

## Interview with Dr. Paul Ridker, the Lead Investigator of the Jupiter Study

Host: Welcome to the first podcast from *Clinical Chemistry*. This is Bob Barrett. The February issue of the journal highlights some of the latest research from several groups regarding C-reactive protein. My guest is one of the authors in this month's issue, Dr. Paul Ridker, the lead investigator of the landmark study, Jupiter. He is the Eugene Braunwald Professor of Medicine at Harvard Medical School and the Director of the Center for Cardiovascular Disease Prevention at the Brigham and Women's Hospital in Boston.

Dr. Ridker, can you tell our listeners what the Jupiter trial was all about? Why even consider doing a study of statin therapy for patients with low levels of cholesterol, but high levels of high-sensitivity C-reactive protein?

Dr. Paul Ridker: We've known for 40 years that almost half of all heart attacks and strokes occur among individuals who actually have average, if not low levels of cholesterol. That doesn't mean cholesterol's not important; it's terribly important. But we've got to move beyond simply screening for cholesterol to understand what high risk is. We've also found that inflammation, the process by which our bodies fight off infection and heal itself, is a major determinant of vascular risk. And so the concept of the Jupiter trial was, let's identify patients who are at risk of heart attack and stroke not because they have high cholesterol, but because they have a high level of a new blood marker for high sensitivity C-reactive protein, or hsCRP. And let's see if statin therapy can lower vascular event rates in this group, which is very relevant because we'd shown many years ago that statins lower C-reactive protein levels in addition to lowering cholesterol.

Host: You had done a pilot for this trial where you evaluated high-sensitivity CRP and cholesterol previously in the Air Force and Texas CAP trial. Is that why you didn't study in Jupiter those with low cholesterol and low CRP?

Dr. Paul Ridker: That's very important. In the AF CAP's/TEX CAP's trial, which we published back in 2001, we showed that if you had low cholesterol and low hsCRP, yes, you got an LDL reduction with statin therapy; but actually, there was no clinical benefit for the patients at all in terms of preventing heart attack and stroke. But in contrast, when the LDL cholesterol were low but the CRP level was high, that group got a very large risk

reduction: fewer heart attacks, fewer strokes, fewer cardiovascular deaths. But that was a post-hoc analysis, and so we knew we had to design a major prospective clinical trial to directly test would statin therapy lower risk in people who normally would not get statin drugs because their LDL is low but their CRP is high. But you're correct, that's exactly why we did not study low cholesterol/low CRP patients. That would be a 50- or 60,000 patient clinical trial, which would be unlikely to show any benefit based on prior science.

Host: Okay. So what did the Jupiter trial find?

Dr. Paul Ridker: Well, Jupiter was quite extraordinary. I had the honor of being the principal investigator of this study, which really organized worldwide; in 26 countries, we had over 1,000 physician participants and nearly 18,000 patients. This trial, though, was stopped nearly 2½ years early by its State of Safety Monitoring Board because of an overwhelming benefit for patients. From the primary trial end point, which was first ever event of heart attack, stroke, revascularization or cardiovascular death, there was a 44% reduction, which is almost twice the magnitude we anticipate when we give these drugs to patients with high cholesterol. For heart attack, it was a 55% reduction, and for stroke a 50% reduction. For bypass surgery, it was cut almost in half. And perhaps the most remarkable finding was that all-cause mortality/total death was down by 20%. These are really unprecedented findings. Normally when we give a statin to patients with high cholesterol, we expect 20-25% benefits. In this trial, we're seeing rates nearly double that. And I think what that tells us is that biologically we have really hit the sweet spot here. By targeting inflammation, we've shown that you can do a remarkable job lowering vascular risk.

It's also important to recognize that the Jupiter investigators enrolled almost 7,000 women and almost 5,000 minority patients. These are groups who really have been understudied in previous trials, and they got very large reductions. In fact, every single subgroup in the trial had a statistically significant benefit, including the individuals who had an elevated hsCRP and no other risk factor at all. So these are people with no hypertension, no diabetes, they don't smoke, LDL is low, HDL is good. Their only risk is an elevated CRP, and event rates are cut almost in half. So all new guidelines are gonna have to very seriously consider, does this mean we should be treating and targeting inflammation as much as hyperlipidemia?

Host: Very impressive study, very impressive. What are the public-health implications?

Dr. Paul Ridker: Well, at a public-health level we have to rethink the guidelines for detecting heart-attack risk and how we go about treating that risk. Right now there are individuals at the NIH whose job is to sit down and think through these data, but there are some straightforward issues at hand. A guy named Robert Glenn, who is the Study Statistician for Jupiter, has estimated that if you took the strategy of screening and treatment that we tested here, you would prevent more than a quarter of a million heart attacks, strokes, bypass procedures, angioplasties and cardiovascular deaths in the United States alone over a five-year period, and that's very conservative because it's not even dealing with patients who have intermediate levels of LDL and a high hsCRP. That's strictly a calculation of people who have low LDL. You have to remember, these people started with a cholesterol level that was -- the LDL was only 108. It dropped down to an LDL of 55, 25% of this trial has an LDL below 40, and these are levels that previously were considered worrisome; but the fact is that we're not seeing any cancer risk, we're just seeing very large benefits.

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So I think we have to recognize two things: first, inflammation on its own is indeed a major determinant of vascular risk, and we now have a class of drugs that can safely lower that risk; and then in general, we have to rethink the whole concept of what is a low LDL cholesterol. We would probably argue physiologic levels of LDL are probably 45, 55; that's what we achieved in this trial. And so these people who had no indication for a statin because their cholesterol was actually considered near optimal, well, we now know those are not near-optimal levels and levels have to come down a great deal more.

Host: Hmm. Many physicians remain confused about high-sensitivity C-reactive protein and regular CRP. What can you tell us about stability of CRP levels over time and why the high-sensitivity CRP test is needed?

Dr. Paul Ridker: Both are important questions. The hsCRP test is crucial for all cardiovascular risk prediction. This has been the test used now for more than a decade in the research community and allows us to measure the CRP levels with great fidelity in the low range that's necessary for this process. Perhaps equally

important is the confusion about the units these are reported in. The so-called regular CRP test is traditionally reported out in milligrams per deciliter (mg/dL); the hsCRP test which is needed for this purpose is reported out in milligrams per liter (m/L). That's a tenfold difference. So a lot of physician and patient confusion is simply on the basis of ordering the wrong test. This is something that the Clinical Chemistry community can help us to sort out. We really don't have to have this confusion, and from the primary-care physician's perspective and I suppose the patient's perspective, this is just unfortunate confusion.

Host: So what's the bottom line here? Should all patients have a high-sensitivity CRP evaluated at the same time they get cholesterol checked and, if so, what age should they start?

Dr. Paul Ridker: Well, we have to wait for the guidelines to come out and they likely will change at some point in the next six to eight months. I think the research clearly tells us that knowledge of your hsCRP, along with knowledge of your total and HDL cholesterol, helps to better predict vascular risk. We publish something called the Reynolds Risk Scores, which are available free on the internet that really encompass this idea by including a marker of inflammation -- that's the hsCRP -- and a marker for genetics, a yes/no question of family history, and it greatly changes who is at high risk and who is at low risk and that tells us we can do a better job.

The question then is when do you do this. I think that the standard is probably to start around age 40 or age 45, the same time we would consider therapy for those individuals who are at elevated risk. The real issue, of course, is if your CRP is elevated, just as if your cholesterol is elevated, the first step is not a statin; the first step is diet, exercise, smoking cessation and getting into a good preventive program. What Jupiter does say, however, is that beyond lifestyle efforts, it's now very clear that a pharmacologic approach can result in major benefits.

Host: Would family history change the age you'd start having these tests?

Dr. Paul Ridker: Yes, it does. If your family history of heart disease is strong, and what I mean by that is a brother or a father who's had a heart attack before age 55, a mother or a sister with a heart attack or stroke before age 60, that's what we consider

premature heart disease. Then I think we would screen actually in your 20s.

Host: Okay. Well, last, give us a glimpse of where your research in this field is going. Is there anything beyond statin therapy that we should know about?

Dr. Paul Ridker: Well, the statins are really quite extraordinary because they're twofers: they both lower cholesterol and lower inflammation, and the benefit of these drugs has been proven again and again. So that's a very straightforward issue.

The Jupiter trial will probably have impact in terms of the numbers of individuals who go on statin therapy, and again that's the public-health balance from the cost of this approach and the benefit we have for preventing disease. But the future of this field is asking questions about if inflammation, which is what the hsCRP test detects, is so crucial to vascular biology, can we actually target inflammation itself as the next wave of cardiovascular prevention studies. So our group and many others are now putting together clinical trials that will use targeted anti-inflammatory drugs and see whether or not these agents can lower vascular risk; but these are drugs that, unlike statins, do not also have a beneficial effect on cholesterol or, unlike aspirin, do not have a beneficial effect on platelet function and therefore will allow us to directly test this atherosclerosis hypothesis. That's crucial. One of the important issues in this field is to recognize that the hsCRP test is very useful clinically; but we don't yet know if CRP itself is causal -- that's a very controversial arena -- and we don't yet know what component of inflammation we need to target to lower vascular risk. It could be the cytokines' driving this process, it could be the underlying biochemistry here. That's what the future is all about: how do we target inflammation itself as a way of lowering cardiovascular risk.

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Host: So we've come a long way, but there's still a long way to go.

Dr. Paul Ridker: We've come a long way; but it's remarkable, because the number of cardiovascular deaths, heart attacks and strokes we can now prevent is very, very large. The whole understanding, a real paradigm shift has occurred here that tells us, yes, cholesterol is important; but this inflammatory process is equally important, and when you have both the risk is very high. We now teach the Harvard Medical School students right at the beginning, atherosclerosis, yes, is a disease of lipid

accumulation; but it's a disease of inflammation fundamentally, the same way we teach the students rheumatoid arthritis is a disease of inflammation. That shift in our thinking is what this is really all about, and I think that shift is what will drive the research for the future.

Host: Doctor, thanks so much; this has been great.

Dr. Paul Ridker: It's a pleasure.

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