Bob Barrett: This is the podcast from *'Clinical Chemistry'*. I am Bob Barrett. Cardiac troponin is a cardio specific protein that is detectable in the blood of patients with myocardial injury with sensitive and specific assays.

Cardiac troponin is recommended as the preferred biomarker for the diagnosis of myocardial infarction for risk stratification and for therapeutic guidance regarding anticoagulation therapy and invasive management. But is it the most important biomarker to consider when screening for myocardial infarction?

In the January 2012, issue of *Clinical Chemistry*, Dr. Evangelos Giannitsis and Dr. Hugo Katus from the University of Heidelberg joined with Dr. Christian Mueller, an Associate Professor and Head of the Outcomes Research and Processes at the University Hospital Basel, in Basel, Switzerland in a point-counterpoint feature on the importance of screening for cardiac troponin.

Doctors Katus and Mueller have joined us in this podcast to further discuss their respective positions. First, Dr. Katus, do you think this is an issue that can be resolved?

Dr. Hugo Katus: Yep! That said, it is a very important point of the troponin story. So always when troponin is elevated, it indicates myocardial injury, and so it is really challenging for the clinician to really be certain that this injury is clinic or has any other causes.

So what needs to be done is that as we have done it also in past is that we need to do additional testing to understand the cause of troponin elevations, and that is what we have done in clinical practice anyway.

So you do need additional testing to account for the many possibilities of troponin elevation such as heart failure or toxic injury or inflammation and so forth. So it's clinical work. It needs to be done with the patient, but that's not a problem for a good physician I believe.

Bob Barrett: Well, what would your recommendations be for clinicians? Do you have a strategy for interpretation of these results?

Dr. Hugo Katus: Yes. So when you see a patient who has an elevated troponin and you do not see any evidence on the ECG for myocardial infarction, and he has no typical

 

chest pain indicative of myocardial ischemia, you need to do additional testings.

That includes: you need to test, in your blood analysis, also for inflammatory disorders. You need to take a careful history if a patient has had any chemotherapy. You need to do cardiac ultrasounds to understand his myocardial function, and if he has shortness of breath, you need to do a CT scan to exclude pulmonary embolism.

So a patient has to undergo a very sophisticated and careful workup since we know that an elevated troponin in those who do not rule myocardial infarction still have a high risk and need to be identified properly.

Bob Barrett: More sensitive troponin identify acute and chronic cardiovascular disease, including ACS and non-ACS conditions earlier and at earlier stages of disease, how far can management of high sensitivity cardiac troponin improve management of patients?

Dr. Hugo Katus: Very markedly. So if you have a patient who comes with a chest pain with minimally elevated troponin and he has chest pain, so then you are certain that if he shows an increase of troponin that he has on-going ischemia. So this patient is already identified as a high-risk subset of patient, and needs to go to coronary care unit, and needs to be investigated and basically not at the same point in time, but within 24 hours.

And vice versa, if you do have a patient coming with chest pain, who remains negative for a high-sensitive troponin. On admission and a three hours follow up, then you really know this patient has a low risk and he has no on-going ischemia, and you can really send this patient home without any major concern. So you still have to do your clinical examination, that's all that's needed, but he is definitely a low-risk patient.

Bob Barrett: Are there differences between more sensitive cardiac troponin assays regarding diagnostic or prognostic performance?

Dr. Hugo Katus: Yes there are. There are so many different troponin assays available and many claim to be high-sensitive assays, not so many are really and even if you compare to high-sensitive troponin assays as we need for example the troponin T and the troponin I assay.

We did observe, rather comparable numbers of elevated or patients with elevated markers, but the prognostic information was different between this high-sensitive troponin T and this specific troponin I assay.

(00:05:12)

So it was we observed that the prognostic information was much more robust as the troponin T high-sensitive assay as compared to say troponin I assay which was measured by us as comparative.

So I believe it's very important that as a physician who uses the high sensitive assay must know clinical data associated with this assay since there is much of a difference in diagnostic performance and also in the quality of risk certification.

Bob Barrett: Well, do you support measuring troponin routinely in settings other than ACS, for example in heart failure or stable coronary artery disease or even the general population?

Dr. Hugo Katus: Yes, that's an interesting point. I believe in heart failure, it should be done. In the meantime so much evidence from so many clinical trials said if you do have a heart failure, patient who has an elevated troponin, he has a higher risk which is very similar to atrial natriuretic peptides or even this more prognostic information.

So yes, you need to do it for risk certification and to better understand that this patient really has a decompensated heart failure.

Now interestingly is that the second question, or interesting second question, that means, do we need to test now our patients, which we see with a presumably stable coronary artery disease, those patients who have only chest pain on exercise and who are seen in our outpatient departments?

So I believe again based on the data we have that we will find in these patients or presumably stable patients, some 20% with elevated troponin levels and again these high-sensitive troponin results indicate high risk subset.

And we believe that these 20% of patients who are troponin-positive and are classified as stable coronary artery disease in fact are not stable coronary artery disease, but need to be re-classified

as unstable coronary artery disease and the outcome of these patients indeed is very similar as we know from patients with unstable angina.

So we are now about to set up routine testing of high-sensitive troponin T in our outpatients department that we see our stable patients with coronary artery disease since we really believe that we need to reclassify these patients more precisely.

The last point was what is role of such high troponin markers in general populations? And again, you have so much clinical evidence and epidemiological evidence by now, so the data are consistent.

If you do have a measure of the troponin and these increasing troponin concentrations within normal, presumably half the populations and those who have a measurable troponin have a higher risk as those who do not have an elevated troponin.

So again, even in presumably half the populations, we find these subjects with elevated troponin and now you may speculate why you said so that we have in presumably half the people elevated troponins and so I believe it's those patients with subtle coronary artery disease or those who have myocarditis or some that have heart failure and release of troponin or other forms of heart damage, so you do identify this troponin even if the half the population shows at high cardiac risk.

I do believe, however, that this is only at present for scientific purposes. It's very interesting data, but, I don't believe that you should go out and now test populations for high-sensitive troponin, but it's different for those with cardiac diseases. So I believe it needs to be done even in those who seem to be with stable coronary artery disease.

Bob Barrett: Well finally doctor, what are the fields that still need to be improved?

Dr. Hugo Katus: There is always room for improvement. There is room to improve analytical issues, so this still can become even more sensitive with the assays. This will improve analytical precision of the test, so there is room to be improved. From a patient perspective, it is important that we take more into considerations [for] aging populations.

(00:09:56)

So almost biomarkers are investigated in the middle-aged patient populations and send -- apply all these tests to our general disease population, which is significantly older than which we see in those larger trials.

So you need to study these markers also in the elderly. We are still not certain what is best cut off for discriminating let's say myocardial infarction from other forms of minor cardiac injury so where do we separate source in population.

So it's that minor elevations from source that are into early phase of developing a small myocardial infarction. So we still have much of work to do to better understand the role of troponins, the high sensitive troponins into lower range.

And finally, this then also relates to translation of clinical care. So what are our therapeutic consequences when we identify high-sensitive troponin in a presumably stable patient with coronary artery disease?

Thus you have to go to coronary angiography, do we need to intensify his medical treatment? So these therapeutic consequences are still not settled and need to be started in the near future.

Bob Barrett: Thank you Dr. Katus. We are underscoring the importance of the use of troponins in cardiac disease. Now we turn to Dr. Christian Mueller, who has his eyes on future roles and procedures.

Dr. Mueller, current guidelines including the universal definition of MI give cardiac troponin an eminent role in the diagnosis of AMI. Do you believe that this is justified?

Dr. Christian Mueller: Absolutely. So I am convinced that the really eminent role that cardiac troponins have as part of the definition of acute myocardial infarction is strongly justified. It's based on the very strong association of elevations in cardiac troponin observed in patients with an acute coronary syndrome, and event rate regarding death during follow-up.

So this has been really very, very consistent both for Cardiac Troponin I as well Cardiac Troponin T and that lead to the replacement of previous markers of myocardial necrosis including CK-MB by cardiac troponin within the last I would say, 15 years.

Bob Barrett: Are there methodological or conceptual limitations in the troponin building?

Dr. Christian Mueller: Well, I think perhaps two limitations to highlight: regarding conceptual limitations if you wish, I mean cardiac troponin is a structural protein in cardiomyocytes.

So therefore, it's clear that it takes a substantial severity of injury, and also I think some time delay until injury can result in the release of this marker into the bloodstream, and then the marker become available for formation and in the peripheral circulation.

So I think the effect that it strongly bounds makes it a robust marker, but also may point to a potential limitation regarding the early diagnosis, and perhaps to add one, methodological limitation, troponin is a marker that is validated extensively, and it's so strong in the guidelines and so robust, but that's one key limitation.

And so until now, there hasn't been a single intervention study, kind of a randomized controlled study that would have proven by using appropriate heart clinical endpoints that clinical management of patients for example with acute chest pain, this cardiac troponin testing would be superior to any other way of diagnosing or managing patients.

So if you wish, these are perhaps two limitations to mention, but still of course, there are limitations that they shouldn't end up questioning, all the other important achievements that we have for troponins.

Bob Barrett: Well, do you see any new markers that might fill the gap?

Dr. Christian Mueller: Of course, I mean there are multiple marks that has been evaluated, that are currently undergoing clinical testing, and perhaps I think it might be helpful to highlight two of them, because overall I think and that's a point to state that quite clearly, overall I think the room for additional markers is rather small.

I think there might be some opportunity to improve clinical care but I think with the development of high-sensitive cardiac troponin assays, the room for improvement for sure has become small.

(00:14:56)

But I think there are two biomarkers that really are unique in the way that I think they are much closer than anything else in perhaps being answer to the remaining unmet clinic needs.

The two markers that I would like to highlight is copeptin, so the C-terminal part of the vasopressin prohormone on the one hand and the Heart-type fatty acid binding protein on the other hand.

Bob Barrett: Well, let's start with copeptin, can you tell us more about that?

Dr. Christian Mueller: Oh sure! So particularly in the setting of the early diagnosis of acute MI is that the copeptin story started only very, very recently. So we have a chance in the year 2009 to report a study in about 500 patients, in which we were able to evaluate a novel hypothesis, the hypothesis that the combination of two pathophysiologically different signals might be beneficial in the early diagnosis that a combination of cardiac troponin on the one hand and copeptin as a marker to quantify endogenous stress on the other hand.

So given that endogenous stress is present at the very, very onset of acute myocardial infarction, we had hypothesized that this signal might help to overcome the sensitivity deficits that conventional troponin assays have in the early diagnosis of acute MI.

Of course, it can only be a combination of the two, because as a marker of endogenous stress, copeptin is rather unspecific and elevated in multiple disease states, and multiple other severe diseases.

If I may add. In fact, our results were very, very encouraging and showed that the combination of cardiac troponin T is at a fourth-generation assay with copeptin at initial presentation resulted in an area under the ROC curve of .97.

Such high number at least to my knowledge has never been observed in this setting before And of course, this was highly significant superior to the performance of Cardiac Troponin T alone.

We were very happy to see that our results were confirmed by a doctor from, Stefan Blankenberg in his large cohort, both for the combinations of Cardiac Troponin T as well as the Cardiac Troponin I as measured with the Siemens Ultra and more recently

 

our findings have also been confirmed by a doctor from the group from Heidelberg as well as from a French team, yes.

Bob Barrett: Well, you also mentioned heart-type fatty acid binding protein which of course is not a new marker. It's been around for quite some time. Why did you highlight this in your review?

Dr. Christian Mueller: Again, because I think from its characteristics, maybe quite appropriate to be used as an add-on marker to Troponin. As you know, heart-type fatty acid binding proteins are small unbound cytosolic protein present in high concentration in the cardiomyocytes.

And because it's rather specific for cardiomyocyte and because it is released earlier and in response to less severe injury as compared to the strongly-bound Cardiac Troponin, it may be a signal to capture that provides clinical useful information in addition to Troponin.

And in addition to this pathophysiological consideration, there's strong evidence from recent clinical studies that at least for risk prediction, heart-type type fatty acid binding protein seems to provide additive information to Cardiac Troponin testing.

To what extent it might be able to provide clinical additive information for the early diagnosis, I think that's too both for copeptin as well as for heart-type fatty acid binding protein in addition to high-sensitive Cardiac Troponin and I think that's the key remaining question, which is currently evaluated in large multicenter studies.

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. And Dr. Hugo Katus is a Senior Physician from the University of Heidelberg. They have been our guests in this podcast from *'Clinical Chemistry'*. I'm Bob Barrett, thanks for listening!

Total Duration: 20 Minutes