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### Expert Interview

## C-Reactive Protein -- Inflammatory Marker and More in Cardiovascular Disease: An Expert Interview With Paul M. Ridker, MD, MPH, FACC, FAHA

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**Interviewer:** Linda Brookes, MSc

### **Editor's Note:**

*Paul M. Ridker, MD, MPH, FACC, FAHA, is Eugene Braunwald Professor of Medicine at Harvard Medical School, Boston, Massachusetts, and directs the Center for Cardiovascular Disease Prevention, a translational research unit at the Brigham and Women's Hospital in Boston, Massachusetts, that focuses on the molecular and genetic epidemiology of cardiovascular diseases.*

*Dr. Ridker's primary research brings together classic tools of large-scale, population-based epidemiology with emerging genetic and molecular techniques designed to improve our ability to predict and prevent thrombotic occlusion. Particular areas of interest involve molecular and genetic determinants of hemostasis, thrombosis, and inflammation with a focus on "predictive medicine," early disease diagnosis, and the underlying causes and prevention of acute coronary syndromes. Dr. Ridker's work on inflammation and C-reactive protein (CRP) led to the first set of federal guidelines advocating CRP evaluation as a new method for cardiovascular disease detection. Dr. Ridker is listed as a co-inventor on several patents filed by the Brigham and Women's Hospital that relate to the use of inflammatory biomarkers in cardiovascular disease. Dr. Ridker spoke with Linda Brookes for this interview with Medscape Cardiology.*

**Medscape: CRP is well known as a marker of inflammation that has aroused huge interest in global cardiovascular risk prediction. Is CRP just a prognostic marker or is it directly involved in the atherothrombotic process?**

**Dr. Ridker:** It is overwhelmingly clear that CRP, or more specifically, high-sensitivity C-reactive protein (hsCRP), is an important marker of risk that adds prognostic information at all levels of low-density lipoprotein (LDL)-cholesterol, at all levels of the metabolic syndrome, and at all levels of the Framingham Risk Score. hsCRP levels of < 1, 1-3, and > 3 mg/L correspond with lower, moderate, and higher vascular risk across wide groups of patients. That has been clearly demonstrated in prior work, much of it from our group at the Brigham and Women's Hospital. What is evolving more recently is that CRP may be more than just a marker, and may be directly involved in the atherothrombotic process itself. Evidence in support of this idea is coming from many different areas, including direct effects of CRP on inflammation itself, from transgenic mouse models that have demonstrated increased thrombosis, when the human CRP gene was introduced into mice, to a series of studies looking at the induction of (or changes in) platelet function in clotting and in inflammatory function when CRP is exogenously introduced. However, I believe it is important to say that at this point in time, whether CRP is a player in the process remains an open question, although the data are far more abundant now than they were 3 or 4 years ago. That question does not really have an impact on clinical use, as it is already well demonstrated that CRP is a useful clinical marker in daily practice.

**Medscape: What do we currently know about the role of CRP as a prognostic marker for primary prevention?**

**Dr. Ridker:** Almost 10 years ago, in 1997, we published the first major study showing that by measuring hsCRP in healthy individuals, physicians could predict the onset of future heart attack, stroke, and cardiovascular death, and could do so independently of traditional cardiovascular risk factors.<sup>[1]</sup> So in many ways, this field began in primary prevention, and since that time data have been amassed from over 30 major studies of primary prevention, all of which have found that CRP levels at baseline in healthy individuals are associated with increased cardiovascular risk over the rest of their lives. The 9 largest of these studies,<sup>[1-8]</sup> the ones that have adequate power, all showed that CRP adds predictive information beyond traditional risk factors. That is now accepted by almost everyone, and in early 2003 the American Heart

Association (AHA) and the US Centers for Disease Control and Prevention (CDC) issued joint clinical guidelines for the use of hsCRP,<sup>[9]</sup> which made it clear that the physicians had a new option to use for risk detection. The AHA/CDC document was actually a conservative guideline, but even so it argued, without benefit of all the newest data, that physicians really could do a better job with markers of inflammation and that of the inflammatory markers that were available, hsCRP was the only one that has proven to be of use. So the use of hsCRP in primary prevention is already well established.

**Medscape: What types of individuals would CRP measurement identify as needing primary prevention?**

**Dr. Ridker:** Half of all heart attacks and strokes in the United States occur in people with normal cholesterol levels, and 20% of all events occur in people with no major risk factors. It has been demonstrated many times that hsCRP levels, when added to the traditional ways of measuring risk, provide a better way of detecting who is a high-risk patient. Once detected, we would encourage these individuals at high risk to stop smoking, to diet, to exercise, and to talk to their physicians about pharmacologic interventions that they may need for prevention.

**Medscape: What do the recent reports from the Pravastatin or Atorvastatin Evaluation and Infection Therapy -- Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22)<sup>[10]</sup> and Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL)<sup>[11]</sup> trials tell us about the use of CRP in secondary prevention?**

**Dr. Ridker:** It is important to understand that over the past 8 years, we have also accumulated data indicating that CRP levels in the setting of acute myocardial infarction, during the stable phase, are also very predictive of recurrent coronary events. However, most people and even I myself have said until recently that there is not much reason to use CRP in secondary prevention, because you already know that these are high-risk patients, so there is no need to measure it. This is radically changed with the new studies, PROVE IT-TIMI 22 and REVERSAL, because we now know that it is crucial that we measure CRP in secondary prevention if we are to deliver the best care for our patients. In brief, both studies show that in secondary prevention of high-risk patients taking statin therapy, it is no longer enough to monitor the LDL-cholesterol; rather, we need to move toward what I would call "dual-goal therapy" of not only an aggressive reduction of LDL but also an aggressive reduction of the CRP levels.

The data are quite striking. The PROVE IT-TIMI 22 trial compared intensive vs moderate statin therapy in patients who had been hospitalized for an acute coronary syndrome and, as reported in 2004,<sup>[12]</sup> showed that there was a benefit of intensive therapy. We had shown, as far back as 1998, that statins are what I would call "2-for-1 drugs," ie, they not only lower cholesterol; they also lower CRP,<sup>[13]</sup> but until now we did not have evidence that the reduction in CRP was clinically meaningful. So, because we already knew that statins lowered CRP levels as well as cholesterol levels, we hypothesized that both of these would be important in predicting the efficacy of statin therapy. The bottom line of the PROVE IT-TIMI 22 CRP data is that among patients with acute coronary ischemia who were treated with very aggressive therapy, the best survival was observed among those individuals who not only got their LDL-cholesterol below the recommended level of 70 mg/dL,<sup>[14]</sup> but who also got their hsCRP levels below 2 mg/L.

In other words, it was not adequate to monitor only their cholesterol; it is equally important to monitor their hsCRP levels as well. The best group, in terms of overall survival free of recurrent cardiovascular events, was the group of patients who both got their CRP down *and* their LDL-cholesterol down. We did some other analyses that showed that patients had even better outcomes if their CRP decreased even further, to below 1 mg/L.

**Medscape: Does that mean that there is no relation between CRP and LDL-cholesterol?**

**Dr. Ridker:** Yes, it does and this is a crucial issue. It means that a physician cannot predict which patients are going to get a CRP reduction on the basis of LDL-cholesterol reduction. They have to measure both LDL-cholesterol and hsCRP, and I would argue that the new data strongly suggest that we need to measure and manage CRP in the same way that we currently measure and manage LDL-cholesterol, if we are going to achieve the greatest benefits for our patients. That is really the bottom line of the PROVE IT-TIMI 22 CRP analyses; it was more important for the patient to achieve the dual goals of an LDL-cholesterol < 70 mg/dL and a CRP < 2 mg/L than it was which particular drug they were actually taking.

Some patients who were taking the so-called moderate therapy did, in fact, get their cholesterol to below < 70 mg/dL and their CRP below < 2 mg/dL, and those patients are doing very well and there is no need for them to titrate or change drugs. There were other patients who, despite getting very intensive therapy, did not get their LDL-cholesterol or their CRP down. So just being on one therapy or the other did not fully predict which group a patient would be in. We have to measure both LDL-cholesterol and CRP to find out, just like we currently do for other things in medicine.

**Medscape: So these patients should be monitored over time for both LDL and CRP?**

**Dr. Ridker:** That appears to be the case. Up until now, I have said that I believe that CRP is a very effective tool in primary prevention. Remember, half of all heart attacks and half of all strokes occur among individuals with normal cholesterol levels, and about 20% of heart attacks occur in people who do not have any major risk factors whatsoever. So we must move beyond the traditional ways of thinking in order to better detect and manage cardiovascular disease. Until the PROVE IT-TIMI 22 and REVERSAL results appeared, I could only recommend that in primary prevention, trying to find high-risk people, CRP is a very valuable tool and should probably be widely used, as was recommended by the AHA and the CDC.

With the new data, however, I would now argue that we also need to measure CRP along with LDL-cholesterol in secondary prevention, if we are going to do a better job managing our patients. If we have a simple and inexpensive blood test that can tell us how to get the right dose of the right drug to the right patient, I think that we should use it. That is exactly what is going on here for hsCRP. If we only rely on LDL-cholesterol, we cannot select the right statin dose and the right statin drug. We need to rely on both the LDL-cholesterol and the CRP to determine how to treat our patients.

**Medscape: What did the REVERSAL data add to our knowledge about CRP for secondary prevention?**

**Dr. Ridker:** REVERSAL was very important because with the surrogate end point of atherothrombotic progression, measured by intravascular ultrasound, almost identical findings were obtained over an 18-month period. Nissen and colleagues<sup>[15]</sup> previously concluded from the main REVERSAL results that if you lowered LDL-cholesterol more aggressively, you could slow down the progression of coronary atherosclerosis in patients with coronary heart disease, a very important clinical observation. However, when the REVERSAL investigators measured CRP levels, what they observed was essentially identical to what we found in PROVE IT-TIMI 22, ie, the patients who had the most progression over the 18 months of observation were those who failed to get both the LDL-cholesterol and the CRP down. Those who only got the LDL-cholesterol down had some slowing of the progression; those who only got the CRP down actually got regression; and those who got both the cholesterol and the CRP down got the greatest regression. So that was entirely parallel to our findings about event rates in PROVE IT-TIMI 22, that the lowest rates occurred among those who reduced the levels of both LDL-cholesterol and CRP.

The other important point is that the patients in REVERSAL had stable disease. So the investigators were able to measure the change in CRP from beginning to end, and they also observed, as we did, that there is almost no relationship between the change in CRP and the change in LDL-cholesterol. Once again, therefore, the conclusion that must be drawn is that if you want your patient to get the greatest benefit from these drugs, that is, actual regression and the lowest event rates, it is not enough to lower their LDL-cholesterol; they need to lower their CRP as well.

So these 2 observations together produce a very powerful shift in the entire paradigm, which is simply that from a clinician's point of view: In order to optimize the benefit for the patient, it is no longer enough to lower the LDL-cholesterol; we need to measure and monitor the CRP and treat that the same way we treat cholesterol.

**Medscape: Is there any information about which statin and which dose best achieve the LDL-cholesterol and CRP reduction simultaneously?**

**Dr. Ridker:** This is somewhat complicated. My personal view is the crucial issue of achieving the goals of a low LDL-cholesterol and a low CRP, and that this is more important than which statin the patient is actually on. However, it is also clear that more intensive statin regimens are more likely to get patients into the low-LDL-cholesterol plus low-CRP category, so it makes sense to consider more potent agents up front. That being said, according to our data from PROVE IT-TIMI 22, less than half the patients who got the most intensive statin therapy actually achieved low LDL-cholesterol and low CRP. So you cannot be content simply by putting people on 1 dose of statin. It is really achieving these goals that is the most important issue.

There is another message here that is crucial. If a patient appears to need their CRP lowered, even if their LDL-cholesterol is already reduced, the best ways to do so is by diet, exercise, and smoking cessation. So the message to our high-risk secondary-prevention patients is: Just because your physician has done everything possible in terms of medications, you are not off the hook. You still need to go to the gym, lose the weight, and must stop smoking, because these are very powerful ways to reduce CRP levels and more importantly to reduce vascular risk.

**Medscape: What other major clinical trials are expected to provide more information on lowering CRP as primary**

**or secondary prevention?**

**Dr. Ridker:** The biggest ongoing clinical trial of CRP is the Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER).<sup>[16]</sup> Worldwide JUPITER will recruit a total of 15,000 individuals with no prior heart disease. These subjects do not qualify for statin therapy because their LDL-cholesterol is low, < 130 mg/dL; they are at high risk because their CRP is elevated. They are being randomly assigned to treatment with rosuvastatin or placebo. The trial is asking what I think is the crucial clinical question right now: Should we be giving statin therapy to people who do not have high cholesterol but do have a high CRP?

**Medscape:** They would seem to be a healthy population already.

**Dr. Ridker:** No, they can have other risk factors, although not diabetes. The entry criteria are simply LDL < 130 mg/dL and a CRP above 2 mg/L. They could be on antihypertensive therapy, and many will probably be on aspirin, but they are not taking lipid-lowering drugs because their LDL-cholesterol is low.

**Medscape:** How long is JUPITER likely to run?

**Dr. Ridker:** We are still in the enrollment phase with about 3000 participants already in the trial. We probably have 3 or 4 years to go as JUPITER is an end-point-driven trial.

**Medscape:** Are there any other drugs that would lower CRP as well as statins?

**Dr. Ridker:** There are many drugs that lower CRP levels, but that is not the crucial question. The question is whether there is evidence that these agents lower cardiac risk for our patients. So the CRP reduction becomes a very interesting way of evaluating new drugs, but ultimately for our patients the question is: Does the new drug lower the risk of having an event? That is why these new trials have to get done.

**Medscape:** You are also chairman of a clinical trial of CRP lowering in hypertension, the Valsartan-Managing Blood Pressure Aggressively and Evaluating Reductions in hsCRP (Val-MARC) trial.

**Dr. Ridker:** Val-MARC is a study investigating whether blood pressure reduction with an angiotensin receptor blocker (ARB), valsartan, also lowers CRP levels. It is very similar to the study that we did years ago when we demonstrated for the first time that statins lowered CRP levels.<sup>[13]</sup> So it is not an end-point trial. If it is positive and shows that an ARB can lower CRP levels, then there will be a rationale for setting up another study to determine whether lowering CRP in the setting of hypertension lowers event rates.

**Medscape:** How long will Val-MARC run?

**Dr. Ridker:** We will probably close it up by the end of the year.

**Medscape:** Are there any other trials that are measuring CRP that you are interested in?

**Dr. Ridker:** At this point in time, almost all major clinical trials dealing with atherosclerosis, metabolic syndrome, and diabetes are going to be measuring CRP.

**Medscape:** CRP has been proposed as a factor for metabolic syndrome. The various definitions worldwide do not include it at present, but a new definition is expected to be announced this year. What do you think about this?

**Dr. Ridker:** I think that CRP should be part of the definition of metabolic syndrome, because it solves the puzzle of trying to measure hypofibrinolysis and measure inflammation. Because CRP tracks with insulin resistance, it provides a very simple and elegant way of picking up the part of the metabolic syndrome definition that we are currently missing. I think that this is an easy decision.

**Medscape:** How does CRP track with insulin resistance?

**Dr. Ridker:** As insulin resistance rises, so do CRP levels. Insulin resistance is not part of the US definition of metabolic syndrome because we do not have a simple way of measuring it. CRP provides a nice correlation to insulin resistance, but is very simple to measure. We and others have consistently shown that hsCRP levels > 3 mg/L greatly increase the

risk of developing both diabetes and coronary disease, even among those already defined by ATP-III as having "metabolic syndrome."

**Medscape: Many studies previously showed that different statins can significantly lower CRP, so how does a physician know which statin and dose to start such a patient on?**

**Dr. Ridker:** I think that you need to measure and manage the CRP in an analogous manner to how we currently measure and manage LDL-cholesterol. Both of these are going to be important in the future.

**Medscape: How should a physician treat a patient whose CRP has not been successfully lowered with the first statin dose?**

**Dr. Ridker:** If the LDL-cholesterol is reduced and the CRP is not reduced, we may need to change the dose or switch the drug. That is what the new data say. Personally, I would increase the dose first, and if that did not work, I would switch to a more aggressive statin. We know that the more aggressive the statin, the greater the LDL-cholesterol reduction and the greater the CRP reduction.

**Medscape: Would rosuvastatin be such an aggressive statin?**

**Dr. Ridker:** We elected to use rosuvastatin in our JUPITER trial, as it is a very potent agent both for LDL and CRP reduction.

**Medscape: CRP levels are known to be raised in the presence of infections, rheumatoid arthritis, etc, and people talk about its being nonspecific. Could this lead to confusion about the meaning of raised CRP levels?**

**Dr. Ridker:** CRP levels are highly specific as predictors of future heart attack, stroke, and cardiovascular death. They do not predict the onset of other inflammatory diseases. It is true that patients with rheumatoid arthritis are more likely to have somewhat higher CRP levels, but these patients are also at higher risk for heart disease. Many people raise this issue of "nonspecificity," but I do not think that they have actually considered that the very patients who have higher levels of CRP are also the patients who have a higher risk of heart disease. So there is nothing nonspecific about CRP as a predictor of risk from a clinical perspective.

**Medscape: What do you say to doctors who argue that there are already too many numbers that they already have to measure and CRP is just another one?**

**Dr. Ridker:** I would say that there are too many heart attacks and premature deaths from cardiovascular disease, and that better efforts to prevent these events are far more important than physicians having to learn one more number.

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