

Host: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

Two articles recently published in the *New England Journal of Medicine*, explained the use of high-sensitivity cardiac troponin. These articles emphasize important concepts for clinicians, but some aspects of the studies require clarification.

The March issue of *Clinical Chemistry* published a perspectives article by Drs. Alan Jaffe and Fred Apple, and they examined the articles, separated out new data from hype, and propose that further progress depends on clinicians learning about analytical issues and laboratorians understanding the challenges that new high-sensitivity assays pose.

Dr. Alan Jaffe is a cardiologist who spent his career working in the area of cardiac biomarkers. He is presently Professor of Medicine and Chair of Core Clinical Laboratory Services at the Mayo Clinic in Rochester, MN, and he is our guest in this podcast.

Tell us Dr. Jaffe, could you explain which assays are high-sensitivity assays and which are not?

Dr. Allan Jaffe: Well, I think there is confusion about this, and part of that problem had to do with the recent *New England Journal* article papers which sort of gave the impression they were using super-sensitive brand new assays. And the reality is that most of the assays used there were contemporary assays, assays that are now being used in laboratories around the United States.

In one of the papers, there were a couple of research assays, but most of them were just regular traditional assays, and companies would like us to think that their assay is the biggest and the most sensitive and the best. But in point of fact, the contemporary assays we have today are good. They are reasonably sensitive, but they are not the novel super-sensitive assays that we will eventually some day have.

Host: So considering a clinician's ability to rule in or rule out disease, is the finding of a high number of early rule-ins new?

Dr. Allan Jaffe: Well, it actually isn't. What these papers did I think, which was a benefit, was it brought to light the fact that if one utilizes troponin in the proper way with the proper cutoffs that one has a large number of patients, who very early after the onset of symptoms, and therefore early after they arrived at the hospital can be diagnosed by having an

elevated troponin. We first reported this in 2006 actually, and it's very, very clear that this is something can be done with almost all the contemporary assays assuming they are used properly.

Host: And exactly how does troponin work to rule in so many patients so early?

Dr. Allan Jaffe: Well, I think the key and the difference between these papers and what happens so often in the community and indeed it was the comparator that was used, was what happens in the community was that in the community people do not use these assays using the 99 percentile value, which is what all of the guidelines recommend.

Many clinicians are concerned that there will be too many elevations they won't be able to understand or explain, and therefore used for higher cutoffs.

Indeed, if you look at the papers in several of them, the assays that were being used as the comparator were actually these exact same assays as used in the papers. But clinically they obviously were being used with cutoffs that were far higher. Because of this concern on the part of clinicians, for elevations they couldn't explain.

So the trick is, you use troponin and you use the cutoff value that all the guidelines recommend of the 99th percentile, then one gets very, very early diagnosis in a very large number of patients, somewhere between 80+%.

Host: Now in your opinion are the recent *New England Journal of Medicine* studies correct in the designing conclusions?

Dr. Allan Jaffe: Well, I think like any study there are strong points and weak points. Some of the patients that were included in the *New England Journal* studies may have had elevated troponins for reasons other than having a myocardial infarction, such as pulmonary embolism or sepsis. And it was a sub-analysis done in one paper that looked at that. But by and large, the authors took credit whenever there was an elevation irrespective of the cause.

In addition, we know that many patients who have cardiovascular comorbidities, even patients who have stable angina, could have a mildly elevated troponin. The way in which we distinguish between those patients and patients who were really having an acute myocardial infarction or an acute coronary syndrome, is we look for a rising pattern of values.

(00:04:55)

This wasn't done as well. So the authors again took credit for those chronic elevations, which made their numbers look still better than what I think they would be, had they been more fastidious about excluding those people with alternative explanations for disease, and making sure that there was a changing pattern.

There was one sub-analysis that started to get at that and this was referred to by Dr. David Morrow in his editorial, and it's an important caveat, which is, as you go down lower-and-lower, the number of elevations that are going to be due to coronary artery disease will become less. And so the specificity of the measure of the rule-in for coronary disease gets diminished. He estimated it went from 70 to 50%.

Host: With that in mind, what do these data say about our ability to rule out disease?

Dr. Allan Jaffe: Well, there is this implication that if most patients rule in early then that's all you have to do. But these studies didn't specifically probe how long it takes to know with real certainty that there are not going to be small number of people who could rule-in late. This is a major issue, because of the people who come to emergency rooms and emergency facilities in the United States, a very small percentage rule in.

As the matter of fact, it's no more than 20% and often if one excludes the patients who you can tell right at the door, don't need values drawn on them. That number goes down even lower. So, in the trials done, say investigating new techniques such as CT angiography, the rule-in rate is something like 6 or 8%. In Europe, and these studies both came from Europe, they do a much different job of screening patients, and they also included all of those patients who you could tell from the front door or by the ECG had disease.

So, they inflated their numbers at the front side, but again, they did not look out late enough in particularly in those patients in whom there is concern, and that's the most, more subtle thoughts of presentations or the intermediate risk patients to ask the question how late does one need to go to know that we have really excluded infarction to metric the emergency rooms like the uses is that you shouldn't send people home if they have anything more than 1% frequency of having an event. And we don't know that from these data.

Host: Well high-sensitivity assays make rule-ins and perhaps rule-outs faster?

Dr. Allan Jaffe: I think they probably will. What you have seen is, the assays that were used in these studies are solid assays, rule-in and rule-out studies had not been published in the highly visible literature for a long time. And it's quite clear that the leap we've made in sensitivity already, will allow us to diagnose many patients far earlier.

When we get to still more high-sensitivity assays, the really high-sensitivity assays, this trend will be facilitated and as opposed to making the diagnosis in 80 or 85% as claimed by these articles. Those numbers with really high, high-sensitivity assays, maybe 90 or 95%, and the time that it takes to rule them all in, will become still shorter. So, maybe instead of six hours, it will become three hours, or four hours, it will become two hours. We don't know those things yet, but it's likely then if you make all the rule-ins early, then by definition the rule-outs will be quite modest and small.

So, there is great hope that the next leap in the sensitivity will markedly improve still the data that we've seen here. It is fair to say, however, that what's called the high-sensitivity that was used in the study and that was the high-sensitivity Troponin T assay from Roche. That is such a high-sensitivity assay we believe. And it was not statistically different from the other assays, although the area under the curve was a little bit better.

And what that says is that the vast majority of patients with myocardial infarction are pretty overt in regard to what the biomarker signals they give you.

The high-sensitivity assays are going to pick up and marginally increase number and those are going to be the more subtle cases I talked about and read about earlier.

So, I think those assays maybe really key from the perspective of identifying the subtle patients and also facilitating how rapidly we can exclude infarction.

(00:10:00)

Host: Well, finally, what do you see is the potential downsides of these findings?

Dr. Allan Jaffe: Well, and I think this is key to understanding these data, as we go down in the more-and-more sensitivity with the troponin assays, we are going to find that there is going to be more chronic elevations, whether it's due to patients who have chronic coronary disease, patients with renal failure, some patients with hypertension.

So, for example, using the Troponin T assay, which was used as a comparator in one of these studies, it was found that nearly 1% of the population in Dallas had an elevated troponin, and they all had cardiovascular disease. If it's 1% in the community, maybe it's 5% in the emergency room, and maybe it's 10 or 15% in the hospital, and if you then increase the level of sensitivity still further, say another log unit, one is going to see even more such elevations, maybe it would be 10 or 5% in the community, 20% in the emergency room, 25% in the hospital.

So, we are going to have to be very careful about these chronic elevations, and from that perspective, looking and seeing that the pattern is changing, which is what we used to say that an acute event is occurring, is going to be terribly important.

It's also going to be terribly important that we continue to understand that elevations in troponin are not specific for ischemic heart disease. So they may occur in patients who have pulmonary emboli, myocarditis, who've got shocks resuscitated or drug intoxication such as carbon monoxide poisoning.

So, this is going to take a fair amount, more sorting, even if we see a rising pattern indicative of an acute event, to make sure that we call out clinically the patients who have heart attack and distinguish them from patients who have other diseases that can also damage the heart.

Host:

Dr. Allan Jaffe is Professor of Medicine and Chair of Core Clinical Laboratory Services at the Mayo Clinic in Rochester, MN, and he has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening.

Total Duration: 12 Minutes