

Bob Barrett:

This is the podcast from Clinical Chemistry. I am Bob Barrett. In 2007, cardiac troponin was recognized as the sole biomarker for diagnosis of myocardial infarction. 4 years later this protein is again causing a stir. This time resurfacing in so called high sensitivity assay formats. Studies are now starting to address the role of high sensitivity cardiac troponin in primary prevention.

In the April issue of *Clinical Chemistry*, Dr. Fred Apple, Medical Director of Clinical Laboratories at Hennepin County Medical Center in Minneapolis, Minnesota, provided his perspective on several of the latest papers that are exploring the role of high-sensitivity cardiac troponin in healthy populations. He's our guest in this podcast.

Doctor, before we address the clinical implications of high-sensitivity cardiac troponin assays, can you tell us what distinguishes high-sensitivity assays from other assays currently used in clinical practice?

Dr. Fred Apple:

There are several points I would like to make regarding what's unique about high-sensitivity cardiac troponin assays. First, let's just talk about the nomenclature. This high-sensitivity designation is about the assay, and that's very important. We measure troponin with many different names of assays. But the high-sensitivity relates to the ability for the troponin assay to measure very low concentrations. For example, within the normal reference range of a population, the current generations of assays may only measure 10% to 20% of actually giving a number related to a normal subject. The high-sensitivity assays are able to measure to 80% to 100% of normal subjects giving it value and concentration above the limit of detection.

In addition, which is very important, the precision of these assays at the 99th percentile of that upper reference limit are now less than or equal to 10% coefficient of variation. The importance of this: it meets the recommendations by the Global Task Force and the NACB for the definition of myocardial infarction to use troponin assays.

Another important issue regarding these high-sensitivity assays is that these assays measure at concentrations that are even below the limits of detection of our current assay that we have in clinical practice. Where that implies a clinical implication as we'll get to later in our podcast, is that now we can develop and determine biological variation; the true variation that occurs in normal people. And what we have found that these high-sensitivity assays have biological variations that range between 40% and may be 80%. So when we're looking at interpreting clinical concentrations on patients, we will now know using these assays that a 20%, 40%, 60% change might be within the normal biological

variation, and does not point toward actual pathological change.

We couldn't even do that with the current assays and therefore these criteria set apart these high-sensitivity assays and the current assays in practice.

Bob Barrett: So how have cardiac troponin assays been used to determine risk or outcomes in patients with acute coronary syndrome?

Dr. Fred Apple: These high-sensitivity assays have taken the ability to re-stratify patients with symptoms suggestive of acute coronary syndromes beyond the initial studies back from the 90's. First, we learned that major adverse cardiac events could be separated between a patient's concentration at admission. If a patient with increased concentration versus a patient's concentration who was normal, we're seeing that 4- to 5-fold odd ratio of an adverse event, comparing those two.

Now those are often moderate to high-risk patients. And what we've learned is that medical therapy could have been instituted based on those, such that if you took a patient who came in with a baseline increase, treated them with certain anti-thrombolytic agents, anti-clotting agents, that we could reduce the risk about say, 15% of patients having an adverse event, down to about 3%, similar to as if that patient had a normal concentration. And those are based on the on the contemporary sensitive assays.

With these new high-sensitivity assays, we now have found that these assays are again being able to measure very low concentrations. We can look at a group of patients for an example, there was a paper published in the New England Journal of Medicine out of the Boston Brigham Hospital, looked at over 3000 patients with stable coronary artery disease, and they were able to show that looking at quartiles even within the normal range, that there was a strong-rated increase in cumulative incidents of cardiovascular death, with a hazard ratio of about 2.0, and also a graded increase in heart failure has a ratio about 3.0 as you saw increases even again as I mentioned within the normal range.

Therefore the importance of this is that now numerous studies, the one I gave you an example, have not only shown that within a stable population, but we also have learned, if we take patients that don't even have ACS, the non-ACS pathologies, that you can see a difference in risk stratification with a higher risk in patients who show up with non-ACS pathologies compared to ACS pathologies.

These small changes that occur make the clinicians have to think that you cannot overlook the implications of the risk and the potential to evaluate a patient differently due to the possibility of an adverse poor outcome predicated on a number, which clinicians used to not even be able to measure.

Bob Barrett: High-sensitivity cardiac troponin measurements were used in studies of three populations of healthy subjects that you reviewed in your perspective article. Can you tell us about that?

Dr. Fred Apple: Yes, there were three studies that I mentioned in my perspective to talk about the use of these high-sensitivity assays in primary prevention of population screening.

One of the studies first I'll address is the Dallas Heart Study published in JAMA in 2010. It looked at over 3000 adults, ages in the 30-65 year range, and they showed that 25% of these subjects had measurable troponin values using these high-sensitivity assays compared to the routine Troponin assay, in this case, they used cardiac troponin T, where only 0.7% of these patients had a measurable value.

When they further look deeper and looked at the relationship of these low concentrations, they found that the concentrations were higher in older-age subjects, in males, and in African Americans.

They also identified that the increases along a gradient were associated with structural heart diseases that were more prone to left ventricular hypertrophy and systolic dysfunction, and also that were more prone to a chronic renal dysfunction.

When they looked at a follow-up of these patients, which was approximately over an 11-year period. Again, there was an increase in all-cause mortality from 1.9% to 28% across a group of these patients that had an increasing troponin value again looking at the use of a high-sensitivity Assay.

Amazingly, that about 95% of these changes, these increases that occurred over time were measurable below that 99 percentile, a value which we would not even be able to detect, if we were using the routine cardiac troponin T assay.

The second interesting think about this Dallas Heart Study is that these results remained significant even after adjustment for the traditional risk factors such as renal function and other biomarkers such as NT-pro-BNP and high-sensitivity CRP levels.

The second study that was studied and published by a different group, this study was published in a group of patients from the Cardiovascular Health Study as well as the Atherosclerosis Risk in Communities Study. This is the paper published by Kristy Philippi also in the same issue of JAMA in 2010.

They looked at over 4000 and 9000 subjects, respectively in those two studies ages over 50 years of age, and what they found which again, was a very unique finding, they had about 11 to 12 years of follow-up data.

They started by looking at serial measurements and looking at a second measurement two to three years after a baseline measurement that had increased by 50%, increased the hazard ratio of risk of death or heart failure, and they also show they looked at a decrease of 50% for the Troponin value measured by the High-Sensitivity Assay, they could show that the risk decreased.

The hazard ratios were in the order of 2.9 for cardiovascular deaths and about 2.5 for heart failure, and again, when adjusting for Framingham risk factors and another biomarkers like NT-pro-BNP, and again high-sensitivity CRP added no value to the Troponin measured by this High-Sensitive Cardiac Troponin T assay.

The last study, which was really just a study published as an abstract form. It's not published yet in pure review. It was an abstract discussed at the American Heart Association meeting. I was involved with that study for full disclosure. The primary investigator was Russell Luepker. It was from the Minnesota Heart Survey study, which has been ongoing population study from 1980s.

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Dr. Fred Apple: There was surveillance study. And then our nested case-control study looking at 137 cardiovascular deaths compared to about 230 case-controls, we identified in a seven biomarkers study that the Troponin measured by the high-sensitivity assay had a odds ratio of 6.7 for cardiovascular deaths.

So overall, these findings provide a new wealth of information looking at the very strong prognostic values, of looking at healthy populations to identifying underlying structural defects that would not be even detected by the imaging and/or biomarkers we currently have in practice.

Bob Barrett: You suggest that all clinical trials and studies which measure biomarkers must include a High-Sensitivity Cardiac Troponin assay. Isn't that somewhat premature or controversial?

Dr. Fred Apple: Yes, I would say it is little controversial. One of the things you get to do in perspectives is to voice your thoughts on a topic I know fairly well. And the reason I make that statement is, and I use as an example, my perspective is the largest Biomarkers study to date was a paper published out of Germany by Stefan Blankenberg where he looked at two very large disease-free cohorts; about 7000 men and women from the FINRISK97 population and about 2500 men from the Belfast Prospective Epidemiology Study of Myocardial Infarction; acronym prime.

He looked at 30 biomarkers which were representatives of multiple pathophysiological pathways. And what he found was that no single biomarker improved the risk estimation of cardiovascular events over a 10-year follow-up period, based on, again, on a baseline specimen value even after adjustment for classical risk factors.

The big key here was that, in their study, the High-Sensitivity Troponin Assay was not evaluated in the study. And when he dug deeper into the study, he actually came up with an interesting concept. He developed what they called a multi-biomarker score, which improved the predicted ability to look at cardiac events. And in that score he -- this biomarker score -- included NT-pro-BNP, high sensitivity-CRP, and a contemporary Troponin I assay.

And what that tells me is that there's a little hint that Troponin does play a role in predicting the death. It would have been most excitedly to see if they use that assay, the high-sensitivity assay, I am a firm believer that the risk would have showed up as an independent predictor.

So based on this study, the findings, and the three studies I discussed before that, that did use high-sensitivity assays, to me the future of all these types of trials and studies need to incorporate this assay to prove or disapprove at least my thought process and others too.

Bob Barrett: Over what timeframe do you see that these High-Sensitivity Cardiac Troponin assays will be available for routine clinical use in the US?

Dr. Fred Apple: The timeframe for implementations into at least the United States is not going to be in the near future. Currently, one high-sensitivity Troponin assay; the high-sensitivity Troponin T assay is available throughout the world, it's marketed by Roche. It's not FDA Cleared yet but they are selling it in Europe and Asia, I think even in Canada.

Currently the other assays and Roche assays included is, at least 3 or 4 high-sensitivity Troponin I assays and the high-

sensitivity Troponin T assay, the assay undergoes at some point of the process, during clinical studies to gather analytical and clinical information for diagnostic accuracy and risk stratification data to submit to the FDA for 510(K) Clearance.

One of the reasons that this process will be probably a year, to a year-and-a-half off, is that the FDA has a document they published in April 30th of "points to consider" on how to put together a clinical study. And unfortunately the FDA, at the present time does not have a clear-cut guidance document they can give to the manufacturers that are trying to do studies to get these high-sensitivity assays cleared. And therefore, the message and the exact protocols are not often uniform.

So I think with the not so clarity of what they need to do and then the amount of work that they consider that has to be done based on the FDA "points to consider" document to enroll probably 500 to 1000 patients at multiple sites, will be a good year process plus the time for submission. So I am expecting a year to year-and-a-half away before we see a high-sensitivity assay cleared by the FDA.

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Bob Barrett:

Well, do you think that High-Sensitivity Cardiac Troponin Assays will truly become a biomarker, used for primary prevention similar to what's commonly done by lipid and cholesterol testing screening?

Dr. Fred Apple:

There are several questions, that when you think about that question that you have to think about.

First, were these new assays -- would the High-Sensitivity Troponin Assay, provide information that could be put to productive clinical use?

Second question that comes to mind is, will it impact the decision-making in a substantial way such that there may be a change in how the patient is managed, and will there be an ability like all these studies need to do to have some type of measurable clinical outcome?

So what we've learned is that the preliminary data on the two papers plus the abstract looks very promising. This evidence base is starting to support this assay is a very important tool for future studies that cannot be overlooked. But the type of things that these studies have to be looked at is to see whether or not when we look at these studies, what are effects that have been overlooked?

For example, the chronic release of these small concentrations, which is not uncommon, we're learning now

in asymptomatic adults, that identify unrecognized structural heart disease and therefore put these patients at a higher risk of cardiovascular death or maybe heart failure.

What kind of changes can be implemented in study to see if this actually will have an impact? For example, the effects of life style, different medical treatments, better and long-term follow-up, and we still have to learn about the effects of age, gender, ethnicity characteristics, and even other concomitant pathologies.

So I am optimistic that this assay that will provide the ability to measure low concentrations will become a very prominent tool. But we will have to wait and see to make sure as they start off with that this test does provide productive information that is going to be useful for the clinician that may affect their management.

Now what's our overall goal? It's patient care, and as you and I one day end up in the hospital, I think if we can have a test like this that'll direct the right type of therapy for the right patient, I think that would be a wonderful thing that a biomarker such as Troponin measured with a High-Sensitivity Assay would provide.

Bob Barrett:

Dr. Fred Apple is the Medical Director of Clinical Laboratories at Hennepin County Medical Center in Minneapolis, and our guest in this podcast from '*Clinical Chemistry*'.

I am Bob Barrett. Thanks for listening.

Total Duration: 18 minutes