Measuring hsCRP—An Important Part of a Comprehensive Risk Profile or a Clinically Redundant Practice?

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With the publication of the JUPITER trial [1] there is now considerable interest in measuring high-sensitivity C-reactive protein (hsCRP). While treatment with rosuvastatin decreased the chance of clinically important events in the JUPITER trial, does this necessarily justify treatment based on hsCRP measurements? Here, we discuss issues surrounding hsCRP measurements in patients.

What Is the Suggested Role for hsCRP Measurements?

The median values for hsCRP are 2.5 mg/l (American women) and 1.5 mg/l (American men) [2]. Typical recommendations are to measure hsCRP in “intermediate risk” patients to help classify them into either a higher or lower risk category [3,4]. Intermediate risk is usually, and arbitrarily, described as either a 10%–20% [3,4] or 5%–20% [5,6] 10-year risk of developing coronary heart disease (CHD). It has been suggested that hsCRP levels <1, 1–3, or >3 mg/l represent lower, moderate, and higher relative risk of future heart disease, respectively.

How Accurate Is hsCRP Measurement?

Between-subject standard deviation for hsCRP measurement is 1.7 mg/l. Within-subject standard deviation is 1.2 mg/l [7]. Clearly, within-subject standard deviation means that a patient with a reported hsCRP of 2 mg/l (moderate) when re-measured could readily be placed in a low (<1 mg/l) or high (>3 mg/l) range [7]. Some authors have therefore suggested hsCRP needs to increase or decrease by 120% to 175% before a “real” change can be considered to have occurred [8]. It has been estimated that “in order to reduce the intra-individual variation sufficiently, each subject is likely to require blood samples collected on at least 10 occasions” [9].

Does Measuring hsCRP Add Value to Already Established Risk Factors When It Comes to Assessing CHD or Cardiovascular Disease Risk?

Several studies have confirmed that using hsCRP in addition to established risk factors (age, gender, blood pressure, cholesterol, smoking, and diabetes) does not improve the estimation of risk of cardiovascular disease (CVD) to a clinically important degree. Folsom et al. found that elevated hsCRP was associated with an increased risk of CHD (hazard rate ratio 1.19, p<0.001) but that it was similar to, or less important than, many other markers including D-dimer (1.36), interleukin-6 (1.28), and lipoprotein-associated phospholipase A2 (1.17) [10]. Wang et al. used C statistics to assess CVD predictive models and found age, sex, and traditional risk factors provided 0.76 value compared to the 0.77 value when ten different biomarkers (including hsCRP) were added [11]. Shah et al. also assessed the additive value of hsCRP and found that “hsCRP does not perform better than the Framingham risk equation for discrimination. The improvement in risk stratification or reclassification . . . is small and inconsistent” [12].

How Does Measuring hsCRP Affect Absolute Risk Estimates of CVD in Individuals?

The Reynolds Risk Score [13] is an online calculator that incorporates hsCRP measurement with other risk factor information (age, sex, systolic blood pressure [SBP], smoking history, total cholesterol, high-density lipoprotein [HDL] cholesterol, and family history) to compute the risk (%) of heart attack, stroke, or other major heart disease in the next 10 years. We used two patients, one male and one female with a “moderate” hsCRP level (2 mg/l), and adjusted other factors so that they would have an overall absolute risk estimate of 15%—in the middle of the “intermediate” risk category. We then changed hsCRP to 0.5, 5, or 10 mg/l to see what would happen to their calculated risk (Table 1).

Absolute risk estimates changed by just ±2% (male) and ±3%–4% (female). It is important to appreciate that the magnitude of these risk estimate changes are equal to or less than the confidence interval (CI) on the original risk estimate. Anderson et al. noted for the Framingham dataset that the 95% CIs for 10-year predictions of CHD of less than 10%, 10%–20%, and 30%–40% were ±1.5%–

References:

Citation: McCormack JP, Allan GM (2010) Measuring hsCRP—An Important Part of a Comprehensive Risk Profile or a Clinically Redundant Practice? PLoS Med 7(2): e1000196. doi:10.1371/journal.pmed.1000196
Published: February 2, 2010
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Funding: No specific funding was received to write this article.
Competing Interests: The authors have declared that no competing interests exist.
Abbreviations: CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; SBP, systolic blood pressure.
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Provenance: Not commissioned; externally peer-reviewed.
It seems obvious that the baseline risk estimates are actually changed by the percentage suggested; are these changes in risk estimate clinically relevant? First, in these scenarios, one can see that none of the revised risk estimates actually ended up recategorizing our particular patients into a different risk category. Second, would knowing a person’s risk be 17% or 15%, instead of 15% lead to a difference in the decision to consider taking a drug?

Let’s assume statins produce a 25% relative risk reduction in CVD. If a patient has an absolute baseline risk of 17%, their risk, if they took a statin, would decline to 12.75%, an absolute difference of 4.25%. If their baseline risk was 15%, a statin would lower their risk to 11.25%, an absolute difference of 3.75%. In other words, in this patient, if the absolute risks were indeed different the difference in the estimate of absolute benefit would be 0.5% (4.25% minus 3.75%); a difference unlikely to change the decision to use or not use a statin.

**Don’t Studies Show hsCRP Measurements Reclassify Patients into Different Risk Categories?**

Ridker et al. have shown that incorporating hsCRP “reclassifies” people into different risk categories [6,16]. For instance, 14% of women and 12% of men were recategorized from intermediate to low risk. However, others have disputed these findings and found that only 5.6% of participants would end up being reclassified [17]. What is likely happening in these “reclassification” papers is a number of patients with risks just above or below these arbitrary thresholds (say an estimated 18%–19% risk) will be bumped up or down to a different risk category because their estimate has now changed by 2%–3%, but these absolute changes, as discussed above, have little clinical relevance [13].

In the JUPITER trial (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), rosuvastatin was shown to reduce the chance of developing a clinically important cardiovascular event. Table 2 outlines the impact of other drugs on hsCRP and cardiovascular events. Although each drug has various pharmacological effects the impact of lowering hsCRP with medication on cardiovascular events is consistently inconsistent.

### What Were the Outcomes of JUPITER?

The JUPITER investigators screened almost 90,000 people to enroll 17,802 who had an hsCRP $\geq 2$ mg/l and an LDL $\leq 3.4$ mmol/l (130 mg/dl). Participants (mean age 66, median LDL of 2.8 mmol/l, average hsCRP of 4.2 mg/l) were randomized to rosuvastatin 20 mg daily or placebo. Based on the baseline characteristics of these participants, using the Reynolds risk score, the average participant in this trial would have had a 10-year risk of approximately 10%–15% [13]. The trial was stopped early, after a median follow-up of 1.9 years revealed that the combined endpoint of myocardial infarction, stroke, or death from cardiovascular causes occurred in 0.9% of participants taking rosuvastatin compared to 1.8% of participants taking placebo.

Ideally, the effects of hsCRP on risk assessment and treatment decisions would be evaluated using a randomized trial with two groups: one in which a risk assessment included hsCRP and one that did not. Then participants in each group would receive a drug known to improve cardiac outcomes at a predefined risk level. To date no trial, including JUPITER, has been designed to answer the question “Does the use of hsCRP in clinical practice result in reduced CVD outcomes and improved health?” A meta-analysis had already demonstrated that primary prevention with statins lowers the risk of CVD [18]. JUPITER might be considered unique in that the study participants had a reduced low-density lipoprotein (LDL) but ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm) has already demonstrated that primary prevention patients at risk for CVD benefit from a statin despite a lower than “normal” LDL, albeit not as low an LDL as was evaluated in JUPITER (ASCOT-LLA mean LDL 3.4 mmol/l, JUPITER median LDL 2.8 mmol/l) [19]. It is important to remember that JUPITER was an evaluation of a fixed dose of rosuvastatin and thus getting subjects to “targets” is purely extrapolation, as none of the statin studies done to

### Table 2. Examples of drugs that lower hsCRP and the impact these drugs have had on clinical outcomes.

| Drug | Approximate % Decrease in hsCRP [References] | Effect on Clinical Outcomes [References] |
|------|-----------------------------------------------|----------------------------------------|
| Rosiglitazone | 40 [23] | ↓ [24] |
| Rofecoxib | ↓ [25,26] | ↓ [27] |
| Fibrates | 30–85 [23] | ↔ [28,29] |
| Vitamin E | 50–80 [23] | ↓ ↔ [30,31] |
| Niacin | 25 [23] | ↓ [32] |
| Ezetimibe | 10 [33] | ↔ [34] |
| Statins | 15–50 [23] | ↓ [35] |

$\uparrow$ Consistent evidence is available that the drug increases the risk of cardiovascular events. $\downarrow$ Evidence is incomplete or inconsistent as to the effect the drug has on cardiovascular events. $\leftrightarrow$ Consistent evidence is available that the drug decreases the risk of cardiovascular events.

*Rofecoxib reduces hsCRP more than placebo but not enough data is provided in the referenced studies to give a specific % reduction.

doi:10.1371/journal.pmed.1000196.t002

**Table 1.** Estimated 10 year risk of a heart attack, stroke, or other major heart disease based on the risk calculator at reynoldsriskscore.com.

| Patient | hsCRP mg/l |
|---------|------------|
| 0.5 | 2 | 5 | 10 |
| 60 y/o male* | 13% | 15% | 16% | 17% |
| 70 y/o female* | 12% | 15% | 17% | 19% |

* Nonsmoker, no family history, SBP 160 mmHg, a total cholesterol of 6 mmol/l and an HDL of 1 mmol/l.

**Nonetheless, if we assume the changes in risk estimate using hsCRP are exact and the risk estimates are actually changed by the percentage suggested; are these changes in risk estimate clinically relevant? First, in these scenarios, one can see that none of the revised risk estimates actually ended up recategorizing our particular patients into a different risk category. Second, would knowing one’s risk be 17% or 13%, instead of 15% lead to a difference in the decision to consider taking a drug?**

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Is There Evidence That Baseline hsCRP Levels Predict Outcomes from Statin Therapy?

In a post-hoc analysis, Ridker et al. reviewed participants in the AFCAPS/TexCAPS study (Air Force/Texas Coronary Atherosclerosis Prevention Study). They stratified participants according to their baseline LDLs or hsCRPs (A, any hsCRP; H, LDL or hsCRP higher than the median; L, LDL or hsCRP lower than the median) to determine if different baseline levels of hsCRP or LDL could predict variations in the benefit of a statin. The main results are outlined in Table 3.

Key issues to consider about the AFCAPS/TexCAPS data:

1. Only the L/L and the L/A groupings showed a difference in baseline 5-year risk.
2. In three of the categories (L/H, H/L, and H/A), lovastatin produced a reduction in events that was superior to placebo; however, owing to the overlapping CIs, no subset had a statistically different magnitude of outcome from any other subset.
3. Post-hoc analysis of subgroups defined after randomization are subject to a high risk of bias.

Isn’t There Evidence That Reducing Levels of hsCRP Predicts Outcomes?

The AFCAPS/TexCAPS retrospective evaluation was about what happened to subjects based on baseline LDL/hsCRP. Interestingly, no studies have actually looked prospectively at the question of getting patients to a target hsCRP or cholesterol. In the JUPITER study, a fixed-dose rosuvastatin trial, investigators did look at achieved (in contrast to AFCAPS/TexCAPS) hsCRP and LDL measurements to see if there was an association between achieved levels and outcome [22]. The categories they chose (above or below an LDL of 1.8, an hsCRP of 2 or 1) were prespecified. The key findings are outlined in Table 4.

Key issues to consider about the JUPITER data:

1. While some information about baseline characteristics was provided, none was provided for any of the subsets in Table 4 other than the low LDL/low hsCRP.
2. No information is provided regarding how much (relatively) LDL and hsCRP went down in each of the LDL/CRP subsets.
3. Participants who took 20 mg of rosuvastatin and did not achieve an LDL<1.8 or hsCRP<1 (H/H) experienced no clinical benefit. While we are not necessarily endorsing the approach, if one were to follow this evidence, patients who do not attain an LDL<1.8 and a hsCRP of less than 1 or 2 while on 20 mg of rosuvastatin should stop taking the drug as they will not derive a clinical benefit.
4. There is little difference in the results among participants who achieved hsCRP of <1 mg/dl or <2 mg/d, which suggests that as long as you get the hsCRP below 2 mg/dl any further reduction yields no additional benefit.
5. Participants who achieved both an LDL<1.8 and an hsCRP<2 (L/L), had a lower point estimate of benefit than participants who only achieved one of these breakpoints. The authors state that overall there was a p-value for trend across LDL cholesterol and/or hsCRP strata. However, the CIs for a number of the groups clearly overlap to a degree that does not allow one to draw specific conclusions about the differences in benefit between specific subsets.

6. It is unknown if lower LDL/hsCRP levels were attained due to differences in adherence to rosuvastatin, a factor that might help explain why the group that did not achieve specific LDL and hsCRP levels did not appear to benefit from statin therapy.

Conclusion

The substantial intra-subject variation in hsCRP measurements makes it virtually impossible to assess the impact a therapy has on hsCRP in an individual patient. Even if the intra-subject variation is ignored, when hsCRP is used in addition to other established risk factors, the size of

| LDL  | CRP  | Relative Risk of Acute Coronary Event | 95% CI       | 5 Year Risk (%) |
|------|------|--------------------------------------|--------------|-----------------|
| L    | L    | 1.08                                 | 0.56–2.08    | 2.2             |
| L    | H    | 0.58                                 | 0.34–0.98    | 5.1             |
| H    | L    | 0.38                                 | 0.21–0.70    | 5.0             |
| H    | H    | 0.68                                 | 0.42–1.10    | 5.5             |
| H    | A    | 0.53                                 | 0.37–0.77    | 5.3             |
| L    | A    | 0.74                                 | 0.49–1.11    | 3.6             |

Data are from Table 2 in [36].

5 year risk (%), risk of an acute coronary event in the placebo arm group (in other words, this is a baseline risk for this population); A, any hsCRP; H, LDL or hsCRP higher than the median; L, LDL or hsCRP lower than the median.

doi:10.1371/journal.pmed.1000196.t003
the absolute changes in risk estimates, even at the extremes of hsCRP levels, are unlikely to change an individual's decision to seek therapy. Finally, the evidence that cardiovascular events are reduced when a patient takes a drug that lowers hsCRP is inconsistent at best. Armed with this information, we hope clinicians can determine for themselves whether measuring hsCRP is an important part of a comprehensive risk profile or a clinically redundant practice.

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