Markers of Plaque Instability in the Early Diagnosis and Risk Stratification of Acute Myocardial Infarction

Bob Barrett: This is the podcast from '*Clinical Chemistry*', I am Bob Barrett. Patient history, electrocardiography and cardiac troponin T form the diagnostic and prognostic cornerstones of the clinical assessment of chest pain patients, but these are not the definitive signs of a heart attack. Plaque erosion and plaque rupture occur early in the pathophysiology of Acute Myocardial Infarction.

Could the markers of plaque instability be useful in the early diagnosis and risk stratification of acute myocardial infarction? In the January 2012 issue of Clinical Chemistry, Dr. Christian Mueller, an Associate Professor and Head of the Outcomes Research and Processes at the University Hospital Basel, in Basel, Switzerland, examined data gathered from 2006 to 2008 in order to find out if the biomarkers of plaque instability help in the early diagnosis of acute myocardial infarction. Dr. Mueller is our guest in this podcast.

Doctor, what is the unmet clinical need that your study tries to address?

Christian Mueller: So our study targets the early diagnosis of acute myocardial infarction. So as you know, acute myocardial infarction is a major cause of deaths and disability worldwide, and also we have excellent clinical tools for its diagnosis including patient history, the 12-lead ECG, and cardiac troponin testing. In many patients, there's still diagnostic uncertainty within the first hours and if for a delay both in rule in and rule out.

Bob Barrett: What's the rationale to evaluate markers of plaque instability in this setting?

Christian Mueller: Perhaps one of the most exciting developments in both, I think, basic research as well as the clinical research is studies that highlight strong association between inflammation and atherosclerosis in general and acute myocardial infarction in particular.

And therefore, we hypothesize that if you could use markers that are associated with the plaque rupture, so the event that really is first in causing acute myocardial infarction, we might be able to quantify a signal that is very early on in the disease process and that might be helpful in the early diagnosis of acute myocardial infarction.

Bob Barrett: Which markers were tested?

Christian Mueller: So in our marker center study we had the opportunity to examine four markers of plaque instability including myeloperoxidase, myeloid-related protein 8/14, pregnancy-associated plasma protein-A, and C-reactive protein. So

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altogether, four markers that had been shown in prior studies to be associated both with plaque progression, plaque destabilization as well as plaque rupture.

Bob Barrett: And are these experimental markers or are they commercially available?

Christian Mueller: In fact, it's a mixture, so some of them are clinically available and more or less worldwide like C-reactive protein, others have been developed to be run on the large platforms like MPO and pregnancy-associated plasma protein-A, and the other marker MRP 8/14, the cardiac state is still an experimental marker.

Bob Barrett: Now doctor, what are your findings regarding diagnostic and prognostic utility?

Christian Mueller: Please let me start with diagnostic utility. So as assessed by the area under the ROC curve, as I think the best accepted test to quantify diagnostic accuracy, all four markers showed only low-to-moderate diagnostic accuracy with an area under the curve in the 60, so around 0.65, so clearly inferior to both conventional cardiac troponin and even more so to a high sensitive cardiac troponin assay.

Regarding a prognostic utility, the markers of plaque instability were associated with the development of tests during follow up, however, again the association was not very strong, and overall there was only moderate prognostic value associated with these markers. But still at least some of them seem to provide incremental value in addition to the clinical information available in these EV patients.

Bob Barrett: Now, are these findings supported by other recent studies?

Christian Mueller: I think yes, they are. So also initial studies particularly for MPO have been quite enthusiastic, more recent research by other group really showed very consistent findings. So consistent findings that the diagnostic utility at least of the currently available markers of plaque instability is low, so there doesn't seem to be a clinical role for them.

And also I think that the second main message regarding more or less moderate prognostic power, also this has been confirmed in at least two or three other large data sets.

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Bob Barrett: Why do you think these markers of plaque instability fail?

Christian Mueller: Good question! So of course I can only hypothesize what were the reasons for the failure. But apparently, the other diagnoses that are in the differential diagnosis of acute

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myocardial infarction, so other causes of chest pain. So many of these are also associated with inflammation and therefore associated with increases in inflammatory markers, and apparently also, the four markers that we had the chance to test are associated with plaque rupture and all the coronary disease process. They also seem to be associated with many other inflammation processes in the body and thereby are in no way specific to what happens in the coronary.

So we have a signal that apparently is not too strong in its amount and it's not really specific in a setting of patients with acute chest pain in the emergency department, and so I assume that these might be the key factors for the overall quite disappointing performance of the markers in our study.

Bob Barrett: Well finally doctor, what do your findings mean to the inflammatory hypotheses of atherosclerosis?

Christian Mueller: I am not sure. I think it's still so strong evidence that inflammation has a role, it may still be a therapeutic target. So what we aim to investigate is kind of whether these markers have a role as diagnostic tools. But the other ongoing studies like a large ongoing secondary prevention study, intervention study will evaluate whether active treatment, for example, with Interleukin-1 beta inhibition as compared to placebo can reduce the rates of recurrent myocardial infarction, stroke, and cardiovascular death among 17,000 stable patients with coronary artery disease.

So I think the ultimate proof whether inflammation itself offers specific targets in the treatment of patients with atherosclerosis will be available in a couple of years when we have the data from this large phase 3 studies investigating specific anti-inflammatory interventions.

Bob Barrett: Dr. Christian Mueller is an Associate Professor and Head of the Outcomes Research and Processes at the University Hospital Basel, in Basel, Switzerland. He has been our guest in this podcast from '*Clinical Chemistry*'.

I am Bob Barrett. Thanks for listening!

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