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High-Sensitivity Troponin: Star Player but No Lone Hero

Article:
Richard Body.
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Guest: Dr. Richard Body is a professor of Emergency Medicine at the University of Manchester in the United Kingdom.

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.

Numerous studies from Europe and the Asia-Pacific Region have demonstrated that ruling in and ruling out myocardial infarction can be expedited using high sensitivity cardiac troponin. However, similar studies conducted in the United States are lacking and currently, there is only one FDA approved high sensitivity cardiac troponin assay. A recent paper by Sandoval et al. in the October 2017 issue of *Clinical Chemistry* compared the diagnostic performance of an investigational high sensitivity cardiac troponin assay, with that of a contemporary assay in a U.S. population.

The authors evaluated the ability of these assays to rule out acute myocardial infarction by use of the 99th percentile alone, and with a normal electrocardiogram. They also determined performance to rule in acute myocardial infarction through serial changes, or deltas, in the troponin values. The results were promising for clinical implementation of high sensitivity troponin assays, but also demonstrated these assays are still not a perfect diagnostic tool. Dr. Rick Body, who authored an editorial on this original research article, joins us for this podcast. He is a professor of emergency medicine at the University of Manchester. His research is focused on the early diagnosis of acute coronary syndrome, including development of clinical decision aids that used troponin to rapidly rule out acute coronary syndrome.

So, Dr. Body, you wrote an editorial on the paper by Sandoval et al. Could you summarize the findings of that work for us?

Dr. Body: Yes, sure. So I think there were really three key messages from this paper. They compared the high-sensitivity troponin I assay from Abbott to the contemporary troponin I assay, which is also manufactured by Abbott. Using serial samples in patients with suspected acute coronary syndromes in the emergency department, and the three key

findings were this: number one, there was no increase in false positives when high-sensitivity troponin assay was used. So, there were no more positive results in patients who didn't have MI. In fact, they adjudicated that diagnosis using the contemporary assay, and then repeated that, learned it through initial adjudication using the high-sensitivity assay. And actually, what you see is, a very marginal decrease in the apparent prevalence of acute myocardial infarction when the high-sensitivity was used.

So, number one, the concerns that actually when we use these highly sensitive assays, that we'll actually have an explosion in diagnoses of acute myocardial infarction, actually, it seems to be unfounded with this assay based on this evidence. The second key finding was with regard to the potential of the assays to rule out the diagnosis of acute myocardial infarction early. And what's really noticeable is that using the 99th percentile threshold, the high-sensitivity assay didn't actually perform any better than the contemporary assay using the first sample drawn on arrival in the emergency department.

So, you're not really getting an advantage there. I think in other papers you can see that you start to get the advantage if you use the limit of detection of the assay. But at the 99th percentile, we're not picking up anymore diagnoses than we would with the contemporary assay. But, by three hours, we start to pick up many more diagnosis and in fact, when they combine the high-sensitivity troponin assay with the ECG, we got 100% sensitivity at three hours. So, no acute myocardial infarction missed.

There is a little caveat on that which is to say that actually, the incidence of death from MI within 30 days was not insignificant in that population. And that probably, hammers home one of the points of the title of my editorial really, which is troponin isn't a lone hero. We still need to take accounts of clinical information before we send all of these patients home.

The third key point, I want to make about this really nice paper from Sandoval et al., is with regards to delta criteria, so we know that in order to diagnose an acute myocardial infarction, we need to detect a rise and/or fall of the cardiac troponin with at least of one level above the 99th percentile. And the question is, what constitutes a rise and/or fall. Well, with contemporary assays, we always accept that a relative change in the troponin concentration is better, a percentage change. And by convention, we say, 20%. But, with high-sensitivity assays, we're realizing more and more that the absolute criteria, the absolute change, simply the maximum troponin minus the minimum troponin, is much

better. And that is what we see here, but interestingly we see that the absolute delta was better with both the contemporary assay and the high-sensitivity assay. But with the high sensitivity assay, probably due to its better precision, a sensitivity and specificity were much better at low thresholds.

So, you can accept a smaller delta and know that there is a real change, and I think that's a real advantage to high-sensitivity assays. It allows it to be more confident of the change that we observe in troponin on serial sampling, that it's actually genuine, and therefore more likely to be due to an acute myocardial injury or an acute myocardial infarction.

Bob Barrett: Overall, what did you think of the paper by Sandoval et al.

Dr. Body: Really important piece of work. It explains a lot about the use of high-sensitivity troponins. I think it will be used to allay a lot of the fears that actually we'll get an explosion of unnecessary investigations when high-sensitivity troponin assays are used. I don't think that fear has any basis based on this evidence, and it really helps us to understand how we can use the delta criteria better in practice to optimize the diagnosis of acute MI.

Bob Barrett: Well, let's get to your editorial. You tell us that high-sensitivity troponin isn't a "lone hero." What do you mean by that?

Dr. Body: So, what I mean is that you can't trust troponin by itself to make your diagnoses. It's a fantastic test. It really has revolutionized the way that we make the diagnosis of acute myocardial infarction, but it should never be used alone. You can't use it as a substitute for going and seeing a patient. So, the laboratory information is so important, but of course it has to be combined with the information that is gleaned from the patients at the bedside, and this evidence really highlights that.

When you look at the sensitivity of the three-hour rule out protocol with high-sensitivity troponin I, you can see that it's only 94.5% for major adverse cardiac events occurring within the next 30 days. Now, that means of course that five and a half percent of all of the major adverse cardiac events that occur are missed by high-sensitivity troponin at three hours.

Now, that does not mean that troponin is no good as a test, but it clearly does mean that if we are to pick up those patients who still do need further investigation after the three-hour troponin results come back, then we have to look at clinical information. We have to consider the patient's

symptoms, their EKG, their entire clinical picture and put that together. Troponin is not telling us everything.

Bob Barrett: Doctor, what do the data tell us about the appropriate delta troponin for use in practice?

Dr. Body: Well, this data so really interesting with regards to the delta troponin. We already know that the absolute delta seems to be better than we use high-sensitivity troponin assays than the relative delta. This evidence from Sandoval et al shows that actually the absolute delta is better with a contemporary assay, but it really highlights the key advantage, or one of the key advantages of the high-sensitivity troponin assay. Their better precision means that a small change on serial sampling is much more likely to be due to an acute MI.

There is another reason to hammer home that point about troponin not being a lone hero though, because our job is not done even after we observe an important delta troponin. So, when we look at the data presented in the supplementary appendix, we can see that an absolute change of over five nanograms per liter at three hours seemed to have a very high specificity for acute MI at 89%, it does seem very good, but when also consider that the prevalence of acute MI is relatively low, that actually means that the positive predictive value of the test with a 5 nanogram per liter delta is only 45.5%. So, over half of the patients who have that delta actually have another diagnosis, other than acute myocardial infarction.

So, again, it just highlights that we can't trust the test just alone by itself. If we did so, we'd make a lot of wrong diagnoses. We need to integrate it with all of the clinical information.

Bob Barrett: Well, finally Dr. Body, do you think these findings will change clinical practice?

Dr. Body: Yes I do and I think that they'll -- particularly, they'll help the case for high-sensitivity troponin assays to be approved in the U.S. This Abbott high-sensitivity troponin I assay is not yet approved for use in the United States. There is only one high-sensitivity troponin assay there is. This will help the case I hope, for this to be approved in the United States because we know that these assays offer significant advantages for patients and they will help us to understand a little bit more about how to use these assays more appropriately to benefit patients, in particular with regard to the test characteristics of three-hour sampling and how we might best use that, those delta criteria.

Bob Barrett: Dr. Rick Body is a professor of emergency medicine at the University of Manchester in the United Kingdom. He has been our guest in this podcast from *Clinical Chemistry*. I am Bob Barrett. Thanks for listening.