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Weekly and 90-Minute Biological Variations in Cardiac Troponin T and Cardiac Troponin I in Hemodialysis Patients and Healthy Controls

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Guest:
Dr. Kristin Aakre is from the Department of Clinical Biochemistry, Haukeland University Hospital in Bergen, Norway.

Bob Barrett: This is a podcast from *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Chronic kidney disease is an important risk factor for cardiovascular morbidity and mortality. This risk is all the more important for patients undergoing hemodialysis. In the presence of clinical signs of an acute myocardial infarction, the universal definition includes the finding of a serum cardiac troponin concentration above the 99 percentile as defined by healthy individuals, together with time dependant changes in serum and troponin concentrations. But in contrast to individuals with normal kidney function the troponin concentrations in patients with chronic kidney disease, but no myocardial infarction, may already be at concentrations higher than the 99 percentile of a healthy population.

A paper in the June 2014 issue of *Clinical Chemistry* examined biological variation of cardiac troponins in both hemodialysis patients and in healthy controls. Dr. Kristin Aakre was lead author of that paper and she joins us in this podcast. She is from the Laboratory of Clinical Biochemistry, Haukeland University Hospital and at the Norwegian Clinical Chemistry EQA Program, both located in Bergen, Norway.

Doctor, in this study you aim to determine the biological variation and the reference change values for two high sensitive troponins assays in patients treated with hemodialysis and in healthy subjects. Now, why is this important?

Dr. Kristin M. Aakre: Well, myocardial infarction is diagnosed based on concentration changes in cardiac troponins and also you need to have a run concentration of a cardiac troponin above the 99 percentile, that's the biochemical definition of myocardial infarction. However, there has been a large debate for several years about the magnitude of the concentration changes which is necessary to diagnose a myocardial infarction. And we thought it was important to know what will the changes be in a clinical stable situation,

how large changes can have just based on analytical and biological variation, because if that is similar to what you suggest as a diagnostic delta criterion, or the diagnostic concentration change, you need to diagnose the myocardial infarction. Well, then, if these two overlap, then this delta criterion you have suggested will not be very specific for the diagnosis. You have a risk of having many false positive diagnoses of myocardial infarction.

So that's just the main reason why we wanted to look at this, to be able to suggest something about what is an applicable delta criterion for myocardial infarction.

The other reason was that biological variation data, they have traditionally been used for decades just to tell what should the analytical quality of an assay be, how good do we need to be when we match the troponins and the guidelines we have now for analytical performance goals with troponins, they are not applicable for the high sensitive assays; they are also not complete, because they don't give any recommendations about bias, the systematic errors or about total errors.

So we thought we needed to determine the biological variation in order to say something about the analytical quality, and we can do that, both analytical variation which needed to be much lower than 10%, which is the present goal. When it is used for assays, for the high sensitive assays it should be much lower, and you can also say something about bias and that was shown a few years ago. It is important to have bias goals also with troponins, because when we had a shift in the Troponin T assay, it suddenly changed from 5/4/6 nanograms per liter in the lower area and that is clinical significant and it's scientifically relevant, and that was due to the recalibration done by the manufacturer since the assay had shifted downward very slowly for a few years, and if we had had bias goals, we could maybe have been able to detect this drift downwards a little bit earlier, so we think that's important.

Bob Barrett: And why did you choose those two populations?

Dr. Kristin M. Aakre: Well, the first reason for choosing these two populations is that they are very different, both, regarding a risk for cardiovascular disease and also regarding based on concentrations for troponins, especially for Troponin T which is very much dependant on what the renal function is and it's very much higher in the hemodialysis population and we wanted to know if the biological variation was dependant on the underlying condition of the patients and the population being included, or if it was assay dependant.

And what we found was that the biological variation was similar for both populations, so it has nothing to do with a condition if it's a very diseased individual or if it's a very healthy individual, it has just to do with the assay.

So the biological variations for Troponin I and T was different, but within the assay it was similar for both populations and this is quite interesting because these populations are so different and then we can maybe speculate that the biological variation is quite similar also for other populations who are not so much diseased as hemodialysis patients are, or not so much at risk, but in between these two populations, so we think that's interesting to see.

Christian Aakre: Another reason to look at the hemodialysis population is that they have chronically elevated concentrations of troponin, especially Troponin T. So the baseline concentration will usually be above the 99 percentile and then you only can make the diagnosis of myocardial infarction based on concentration changes. And then of course, it's very important to know what are the concentration changes in the stable population in order to say something about specificity of the diagnosis as I already talked about.

Also hemodialysis patients are important to look at, because they have this high risk and they are very rarely included into studies. So therefore, we don't know so much about them. And another not so important reason but also interesting was that the Troponin I and Troponin T behaved different in patients with renal disease.

So we wanted to see if that could affect the biological variations, but we didn't find very much there, they are similar as in healthy individuals. So probably the renal function doesn't have much to say, for the biological variations of the assay.

Bob Barrett: Doctor, myocardial infarction may be diagnosed based on changes in proponent concentrations during 3-6 hour period. You conclude that the suggested diagnostic delta values of 20%-50% are applicable for the high sensitivity cardiac Troponin T assay, but maybe not for the high sensitivity cardiac Troponin I assay. Why is this? And do you think one assay has better diagnostic utility compared to the other?

Dr. Kristin M. Aakre: No, I don't think one assay is better than the other, that's probably the most important thing to say and I would rather say it first, but what we saw was the analytical and biological variation was different for the Toponin I and a Troponin T. So it's higher for Troponin I and when the

biological analytical variation is higher then the reference changed values will also be higher and what we saw was that the variation for Troponin I slightly overlap with these criterions, which is suggested by the European Society of Cardiology, of 20%-50% depending on baseline troponin concentration. And that's overlapped with what these saw was a random variation in Troponin I in stable patients.

And this means that a Troponin I assay may have a lower specificity compared to the Troponin T assay when you use these delta values. So maybe it could be better to have a slightly different delta values for the Troponin I assay. Maybe we need to have delta values that are dependant on assay in the same way as we have 99 percentiles which are dependant on the assays.

But we can't say it is very clear and loud based on what we saw in this study. It needs to be validated in clinical studies, but we have an indication that different delta values may be more useful depending on the assay.

Bob Barrett: Doctor, you stated that to diagnose myocardial infarction a patient must have at least one troponin concentration above the 99 percentile. Now in your article you suggest that this specify diagnosis cut-off value may be overkill, and myocardial infarction may be diagnosed based on troponin concentration changes alone.

Why do you think the use of 99 percentile as diagnostic cut-off value may be omitted from the diagnostic definition of myocardial infarction?

Dr. Kristin M. Aakre: As I already said, this is what we usually do in hemodialysis patients, because they have chronically elevated troponin concentrations and then the 99 percentile cannot be used. So then we only depend on the changes and what is known is that the troponin concentrations in hemodialysis patients are very different from one individual to another. So it's not very useful to define a 99 percentile in a hemodialysis population.

What we thought was that may be this is also the case in healthy individuals and that was also what we found not so clear as in the hemodialysis population, but quite clear. And what that means is that one individual might have to increase the troponin concentration by 300%, 400%, 500% to have a diagnostic myocardial infarction by crossing this concentration which is defined as 99 percentile.

And another individual may be only need to increase by 50%-100% to cross the 99 percentile. And then the biochemical definition of myocardial infarction is not standardized, because they have actually been increased

differently in order to be diagnosed. And what we saw here in this data was that the difference between patients is very large compared to within patients. And then it's probably more relevant just to look at changes also below the 99 percentile and you don't need to use it.

But again, to be able to say this very clearly we need clinical studies which can actually look at what will be the outcome on the patient who are diagnosed only based on changes where we don't include the 99 percentile in the definition. So again, we need more data to conclude on this.

Bob Barrett: Well, finally doctor, in your article, you show that the mean concentration of troponins decline during the sampling period from 8.3-14.3, how do you explain this phenomenon?

Dr. Kristin M. Aakre: Well, this is a kind of curiosity, but what we think is that this is due to daily variation of the troponins. Daily variations have been shown from many different biological constituents and it would not be very surprising if it could also be seen for troponins.

So we couldn't find any other explanations, so that's our conclusion, but again, this must be confirmed by others, but if it could be that, I think maybe we need to take this into account when we evaluate several changes in troponins, because it was quite substantial like 10% during 6 hours and we have the individuals with Troponin T, so then we need to take it into account if it can be concerned. But this is the first study showing this, so again, we need more data to be absolutely sure.

Bob Barrett: Dr. Kristin Aakre is from the Department of Clinical Biochemistry, Haukeland University Hospital and at the Norwegian Clinical Chemistry EQA Program, both located in Bergen, Norway. She has been our guest in this podcast from *Clinical Chemistry* on troponins and chronic kidney disease.

I am Bob Barrett. Thanks for listening!