- My name is Paul Ridker. I have the honour of serving as the Eugene Braunwald Professor of Medicine at the Harvard Medical School, and I direct the Centre for Cardiovascular Disease Prevention at the Brigham and Women's Hospital in Boston, which is where I am today.

Outcomes of the CANTOS Study, and the Importance of this Substudy

So the sub-study that we're talking about today has to do with a concept of residual inflammatory risk and residual cholesterol risk among atherosclerosis patients with and without chronic kidney disease, and this is a sub-study of the CANTOS Trial. Now CANTOS, you'll recall, was a major multinational clinical trial that showed that interleukin-1 beta inhibition with a drug called canakinumab significantly lowered cardiovascular events. And that trial is the proof of principle that lowering inflammation lowers cardiovascular event rates, and has been very important for our understanding of the role of inflammation in atherosclerotic disease. One of the things that came out of Cantos, of course, was this notion of well, how important is what we call residual inflammatory risk as compared to residual cholesterol risk? So in the current presentation for the ACC, we're looking at these two concepts, asking the question are there certain populations of patients who have different impacts of lipids on the one on hand, and inflammation on the other? So broadly, what we did is we measured two inflammatory biomarkers, high sensitivity CRP and interleukin-6, and we also addressed two lipid markers, LDL cholesterol and non-HDL cholesterol, and we asked a very simple question, how well do these predict risk of future atherosclerotic events, MACE, MACE Plus, et cetera, stratified by underlying level of EGFR, so those with preserved renal function and those with diminished renal function? And the reason we did that is because there's great interest right now, which I'll come back to, in trying to assess inflammation in the setting of kidney disease, where, of course, patients are at very high atherosclerotic risk. So the methods here are really quite simple. These four biomarkers were measured at the beginning of the cohort. And remember, we're talking here over 10,000 patients with about three years of follow-up on average. Now, to summarise the bottom line, the, as you would anticipate, among people with preserved kidney function, both CRP and LDL cholesterol were strong predictors of recurrent cardiovascular events. That's, of course, consistent with data that's already out there from many cohorts, and a lot of people measure lipids and measure CRP to predict recurrent events, and that makes total sense. In the sensitivity analysis IL-6 and non-HDL worked equally well, so far, so good. What was interesting to us, however, is that in this large population of aggressively statin-treated patients whose LDL cholesterols are already reduced, among people with low kidney function, GFR between 30 and 60, IL-6 and CRP remained very powerful predictors of future cardiovascular risk, but interestingly, LDL and HGL really did not. So the implication of that is that there's something unique about these kidney disease patients, and this apparent differential effect of inflammation predicting risk in CKD as compared to lipids was particularly potent for cardiovascular mortality, and for all-cause mortality such that, in fact, those with elevated CRP or IL-6 really had greatly increased rates of all-cause mortality in the setting of chronic kidney disease. So I think one of the fundamental questions then is well, what's this mean? And from our perspective, the finding is relatively straightforward. We want to lower lipids aggressively in all of our patients, both those with and without CKD. And remember, in CANTOS, everybody pretty much is getting a high-intensity statin. Well, the question becomes, after that statin what's the next step? And our data are suggesting that in the setting of CKD, residual inflammatory risk, in other words, the CRP and the IL-6 have not been addressed, may be a very important target for future therapy. And I think, as many people are aware, we've just launched a multinational clinical trial called ZEUS, the ziltivekimab cardiovascular outcome study using a novel interleukin-6 ligand inhibitor, that's one, so that's one step downstream from IL-1. And that clinical trial is specifically being done among patients with chronic kidney disease, and atherosclerosis, and residual inflammatory risk, defined as a CRP greater than two milligrammes per litre, despite aggressive statin therapy. So the bottom line here is that we think these data are very useful for understanding why this new trial needs to be done, and I think very useful for the clinical community, reminding us, yet again, that in certain settings, particularly chronic kidney disease, we really need to understand the patient's inflammatory response if we're going to do the best for them from a clinical perspective.

Study Design

Well, again, CANTOS was a randomised double-blind placebo controlled trial of three different doses of canakinumab as compared to placebo. And again, the fundamental finding there was that canakinumab at the 150 and 300 milligramme dose reduced major cardiovascular event rates. This particular sub-study is looking at the entire cohort of roughly 10,000 patients, all with atherosclerosis and elevated CRP, and asking the question, how well did the baseline levels of CRP and IL-6 on the one hand, and LDL and HDL on the other hand predict future events in the course of the trial? That's really the structure of the study.

Key Findings

The key findings, as I said, were that the levels of LDL and HDL, non-HDL, as well as IL-6 and CRP all predicted residual risk if the patients had normal renal function, and that's consistent with prior work. What was interesting, and I think important from a biologic perspective was that those individuals who had reduced renal function, GFR between 30 and 60, in that setting, the CRP and the IL-6 were strong predictors of residual risk, but in interestingly, the LDL the non-HDL were not, understanding, of course, that everybody's already on a high-intensity statin. This differential effect, or this potential differential effect was most prominent for people with, for the endpoint of cardiovascular mortality, and all-cause mortality, where in the setting of chronic kidney disease, the CRP and the IL-6 were very powerful predictors of this residual risk after being treated with statins. Well, I think these findings have both scientific and clinical implications.

Influence on Scientific Research

On the scientific side, they really are telling us that patients with chronic kidney disease and atherosclerosis have substantial residual risk based, at in part, on this inflammatory process, and thus, if I'm going to pick a second drug, having given them a high-intensity statin, I may be more concerned about inflammation than I am about lipids, necessarily. And this is very strong support for a new clinical trial that has just been launched called ZEUS. That's the ziltivekimab cardiovascular outcome study where we are trying to find out whether a novel interleukin-6 inhibitor, one step downstream from the interleukin-1 inhibitor that we used in CANTOS could deliver cardiovascular event reduction in patients with chronic kidney disease, atherosclerosis, and elevated CRP. And clinically, I think the findings here are quite important to remind us that when we're looking at our patients who had prior atherosclerotic events already treated with a statin, to make sure we think about measuring CRP, residual inflammatory risk, because if they have CKD, that seems to be a very important issue, and a very important target for therapy and interventions. Well, the CANTOS trial broadly has already changed the practice of medicine in a very dramatic way.

Interpreting the Results from a Clinical Perspective

I think that, you know, we learned from the original presentations of the main trial to really understand now that clinicians need to address the concepts of CRP, the concepts of an inflammation in atherosclerosis, and if we don't do that, we're never going to advance the field for our patients. So we're already, that's already been implemented in guidelines worldwide that we should be thinking about inflammation inhibition. Now, what's interesting, particularly in the European guidelines, is that they've endorsed the use of colchicine because of the LoDoCo two and COLCOT trials showing that this is an inexpensive anti-inflammatory drug that largely was able to replicate what CANTOS had shown with an expensive monoclonal antibody, so that's great we have an inexpensive therapy for inflammation inhibition, but colchicine is a complicated drug to give to patients with kidney disease, because it's renally excreted, and you, and as the GFR continues to go down over time, you probably don't want your patients on colchicine. So again, these data's saying inflammation's particularly important in that subgroup means we need to look for alternative therapies, and that's one of the reasons we're doing the ziltivekimab study. Now, all that being said, I would argue that we should be thinking about diet, exercise, smoking cessation. These are all methods that we know lower cardiovascular event rates in all of our patients. They're extremely important in patients with chronic kidney disease, and they all happen to lower inflammatory biomarkers. So I think that at a general internist level, general cardiology level, these data also reinforce really good primary care general interventions that all of our patients truly need.

Take-Home Messages

I think the take-home messages of these new data are to remember that patients with chronic kidney disease and atherosclerosis have very high unmet clinical need. Their risk is driven at least as much by inflammation as it is by hyperlipidemia. All these patients already receive statin therapies. That's good, but the question becomes how do we address that residual risk? And these data strongly support the idea that targeting inflammation may be a very important part of that process.