C-reactive protein and cholesterol are equally strong predictors of cardiovascular risk and both are important for quality clinical care

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Received 24 September 2012; revised 9 December 2012; accepted 3 January 2013; online publish-ahead-of-print 1 February 2013

Introduction

Physicians do not measure biomarkers simply to predict risk. Rather, they do so to better target therapy and improve the lives of their patients. Thus, when considering the use of any biomarker for cardiovascular risk prediction in primary prevention, thoughtful clinicians, and those writing guidelines should insist that two fundamental questions be answered affirmatively.

First, is there clear evidence that the biomarker of interest predicts future cardiovascular events independent of other risk markers?

And secondly, is there clear evidence that those identified by the biomarker of interest benefit from a therapy they otherwise would not have received?

No imaging biomarker can answer these questions affirmatively, nor can a variety of plasma biomarkers such as lipoprotein(a) or triglycerides. As we will discuss below, the answer to both of these questions is clearly ‘yes’ for C-reactive protein as well as for cholesterol. Yet, while recent European Society of Cardiology guidelines for the prevention of heart disease strongly endorse cholesterol screening, those same guidelines are silent on C-reactive protein.

Evidence that cholesterol and C-reactive protein are equally strong independent predictors of risk

Inflammation is a fundamental component of atherosclerosis. For more than a decade, data from large-scale prospective cohorts in the USA and Europe have consistently indicated that the predictive value of the inflammatory biomarker C-reactive protein is at least as large as that of cholesterol. This observation is important since half of all heart attacks and strokes occur among those with average if not low cholesterol levels.

That C-reactive protein and lipids are equal contributors to vascular risk has recently been confirmed in an elegant 2012 meta-analysis published in the New England Journal of Medicine by the Emerging Risk Factors Collaboration that analysed data from 38 prospective studies and included 166,596 men and women without prior disease. Specifically, for a prediction model that included age, smoking, systolic blood pressure, and diabetes status, the magnitude of change in the C-statistic associated with adding TC to the model was 0.0043; subsequently adding HDL-C to the latter model changed the C-statistic by 0.0050.

These are critical benchmarks for comparison, as all cardiovascular screening programmes worldwide include TC and HDL-C.

How does C-reactive protein evaluation stand up to the reference standards of TC and HDL-C screening? In the same comprehensive Emerging Risk Factors Collaboration analysis, once TC and HDL-C are included in the prediction model, the incremental change in the C-statistic associated with the further addition of C-reactive protein was 0.0039, a magnitude of effect fully comparable with that of the two lipid benchmarks. Since the bar for inclusion becomes sequentially higher as each new biomarker is added to a prediction model, these data confirm that C-reactive protein’s value in predicting cardiovascular risk is at least similar to that of standard lipid measures. This is borne out by further evidence from the emerging risk factors collaboration meta-analysis indicating that the multivariable adjusted hazard ratio associated with a 1 SD increase in C-reactive protein was 1.20 (vs. 1.17 for a comparable 1 SD increase in TC) (Figure 1).

Thus, in terms of discrimination and magnitude of effect, lipids and C-reactive protein are virtually identical in their independent...
ability to discern who is at risk for future cardiovascular events, and each adds equally to the other. This is not and has never been a controversial issue on the basis of published epidemiological data. Nonetheless, some commentators continue to claim that C-reactive protein does not merit inclusion in risk prediction guidelines because its contribution is ‘small’; we can only assume that those same commentators must of necessity believe that total and HDL-C do not merit inclusion either. Others have argued that LDL-C is included in guidelines not because of its predictive value but because it is a causal agent for atherosclerosis. This argument, however, is equally spurious. The causal role for HDL-C is uncertain, yet HDL-C has appropriately been part of all global prediction algorithms for nearly two decades.

Evidence that individuals identified by cholesterol or C-reactive protein screening benefit from a therapy they otherwise would not have received

Many biomarkers predict risk. What matters in clinical practice is whether there is additional evidence demonstrating that individuals identified at risk by the biomarker of interest benefit from a therapy they otherwise would not have received. This is a crucial test for the evidence-based practice of medicine, yet often overlooked in the guideline writing process.

In 1995, the WOSCOPS trial answered this crucial question in primary prevention for those with elevated cholesterol. Prior to this landmark study there was considerable skepticism that statin therapy—known to be effective in secondary prevention—would be beneficial in high risk primary prevention. In brief, in a group of patients without prior myocardial infarction but who all had elevated levels of cholesterol, pravastatin when compared with placebo was shown to reduce the rate of non-fatal myocardial infarction and cardiovascular death by 31%. Largely on the basis of this pivotal trial, guidelines were subsequently written endorsing the use of statin therapy in primary prevention for those with elevated levels of cholesterol.

In 2008, in a fully parallel manner, the JUPITER trial answered this crucial question in primary prevention for those who had elevated levels of C-reactive protein but who otherwise would not qualify for statin therapy as they already had levels of LDL-C below treatment thresholds. In brief, among 17 802 individuals with LDL-C < 3.36 mmol/L (median = 2.7 mmol/L) but who were identified at increased vascular risk due to C-reactive protein levels > 2 mg/L (median 4.1 mg/L), rosuvastatin reduced major vascular events by 44% (P < 0.0001) and all-cause mortality by 20% (P = 0.02). JUPITER also extended the statin literature in primary prevention to include women and non-Caucasian participants, all of whom experienced similar risk reductions. While there was no relationship in JUPITER between baseline LDL-C and subsequent benefit (an observation consistent with many studies in secondary prevention), those with sequentially higher baseline C-reactive protein values in JUPITER had higher absolute risk and higher absolute risk reductions with statin therapy.

Just as WOSCOPS did not randomize those with low levels of LDL-C, JUPITER did not randomize those with low levels of C-reactive protein. Thus, while it is possible that low LDL, low C-reactive protein patients might benefit from statin therapy, no trial data are available to support this contention. Further, the absolute risk for primary prevention patients with low levels of both LDL-C and C-reactive protein is likely to be small. As such, the number-needed-to-treat in this subgroup would be very large even if efficacy were known.

What works and in whom?
A simple, easily applied, evidence-based alternative to guidelines for the use of statin therapy in the prevention of cardiovascular disease

In their recent European Heart Journal commentary on C-reactive protein and statin therapy, Hingorani et al. simulate the JUPITER trial outcome on the basis of absolute risk and LDL-C reduction. Yet if absolute risk and magnitude of LDL-C reduction is all that is necessary to predict statin trial results, similar simulation would not have correctly predicted the null data observed in CORONA, AURORA, 4-D, and GISSI-HF. All four of these quality trials enrolled high absolute risk patients who achieved...
large LDL-C reductions with statin therapy, yet in none was any significant clinical benefit observed. Rather, what the cardiology community learned from these trials is not to anticipate a clinical benefit of statins among those with congestive heart failure or end-stage renal failure.

As such, we prefer to believe that randomized trials matter greatly and that guidelines as well as clinical practice should be based on the principle of ‘what works?’ and ‘in whom?’ rather than on epidemiological modelling and risk simulations.\(^\text{14}\)

In the past, the volume of trial data on the efficacy of lipid-lowering treatments as an adjunct to diet, exercise, and smoking cessation in specific patient groups was limited, safety data were uncertain, and the cost of treatment was relatively high. Thus, it is understandable that those writing older guidelines chose to model outcomes and base prescription on epidemiological risk scales.

In 2013, however, the situation is markedly different and none of the three justifications for having a ‘risk-based’ approach to statin therapy remain. First, data on safety are now abundant, there are no longer concerns regarding cancer, and the benefits of statin therapy on myocardial infarction, stroke, revascularization procedures, and cardiovascular death are known to outweigh the risks even for those at the lower end of the absolute vascular risk spectrum. Secondly, almost all statin agents are now off patent and the cost of treatment has dramatically declined. Thirdly, in 2013 the cardiovascular community has abundant data from many large-scale, randomized, placebo controlled trials that cover a wide range of patient groups so that trial data may be directly applied to clinical care without need for epidemiological extrapolation. This is most relevant for primary prevention where greatest controversy remains (Figure 2).

Given the current abundance of data, a simple evidence-based guideline for statin therapy using the concepts of ‘what works’ and ‘in whom’ can be written in five easily understood paragraphs with no need for complex data modelling:\(^\text{14}\)

1. On this basis of high-quality randomized clinical trial data, statin therapy should be used as an adjunct to diet, exercise, and smoking cessation for secondary prevention patients with a prior history of myocardial infarction, stroke, or clinically apparent atherosclerosis (4S, HPS, CARE, LIPID).

2. On the basis of high-quality randomized trial data, statin therapy can be considered as an adjunct to diet, exercise, and smoking cessation in the setting of primary prevention for those aged 50 and over with either diabetes (CARDS), elevated LDL-C (WOSCOPS, MEGA), low HDL-C (AFCAPS), or elevated hsCRP-reactive protein (JUPITER). To improve relative efficiency and cost-effectiveness, physicians may elect to limit statin prescription to the above groups who also have at least one additional risk factor such as hypertension or smoking. For patients who do not meet these criterion, physicians may consider issues such as genetic predisposition or a strong family history of premature coronary disease when making decisions for individual patients at different ages in primary prevention. For some of these patients, such as those suspected of having familial hyperlipidaemia, referral to lipid or atherosclerosis specialists may be useful for considerations of secondary testing and potential use of alternative or additional lipid-lowering therapies.

3. On the basis of high-quality randomized trial data, when prescribing statin therapy physicians should seek to maximize the intensity of treatment and then focus efforts on compliance and long-term adherence (PROVE IT, TNT, IDEAL). As such, the target dose for an individual patient should be selected as a dose close to or at the highest level the individual patient tolerates without side effects.

4. On the basis of high-quality randomized trial data, the use of non-statin lipid lowering agents as monotherapy or in combination with statin should be limited until there is evidence that such an approach further reduces cardiovascular event rates in specific patient groups (AIM-HIGH, ACCORD, FIELD, THRIVE). It is recognized that there are instances where this approach may be suboptimal, such as in individuals who demonstrate statin intolerance or have familial hyperlipidaemia and exceptionally high LDL-C. Such individuals should be referred for secondary evaluation by lipid specialists.

5. A guideline based on trial evidence (to know what works) and on trial entry criteria (to know in whom) is simple, consistent with evidence-based principles, and thus will result in broad clinical acceptance. New advances in prevention should be incorporated into guidelines as quickly as possible. Thus, if new agents develop evidence of event reduction that is superior to statin therapy alone, develop evidence of event reduction among those who are statin intolerant, or develop evidence of incremental event reduction as an adjunct to statin therapy, updated guidelines should be rapidly developed to address these important advances.

The above formulation is simple, easily understood, and avoids controversy as it is based soundly on trial data.

**Are European patients losing out?**

In the USA, the Food and Drug Administration carefully reviewed the JUPITER data and on merit provided a new labelling claim for statin therapy that included reductions in myocardial infarction and...
stroke among individuals with elevated C-reactive protein and at least one additional risk factor. In 2009, the Canadian Cardiovascular Society guidelines for the prevention of cardiovascular disease endorsed the use of statins to prevent cardiovascular events among patients with elevated C-reactive protein and a 10-year projected risk between 10 and 20 percent.15 In contrast, the only indication provided by the European Medicines Agency based on the identical JUPITER trial data was for a small subset of trial participants defined by the agency on a post hoc basis that did not on its own have evidence for benefit.16 This is an unusual step since JUPITER participants enrolled in Europe had at least as large a benefit as those enrolled in the USA or Canada (Figure 3).

As Prof. Eugene Braunwald has previously written in the European Heart Journal, despite highly consistent evidence favouring C-reactive protein in multiple cohorts as well as randomized placebo controlled intervention data, there continue to be those who will ‘create controversy where in fact none exists’, a process that slows the dissemination of quality care into practice.17 In 2013, just as our primary prevention patients with elevated LDL-C benefit from statin therapy, so too do our primary prevention patients with elevated C-reactive protein. To withhold potentially life-saving therapy because of an unwillingness to address new data is inconsistent with evidence-based practice and a disservice to our patients.

Conflict of interest: P.M.R. is listed as a co-inventor on patents held by the Brigham and Women’s Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease and diabetes that have been licensed to AstraZeneca and Siemens. P.M.R. receives investigator-initiated grant support from AstraZeneca, Novartis, and Amgen. P.M.R., J.J.P., J.G, and W.K. all served on the Steering Committee of the JUPITER trial which was funded by AstraZeneca.

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