin therapy, on-treatment apoB/AI, TC/HDL, and non–HDL-C offered similar prognostic information to LDL-C. However, the addition of hs-CRP to lipid-based measurements significantly improved risk prediction. On treatment CRP measurement may therefore offer additive prognostic information to lipids in ACS patients. (Arterioscler Thromb Vasc Biol. 2009;29:424-430.)

Key Words: statins ■ apolipoprotein ■ inflammation ■ CRP ■ CHD

Low density lipoprotein cholesterol (LDL-C) is the traditional marker for identifying risk from hypercholesterolemia and monitoring the efficacy of statin therapy. However, LDL-C incompletely measures atherogenic lipoproteins such as very low density lipoprotein (VLDL) or intermediate density lipoprotein (IDL) and direct measurement of the concentration of apolipoprotein B (apoB), which is a measure of the number of proatherogenic particles and apolipoprotein A1 (apoAI), which is a measure of the number of antiatherogenic particles, have been proposed by some as being superior measures of atherogenic dyslipidemia.1 Other approaches use standard lipid parameters such as non–high density lipoprotein cholesterol (non–HDL-C), which reflect the total cholesterol content of atherogenic lipoproteins or the total cholesterol/HDL ratio (TC/HDL). The debate regarding the choice of the best lipid parameter has further intensified with apparently conflicting evidence between prospective studies.2–6 However, neither the measurement of atherogenic particle number nor atherogenic cholesterol content assesses inflammation which is an important marker of risk.2 In particular, considerable interest has now centered on the use of high-sensitivity C reactive protein (hs-CRP) to screen high-risk individuals for statin therapy.7 To date only one study (conducted in a statin-naïve all-female primary prevention cohort) has assessed the prognostic utility of hs-CRP in addition to apolipoproteins,2 and previous studies in statin-treated populations have only assessed the prognostic utility of hs-CRP to LDL-C.8 Hence a second question has arisen as to whether hs-CRP adds any prognostic utility to the measurement of apoB/AI ratio or other lipid parameters.
measures among individuals receiving statin therapy. Therefore in the present study, we compared the relationship between on-treatment levels of newer and traditional markers of atherogenic dyslipidemia with and without hs-CRP with the subsequent risk of death or acute coronary events among patients receiving statin therapy after acute coronary syndromes (ACS).

Methods

Study Population
The PROVE IT–TIMI 22 trial was a randomized trial comparing intensive statin therapy with atorvastatin 80 mg versus standard dose statin therapy with pravastatin 40 mg in 4162 patients with ACS and has been previously described. Briefly, patients were eligible for enrollment if they had been hospitalized for ACS within the previous 10 days and were clinically stable and were then followed for 24 months with complete follow-up on 99.8% of the cohort. The study was approved by the institutional review board of each hospital, and all patients provided written informed consent.

Blood Sampling and Analysis
Details of the blood collection protocol for lipid markers and hs-CRP have been previously reported. For full details please see the supplemental materials (available online at http://atvb.ahajournals.org).

Clinical End Points
The prespecified end point for this analysis focused on the composite of death or nonfatal acute coronary events, specifically nonfatal myocardial infarction (MI) or unstable angina (UA) requiring rehospitalization as previously described. All end points were adjudicated independently by a clinical events committee blinded to the study arm.

Statistical Analyses
ApoB/AI levels were available in 3683 patients at baseline, 2998 patients at 4 months, and in 1630 patients at the end of study. Complete case analysis was used in this analysis cohort for the purpose of comparing regressions models. The effect of intensive versus standard dose statin therapy on lipids were compared at 4 months and the end of study using a 2-sample t test where the data were normally distributed or a Wilcoxon test otherwise. The correlation between lipid parameters and lipid parameters and CRP (log transformed) were compared using the Pearson’s correlation coefficient. Cox regression analysis was used to evaluate the association between lipid parameters at baseline and at 4 months (on-treatment) and the subsequent risk of death or nonfatal coronary events. Data are presented as hazard ratios with associated 95% confidence intervals (CI). All models described were constructed identically and were adjusted for age, gender, history of hypertension, history of diabetes, smoking status, body mass index (BMI), type of presenting syndromes (ACS), and use of percutaneous intervention (PCI), and were based on models previously published by our group.

Correlation Between Lipids and hs-CRP
Strong correlations were observed between apoB and LDL-C lipids and between apoB and non–HDL-C, r=0.86 and 0.93 respectively and between non–HDL-C and LDL-C, r=0.91 (all P<0.0001). Similarly the correlation between apoAI and HDL-C and TC/HDL-C ratio and apoB/AI ratio were 0.81 and 0.88, respectively (all P<0.0001). In contrast, weak but significant correlations were observed between hs-CRP and apoB (r=0.21), non–HDL-C (r=0.21), LDL-C (r=0.18), TC/HDL (r=0.22), and apoB/AI (r=0.23), all P<0.0001. Even weaker correlations between hs-CRP and apoA1 and HDL-C were observed r=−0.02 (P>0.05), and −0.05 (P<0.01), respectively.

Results

Study Population
The baseline characteristics of the analysis cohort are shown in supplemental Table I. The average age was 58 years, and the cohort comprised women (22%), subjects with diabetes (19%), subjects with hypertension (51%), and current smokers (36%). Baseline levels of apoB/AI, TC/ HDL and non–HDL-C are shown in Table 1.

Effect of Intensive Statin Therapy on Lipids
At 4 months after ACS, intensive statin therapy reduced apoB to a greater extent than moderate therapy (35% versus 11%), but raised apoAI to a lesser extent (3% versus 9%) (P<0.0001 for each) as shown in Table 1. Overall intensive therapy reduced the ratio apoB/AI by 37% from baseline versus 18% for standard therapy, P<0.0001, with similar differences between statin regimens observed at the end of study (average 2 years). Intensive therapy also reduced both total cholesterol/HDL-C ratio, and non–HDL-C to a greater extent than standard therapy (30% versus 11%, and 37% versus 8% respectively, P for each <0.0001; Table 1). hs-CRP was also lower among subjects allocated intensive therapy at 4 months (1.3 mg/L versus 2.1 mg/L, P<0.0001).

Correlation Between Baseline Lipid Levels and Clinical Outcomes
After multivariable adjustment, which included the intensity of statin therapy, no significant association was observed between a 1 SD difference in baseline apoB/AI ratio (0.25), or total cholesterol/HDL-C ratio (1.42), or non-HDL cholesterol (0.88 mmol/L) and the subsequent risk of death or acute coronary events (HR 1.07, 95% CI 0.97 to 1.18, P=0.19); HR 1.06, 95% CI 0.97 to 1.17, P=0.21; HR 1.06, 95% CI 0.97 to 1.17, P=0.19 respectively). However, in each of these three models (containing baseline apoB/AI, total cholesterol/
HDL-C ratio, or non-HDL cholesterol respectively) use of intensive statin therapy was similarly associated with a reduced risk (HR 0.76, 95% CI 0.63 to 0.92, P = 0.005; HR 0.80, 95% CI 0.67 to 0.96, P = 0.017; HR 0.80, 95% CI 0.67 to 0.96, P = 0.017, respectively, for each lipid model).

**Incremental Predictive Value of Lipid Parameters to LDL-C**

A 1-SD increment in LDL-C (0.82 mmol/L) was significantly associated with recurrent events (HR 1.20, 95% CI 1.07 to 1.35). By way of comparison, the effect estimates for a 1-SD change in apoB/AI ratio (HR 1.10, 95% CI 1.01 to 1.20), TC/HDL ratio (HR 1.12, 95% CI 1.01 to 1.24) or non–HDL-C (HR 1.20, 95% CI 1.07 to 1.35) overlapped considerably. To assess the potential utility of apoB/AI ratio, TC/HDL ratio, or non–HDL-C over and above measurements of LDL-C in predicting recurrent events, we added each additional lipid parameter to models which included LDL-C as well the baseline covariates (Model 1). The addition of either a 1-SD change in apoB/AI ratio (0.22), TC/HDL ratio (1.28), or non–HDL-C (1.0 mmol/L) to models which already included LDL-C produced LLRES values that were virtually identical to models containing LDL-C alone, and hence the predefined cutpoint of 2 mg/L.8,12 (Figure 1) improved the basic models to a greater extent than any of the lipid parameters alone, as reflected by a LRT statistic of 12.2 to 13.4 for hs-CRP versus values ranging from 0 to 8.4 for any given lipid parameter.

**Relationship Between 4-Month Lipid Levels and Clinical Outcomes**

We initially assessed the relationship between “on treatment” levels of each individual lipid parameter or hs-CRP at 4 months and the subsequent risk of recurrent events using the median of each parameter to allow for comparison (Figure 1). The hazard ratio of death or acute coronary events appeared virtually identical to models containing LDL-C alone, and hence the subsequent risk of recurrent events using the median of each parameter to allow for comparison (Figure 1). The hazard ratio of death or acute coronary events appeared to be elevated to a similar extent with considerable overlap across lipids. Compared to the basic Cox model the addition of each atherogenic lipid parameter alone broadly tended to improve the models assessed using the likelihood ratio test (LRT statistic >3.84 considered significant for the model). In contrast, markers of nonatherogenic lipid content or particles alone (HDL-C or apoAI) did not significantly improve the multivariable models and tended to be weaker predictors of risk when used alone. The addition of hs-CRP to multivariable models either as a continuous variable or using the predefined cutpoint of 2 mg/L8,12 (Figure 1) improved the basic models to a greater extent than any of the lipid parameters alone, as reflected by a LRT statistic of 12.2 to 13.4 for hs-CRP versus values ranging from 0 to 8.4 for any given lipid parameter.

**Table 1. Change in Lipids With Intensive and Moderate Therapy**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Pravastatin 40</th>
<th>Atorvastatin 80</th>
<th>Month 4</th>
<th>Pravastatin 40</th>
<th>Atorvastatin 80</th>
<th>End of Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg = 1831</td>
<td>mg = 1852</td>
<td></td>
<td>mg = 1494</td>
<td>mg = 1504</td>
<td>mg = 788</td>
<td>mg = 842</td>
</tr>
<tr>
<td>Apo B, mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>–11%</td>
<td>–35%</td>
<td>–13%</td>
<td>–31%</td>
<td>–11%</td>
<td>–35%</td>
<td>–13%</td>
</tr>
<tr>
<td></td>
<td>P = 0.57</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P = 0.0001</td>
<td>P = 0.0002</td>
<td></td>
</tr>
<tr>
<td>Apo AI, mg/dl</td>
<td>119</td>
<td>120</td>
<td>132</td>
<td>128</td>
<td>118–147</td>
<td>111–140</td>
<td>120–147</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>+9%</td>
<td>+3%</td>
<td>+10%</td>
<td>+7%</td>
<td>+9%</td>
<td>+3%</td>
<td>+10%</td>
</tr>
<tr>
<td></td>
<td>P = 0.83</td>
<td>P &lt; 0.0001</td>
<td>P = 0.0002</td>
<td>P = 0.0002</td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
<td></td>
</tr>
<tr>
<td>Apo B/AI</td>
<td>0.84</td>
<td>0.84</td>
<td>0.67</td>
<td>0.53</td>
<td>0.67</td>
<td>0.53</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>(0.7–1.0)</td>
<td>(0.7–1.0)</td>
<td>(0.6–0.8)</td>
<td>(0.4–0.6)</td>
<td>(0.5–0.8)</td>
<td>(0.4–0.7)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>–18%</td>
<td>–37%</td>
<td>–17%</td>
<td>–31%</td>
<td>–18%</td>
<td>–37%</td>
<td>–17%</td>
</tr>
<tr>
<td></td>
<td>P = 0.57</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
<td></td>
</tr>
<tr>
<td>TC/HDL–C</td>
<td>4.61</td>
<td>4.67</td>
<td>4.1</td>
<td>3.2</td>
<td>4.1</td>
<td>3.3</td>
<td></td>
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<tr>
<td></td>
<td>(3.8–5.6)</td>
<td>(3.8–5.8)</td>
<td>(3.4–4.9)</td>
<td>(2.7–3.9)</td>
<td>(3.4–4.9)</td>
<td>(2.8–4.1)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>–11%</td>
<td>–30%</td>
<td>–9%</td>
<td>–27%</td>
<td>–11%</td>
<td>–30%</td>
<td>–9%</td>
</tr>
<tr>
<td></td>
<td>P = 0.13</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
<td></td>
</tr>
<tr>
<td>Non-HDL-C, mmol/L</td>
<td>3.59</td>
<td>3.59</td>
<td>3.31</td>
<td>2.26</td>
<td>3.38</td>
<td>2.49</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3.03–4.15)</td>
<td>(3.08–4.23)</td>
<td>(2.82–3.95)</td>
<td>(1.87–2.77)</td>
<td>(2.85–3.95)</td>
<td>(2.03–3.10)</td>
<td></td>
</tr>
<tr>
<td>Change from baseline</td>
<td>–8%</td>
<td>–37%</td>
<td>–6%</td>
<td>–31%</td>
<td>–8%</td>
<td>–37%</td>
<td>–6%</td>
</tr>
<tr>
<td></td>
<td>P = 0.15</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P &lt; 0.0001</td>
<td>P = 0.0001</td>
<td>P = 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Absolute values reflect the median (interquartile range), and the changes from baseline reflect the median change.
LRT statistics used to discriminate improvement of one model over another were not significant (apoB/AI LRT statistic = 0.2; TC/HDL LRT statistic = 0.4; non–HDL-C LRT statistic = 0.6; with an LRT statistic > 3.84 indicating nominal statistical significance), providing strong evidence against a significant improvement in risk prediction by using other apoB/AI ratio, TC/HDL ratio, or non–HDL-C over and above LDL-C in this dataset (Table 2). By way of comparison the addition of 1 SD in log hs-CRP to models which included LDL-C significantly improved the model (LRT statistic = 18.2). The inclusion of interaction terms lipid parameter*statin regimen or hs-CRP*statin regimen in models were not significant, suggesting no material differences in the relationships observed by statin regimen. Statin regimen was also not independently associated with outcomes when included in models containing lipids and did not improve the LRT statistic.

### Incremental Predictive Value of hs-CRP to Lipid Parameters

To test whether hs-CRP offered any incremental risk prediction to each of the lipid parameters, a 1-SD change in log CRP was added to model 1 to create a new model (Model 2), which contained both LDL-C and an additional lipid parameter (1 SD increments of either apoB/AI, TC/HDL, or non–HDL-C). The addition of a 1-SD change in log CRP significantly improved model 2 over model 1, irrespective of the lipid fractions included within the models with LRT statistics ranging from 18 to 18.2 (Table 2). Per 1 SD increment in log CRP risk of recurrent events increased by 29% to 30%. When hs-CRP was added to model 1 as a dichotomous variable using the proposed cut point of 2 mg/L (Model 3), the statistical model also improved compared to model 1 irrespective of the lipid parameters included with LRT statistics ranging from 10 to 10.2 (Table 2). A higher hs-CRP (≥ 2 mg/L) appeared to identify individuals with higher event rates versus those with a lower hs-CRP (< 2 mg/L) across the range of lipids (Figure 2). In particular, the difference in risk between subjects with an hs-CRP < 2 mg/L versus subjects with hsCRP levels ≥ 2 mg/L appeared greater than the difference in risk between low and high lipid parameters among subjects with a CRP < 2 mg/L.

We further explored the relevance of different hs-CRP cut points. Compared with subjects with a CRP < 1 mg/L (median 0.5 mg/L) and lipid levels < median (reference group), the hazard ratio increased progressively both with increasing hs-CRP levels (1 to 2 mg/L, > 2 mg/L) and with increasing lipid levels (≥ median) (supplemental Figure 1). Importantly, irrespective of whether any of the lipid parameters were high (apoB/AI ≥ 0.60, TC/HDL ≥ 3.58, non–HDL-C ≥ 2.77 mmol/L, respectively) or low (apoB/AI < 0.60, TC/HDL < 3.58, non–HDL-C < 2.77 mmol/L, respectively), the risk of recurrent events was lowest in those with low CRP levels < 1 mg/L.

### Discussion

In this large trial of ACS patients, intensive statin therapy with atorvastatin 80 mg reduced the ratios of apoB/AI, TC/HDL ratio, and the level of non–HDL-C at 4 months to a greater extent than moderate dose statin therapy with pravastatin 40 mg. We observed that after adjustment for statins none of the baseline lipids predicted risk of future events. However, on-treatment levels of each lipid were associated with risk of recurrent events to a comparable degree and provided similar information on risk prediction to that provided by LDL-C. In contrast, we observed that hs-CRP significantly improved risk prediction models, providing independent prognostic information to each of the lipid parameters. Moreover, the apoB/AI ratio was found to be highly correlated with the TC/HDL ratio and apoB was highly correlated with both non–HDL-C and LDL-C, whereas hs-CRP was only weakly correlated with each lipid parameter, supporting the concept that hs-CRP provides information independent and complementary to that provided by lipid parameters.2,13

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**Figure 1.** Relationship between various 4-month lipid parameters alone or hs-CRP alone and the subsequent risk of death or acute coronary events. All analyses compare levels ≥ median versus < median for each parameter, adjusted for covariates. The improvement in models after the addition of each additional parameter is shown as a likelihood ratio test (LRT) statistic with a value > 3.84 considered as significant.*

<table>
<thead>
<tr>
<th>Lipid Parameter</th>
<th>LRT Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL-C</td>
<td>6.60</td>
</tr>
<tr>
<td>TG</td>
<td>0</td>
</tr>
<tr>
<td>HDL-C</td>
<td>0</td>
</tr>
<tr>
<td>TC</td>
<td>8.40</td>
</tr>
<tr>
<td>Non-HDL-C</td>
<td>5.40</td>
</tr>
<tr>
<td>TC/HDL</td>
<td>3.00</td>
</tr>
<tr>
<td>Apo A-I</td>
<td>0.80</td>
</tr>
<tr>
<td>Apo B</td>
<td>7.40</td>
</tr>
<tr>
<td>Apo B/A-I</td>
<td>5.40</td>
</tr>
<tr>
<td>CRP</td>
<td>13.40</td>
</tr>
<tr>
<td>CRP ≥ 2mg/L</td>
<td>12.20</td>
</tr>
</tbody>
</table>
conflicting findings. For example the INTERHEART case–apolipoproteins over other lipid fractions have also produced
and above LDL-C (eg, by the LRT test).

improved by the addition of the second lipid parameter over
used for the analysis in TNT and IDEAL were statistically
be noted that it was unclear whether the statistical models
another if they focus on the risk estimate. It should therefore
often results in the attenuation of one of the correlated
variables and do not test the superiority of one model over
another if they focus on the risk estimate. It should therefore
be noted that it was unclear whether the statistical models
used for the analysis in TNT and IDEAL were statistically
improved by the addition of the second lipid parameter over
and above LDL-C (eg, by the LRT test).

Studies in statin naïve populations comparing the utility of
apolipoproteins over other lipid fractions have also produced
conflicting findings. For example the INTERHEART case–
control study suggests that nonfasting apoB/A1 ratio as
compared with LDL-C and TC/HDL provided the greatest
odds ratio for myocardial infarction.16 In contrast to the
former case controlled retrospective study, two prospective
studies2,5 have both suggested that non–HDL-C and the ratio
of TC/HDL or even LDL-C were comparable to apolipoprotein
fractions in the prediction of incident CHD. Given the
high degree of correlation between lipids and lipoproteins it is
likely that even larger prospective studies than those currently
published will be required to clarify these issues. One
approach would be to pool, harmonize, and analyze existing
data using an individual participant meta-analysis which
would provide greater power than hitherto possible as the
number of cases accrued even in individual large prospective
studies are small.

In the present study, when hs-CRP was added as a
continuous variable it significantly improved risk prediction
models irrespective of the lipids included. Significantly, we
observed that the improvement in risk prediction provided by
the addition of hs-CRP to the basic model plus lipids was
much greater than that provided by the addition of lipids to
the basic model. Independent of lipids, per 1 SD increment in
log CRP there was a 29% to 30% increased risk of death or
recurrent coronary events consistent with data from statin
naïve populations.2

As a 1-SD increment on a log transformed scale is not
immediately intuitive in clinical practice, we explored
whether the proposed hs-CRP cut point of 2 mg/L offered
meaningful additional risk prediction to lipid parameters. We
found that the dichotomous cut point of 2 mg/L for hs-CRP also significantly improved risk prediction models, suggesting that the proposed cut point of hs-CRP <2 mg/L offers significant clinical utility. As individuals in PROVE IT–TIMI 22 had median hs-CRP levels of 1.3 mg/L in the intensive arm and 2.1 mg/L in the moderate therapy arm at 4 months, we were able to explore the relevance of even lower hs-CRP levels than those proposed by the Centre for Disease Control, ie, <1 mg/L, 1 to 2 mg/L and >2 mg/L. In these exploratory analyses we observed that individuals with an hs-CRP <1 mg/L tended to have the lowest risk of recurrent events irrespective of whether lipids were high or low, with the lowest risk being observed among those with both low lipid and hs-CRP levels. Taken together these data provide further support for the notion that both lipids and a marker of inflammation such as hs-CRP should be monitored to provide more complete risk assessment in patients with coronary artery disease, with a view to perhaps addressing adverse lifestyle issues or uncontrolled risk factors that contribute to an elevation of hs-CRP. Although the present study does demonstrate that hs-CRP improves risk prediction, further work and larger studies, perhaps using individual participant data, are needed to guide the determination of relevant hs-CRP cut points for potential clinical use.

Inflammation is a complex process consisting of a number of different cell types, a variety of cytokines, chemokines, and chemoattractants. hs-CRP is a downstream marker of inflammation and is regulated by the proinflammatory cytokine IL-6. In the absence of inflammatory conditions, it is postulated that hs-CRP reflects the net balance between pro- and antiinflammatory cytokine (and or cellular) activity in the vessel wall. We have previously reported that hs-CRP tracks with uncontrolled risk factors and that there are synergistic effects of conventional risk factors on inflammation. If these synergistic effects translate into increased risk then this may also explain why the addition of hs-CRP improves risk models for incident CHD which otherwise contain traditional risk factors in isolation. Thus hs-CRP may be acting as a global barometer of a number of dynamic processes within the body.

**Limitations**

In this analysis apolipoproteins were not available in all subjects at baseline and at 4 months. However, the characteristics of subjects with informative data were not statistically different to those subjects in whom lipid measurements were not available (data not shown). The analyses performed involve Cox regression models which can control for specified confounders but leave the possibility of residual confounding because of unmeasured variables. Finally, the present analysis assesses risk prediction and not causality, and as hs-CRP is a downstream marker of inflammation we make no inference within the present data about any causal relationship but rather we provide information on whether inflammation as assessed by hs-CRP improves risk prediction.

**Conclusion**

In the present analysis of ACS patients receiving statin therapy apoB/AI, TC/HDL, non–HDL-C, and LDL-C all provided similar information on risk prediction. However, the addition of hs-CRP to lipid-based measurements significantly improved risk prediction. On treatment CRP measurement may therefore offer additive prognostic information to lipids in ACS patients.

**Sources of Funding**

K.K.R. is funded by a British Heart Intermediate Fellowship. The PROVE IT Trial was funded by Bristol-Myers Squibb, Sankyo Co LTD. Funding sources did not make any contribution to the intellectual content of this manuscript.
Disclosures

Please see the supplemental materials.

References


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Arterioscler Thromb Vasc Biol. 2009;29:424-430; originally published online January 2, 2009;
doi: 10.1161/ATVBAHA.108.181735

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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ON LINE SUPPLEMENT

Blood sampling and analysis

Baseline plasma samples were collected in EDTA (before the initiation of blinded study medication) and frozen at the study site at -20°C or lower and then shipped on dry ice to the core laboratories where the specimens were either subsequently stored at -70°C for measurement of apo B, apo AI and hs-CRP. Samples were also collected at 4 months and end of study and handled in a similar manner.

Total cholesterol, HDL-C and triglycerides (TG) were measured immediately on freshly shipped plasma samples, using an enzymatic colorimetric method and the Roche Modular system (LabCorp, Raritan, NJ), but LDL-C was obtained by calculation (total cholesterol-[TG/5+ HDL]). CRP was measured using the validated Denka Seiken assay for hs-CRP (Children’s Hospital, Boston, MA).

Apolipoprotein B100 (apo B) and A I were measured using an immunoturbidimetric assay with a coefficient of variation of <2% on a Hitachi 911 analyzer (Roche Diagnostics) in a core laboratory (LabCorp, Raritan, NJ). The assay used is standardized by the WHO/International Federation of Clinical Chemistry and Laboratory Medicine standard.
### Web Table I Baseline characteristics of study cohort

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.3 +/- 11.2</td>
</tr>
<tr>
<td>Women</td>
<td>801 (22%)</td>
</tr>
<tr>
<td>Prior history of diabetes</td>
<td>682 (19%)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>1341 (36%)</td>
</tr>
<tr>
<td>Prior history of hypertension</td>
<td>1873 (51%)</td>
</tr>
<tr>
<td>BMI (kg/ m²)</td>
<td>29.6 +/- 5.7</td>
</tr>
<tr>
<td>Presentation with STEMI</td>
<td>1245 (34%)</td>
</tr>
<tr>
<td>Presentation with NSTEMI</td>
<td>1328 (36%)</td>
</tr>
<tr>
<td>Presentation with UA</td>
<td>1108 (30%)</td>
</tr>
<tr>
<td>PCI for index event</td>
<td>2533 (69%)</td>
</tr>
</tbody>
</table>

Age and BMI are shown as mean (SD), other variables shown as n (%).
Web Figure I. Relationship between on-treatment apo B/AI and CRP (Panel A), total cholesterol/HDL ratio and CRP (Panel B) and non-HDL-C and CRP (Panel C) and risk of death or acute coronary events. The group with lipid levels <median and CRP< 1mg/L acting as the reference group. All regression models are adjusted.
Disclosures

The TIMI Study Group has received significant research grant support from Accumetrics, Amgen, Astra-Zeneca, Bayer Healthcare, Beckman Coulter, Biosite, Bristol-Myers Squibb, CV Therapeutics, Eli Lilly and Co, Eisai Medical Research, GlaxoSmithKline, Inotek Pharmaceuticals, Integrated Therapeutics, Merck and Company, Merck-Schering Plough Joint Venture, Millennium Pharmaceuticals, Novartis Pharmaceuticals, Nuvelo, Ortho-Clinical Diagnostics, Pfizer, Roche Diagnostics, Sanofi-Aventis, Sanofi-Synthelabo, and Schering-Plough.

Dr. Ray has received honoraria for educational presentations from Pfizer, Novartis, Sanofi-Aventis, Bristol-Myers Squibb, Daichii-Sankyo-Lilly partnership, Solvay and Astra-Zeneca. He has served as a consultant on advisory boards for Pfizer, Merck Schering Plough partnership, MSD, Astra-Zeneca, Daiichi Sankyo Lilly partnership and Novartis. Dr. Morrow has received honoraria for educational presentations from Bayer Diagnostics, Beckman-Coulter, Dade-Behring, Sanofi-Aventis, Siemens and Roche Diagnostics. He has served as a consultant for GlaxoSmithKline and Sanofi-Aventis and on advisory boards for Critical Diagnostics, Genentech, OrthoClinical Diagnostics Siemens and Beckman-Coulter. Dr Ridker reports that he currently or in the past 5 years has received research funding support from multiple not-for-profit entities including the National Heart, Lung, and Blood Institute, the National Cancer Institute, the American Heart Association, the Doris Duke Charitable Foundation, the Leducq
Foundation, the Donald W. Reynolds Foundation, and the James and Polly Annenberg La Vea Charitable Trusts. Dr Ridker also reports that currently or in the past 5 years he has received investigator-initiated research support from multiple for-profit entities including AstraZeneca, Bayer, Bristol-Myers Squibb, Dade-Behring, Novartis, Pharmacia, Roche, Sanofi-Aventis, and Variagenics. Dr Ridker reports being listed as a coinventor on patents held by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and has served as a consultant to Schering-Plough, Sanofi/Aventis, AstraZeneca, Isis Pharmaceutical, Dade-Behring, and Vascular-Biogenics. Dr Cannon currently receives research grant support from the following companies: Accumetrics, AstraZeneca, Bristol-Myers Squibb-Sanofi partnership, Glaxo Smith Kline, Merck, Merck/ Schering Plough Partnership. He also reports to be being a clinical advisor and has equity in Automedics Medical Systems. Dr Braunwald reports to have participated occasionally (max 2-3/yr) in symposia/advisory board meetings/consultancies for companies listed above under the TIMI Study Group.