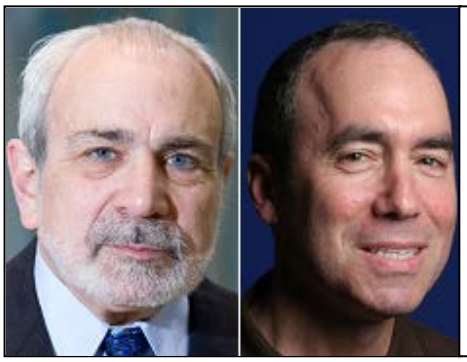
Clinical Chemistry

High-Sensitivity Cardiac Troponin Assays: Isn't It Time for Equality?



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Guests:
Dr. Allan Jaffe is from the Cardiovascular Division and Department of Laboratory Medicine and Pathology at the Mayo Clinic, and Dr. Fred Apple is from the Department of Laboratory Medicine and Pathology, Hennepin County Medical Center in Minneapolis.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I'm Bob Barrett. Women who present with acute coronary events are less frequently to be properly diagnosed and often have worse outcomes than men. Part of the problem may be that women are less apt to manifest increased biomarkers or often receive less aggressive guideline-mandated care. Women also have lower reference values for biomarkers of cardiac injury that are rarely taken into account.

The January 2014 issue of *Clinical Chemistry* is devoted to the area of women's health. It includes two papers examining high-sensitivity cardiac troponin in female populations. Accompanying those papers was an editorial by Allan Jaffe and Fred Apple, who asked the question: Isn't it time for equality in High-Sensitivity Cardiac Troponin Assays?

Dr. Jaffe is from the Cardiovascular Division and Department of Laboratory Medicine and Pathology at the Mayo Clinic; and Dr. Apple is from the Department of Laboratory Medicine and Pathology, Hennepin County Medical Center, in Minneapolis. And they are both our guests in today's podcast.

Dr. Apple, let's start with you. What is the rationale for implementing gender-specific 99th percentiles for men and women into clinical practice for a diagnosis of myocardial infarction and risk outcome assessments?

Dr. Fred Apple: We have learned that with the High-Sensitivity Troponin Assays, just like what we had used years ago for (CK) MB that what we determined the 99th percentile, we see significantly lowered 99th percentile for women compared to men, which sets up the scenario, we have to be very careful if we're going to implement this in the clinical practice. To get an evidence base, database, to understand that, we're going to see different positive and negative values if we don't use the lower female cut-off versus the higher male cut-off. And this will be extremely important as we further discuss today, not only for diagnostic purposes, for ruling in or ruling out of heart attack based on the third universal

definition of myocardial infarction. But also, as we'll discuss, the risk stratification in an ACS as well as a non-ACS patient.

Dr. Allan Jaffe: Well, I think the important issues are going to come down to whether or not there are going to be clinical differences even though we know that there are clearly differences in reference values. And that there are some data starting to emerge that we'll discuss, I'm sure, that suggests that that is indeed the case; and if so, we need to be terribly careful because as we'll talk about, women have not done nearly as well with acute coronary syndromes compared to men over time.

Dr. Fred Apple: Right, I think one thing the audience has to be very, very clear about is, as they evaluate the literature, not to get lost in the concept that all assays are going to give the same male/female gender specific cut-offs. Every assay has to be evaluated independently; there are going to be subtle differences and a 5 nanogram per liter for one assay is not going to be equivalent to an assay from another manufacturer, both for male or female cut-off.

Dr. Allan Jaffe: Absolutely!

Bob Barrett: Well, how do outcomes in women with acute coronary syndrome disease compared to those of men?

Dr. Allan Jaffe: Well, the women tend to do substantially worse than their male counterparts when they present with an acute coronary syndrome. There are probably multiple reasons for that. One part of that, is that diagnosis is harder in women. Because we know over time, there have been several studies to suggest: a, that their symptoms are less typical and there's a recent paper, in the *Archives of Internal Medicine* emphasizing that. In addition, they tend less often to have elevated values of cardiac troponin than do their male counterparts, so that one part of that is diagnosis.

There's a second component and a third component, which is that women who present with acute coronary syndromes tend either to be one of two groups; either the very young with lots of comorbidities like diabetes and obesity, often they are smokers and have used oral contraceptives; or they're quite substantially older. So they have differences and comorbidities and the consequences of these differences and comorbidities plus some diagnostic issues have led to the fact that women get less guideline-recommended therapies than do men, go to the cath lab less often than do their male counterparts, and there's been an argument as to whether or not that means we overtreat men or undertreat women, and probably both are correct. So that these

substantial differences do point to the diagnostic area as one potential way.

And certainly for CKMB, which we used to be used and has led to a lot of the literature that we're talking about today, there were gender-specific cut-offs that were usually ignored by both laboratorians and clinicians. And I think that probably also contributed to missing some of the diagnoses in these women who are additionally hard to diagnose.

Bob Barrett: Yeah, and Allan, as I hear you talk as a cardiologist, and I know your background of lab medicine, do you think that this concept will be essentially conceptualized by the emergency medicine physicians when they're going to evaluate patients, women, men, older women, younger women. Do you think in that educational concept, we can nail that so that this process and thought process will be utilized as you just explained?

Dr. Allan Jaffe: I think it's terribly important that we do and it's one of the reasons why I think talking about it is so important. When the assays have been rolled out in Europe and in much of the rest of the world for High-Sensitivity Troponin-T, this issue was ignored. I think there's more sensitivity with a High-Sensitivity Abbott Assay and the differences between the normal values are substantially different.

So I think this is our opportunity to really start to educate, and I think if we don't make this an important part of our educational programs to emergency physicians, and to cardiologists, and to use our laboratory colleagues as a way of facilitating that, then this won't happen in the interest of "simplicity" and I think that would be a shame.

Dr. Fred Apple: And one other thing I think it's important for the audience to understand here is that a lot of the literature coming out of European-based literature, which is really a good literature, but the patient population that are being evaluated with men and women, whether it's the Abbott High-Sensitivity or the Roche T-Sensitivity is a different population than we will see coming through our doors with symptoms suggestive of ACS. So, the risk stratification and even the cut-offs used, may be significantly different as we unroll literature in U.S. versus the rest of the world. Would you agree or disagree with that?

Dr. Allan Jaffe: I think that's terribly important. There's a heterogeneity in Europe; to be fair, some institutions and emergency rooms do evaluate consecutive patients, but often since cardiologists actually staff many of the emergency rooms in some of the major countries in Europe, the patients are then sub-selected so that the frequency and therefore, the pre-

test probability of any given elevation being due to AMI or an acute coronary syndrome is substantially higher in many of those centers in Europe, including those that have tended to publish in this area. And that means that those data are much less applicable to what we're going to see in the United States than they would be in Europe. That said, there are some places in Europe, like in Sweden, with the publication that Ola Hammarsten had in *Clinical Chemistry,* that take the same approach that we take in the United States. And it's one of the reasons why his data looks so different than the data of so many others from Europe.

Bob Barrett: Well, how good are the data that gender-specific cut-off values will correct this problem?

Dr. Allan Jaffe: Well, as of right now, we're just developing the data out there and as I indicated earlier, the original experiences in Europe and a lot of the published literature, unfortunately, didn't take this into account. But as one begins to scrutinize those patients and begins to look in more detail at what was described, it's clear that often, there seemed to be some gender differences, they are just more articulated and brought out as part of the process. That said, there are now data in multiple different circumstances that suggest that gender-specific cut-offs may be necessary. But, there are also opposing data.

So for example, if one takes, as Fred indicated earlier, this highly enriched population where they have lots of MIs, the frequency of very low values that sort of fit just in that sweet spot between the normal values in men and women is relatively small. And therefore, when one does an analysis, one would say, "Well, maybe the percentage of patients that fall there are not so great." On the other hand, if one intentionally then, as Nick Mills and some preliminary data from the UK has shown, specifically targets men versus women, a big effect is seen in the patients who present with chest pain. So, I think that more data are necessary that looks specifically at this problem.

I think if one scrutinizes the literature, there are signals there that this ought to work. But there are likely going to be because of the way of the studies have been done previously and continued to be done, some ambiguities about it, until such time as we do the appropriate targeted studies which really are now ongoing in several different places. And I think one of the reasons to talk about this is to make sure when we do similar studies in the United States, that we look at this in a very intense way to make sure that we have the data to make this decision in a clear cut manner.

Dr. Fred Apple: So, when we look at our editorial, our subtitle—"Isn't it time for equality?"--and you know what, as a soft aside, between living with my wife and three women in my household, I've been for equality for a long time. But my big concern here is just kind of what you said, if we look at our editorial, when we look at one of our paragraphs as we speak: The Abbott High-Sensitivity Assay has an overall 99th percentile 26 ng/L, from one of the studies that we've looked at. And then when broken down by sexes, 16 for females and 34 ng/L for males.

My concern, and I'd like your opinion on this, is that clinicians are going to get worried that by lowering that cut-off, I'm going to see more positives and the cardiology community will be concerned. Because it's going to potentially increase the rate of positivity that they're going to have to then be concerned, well, speaking of risk stratification, but maybe bring them to some type of procedure. The emergency medicine physician I think will like the concept because they don't want to miss any. So what are your thoughts on that?

Dr. Allan Jaffe: Well, I think that's one of the tensions that really does exist; which is that there is a tension between emergency department physicians who are interested only in sensitivity, and cardiologists who are much more in tuned with wanting to make sure that specificity is served.

I think that that shouldn't interfere with the use of different gender specific cut-offs because I really think the key issue to be looked at here is going to be the change, i.e., the delta, over time. That's something that will be terribly important for all patients, because there are going to be a lot of elevations with high sensitivity. If people try and diminish them by raising the threshold, one will reduce the efficacy and the important diagnostic information that is in the high-sensitivity assays.

So the way to deal with that problem is to emphasize the use of a changing pattern of values because that is more indicative of an acute situation whether it's an acute coronary syndrome or it could be myocarditis or pulmonary embolism, there are varieties of things that can do it. But that's the right way to make that distinction; and I think again, that's something we need to work hard on to make sure everybody, both cardiologist, emergency department, and laboratorians understand that, embrace that concept, and teach it and the lab community can help very much by reporting when there are significant changes in values in their result section, of their laboratory results.

Dr. Fred Apple: And I would really agree with that changing concept, in that from a laboratory medicine point of view, I think the two

manufacturers that have assays out there commercially now have done a really good job and I hope others will, too, with the imprecision of these assays down the middle of the normal range we're seeing imprecisions of five to seven to 10, less than 10%. So we will not have to worry as these assays unroll in the practice that the imprecision is the problem of why we're seeing changes.

Dr. Allan Jaffe: I would say that the one caveat that we need to be very careful about it, whenever we talk about the delta and I just feel obligated to at least state it over and over and over again is that one needs to be careful about the timing. If patients come in early, deltas will work very well but there are going to be subsets of patients who come in late. And one of the problems that occur when one begins to emphasize the delta too much is that sometimes clinicians don't put in that additional thought of what the timing is and if patients come in late, as often patients with acute coronary syndromes do because some of them can have symptoms for days, et cetera. Then one may not see a delta but with that caveat, I think the delta is terribly important to embrace.

Bob Barrett: Well, doctors, if it turns out the gender-specific cut-off values are not needed for patients with acute coronary syndrome, well then, are they needed at all?

Dr. Fred Apple: Well, Bob, I think we have to ask that question, I don't think that will be the final answer, but let's say that were the case, I think the scenario would be, we have other pathologies, other ideologies of patients that come in to the emergency room that aren't ACS and the biggest one group we struggle with, that I'm sure Dr. Jaffe will comment on this is the supply demand population that come in with heart failure, that come in with myocarditis, that come in maybe with a drug-related supply demand issue that are often either classified as a type 2 MI or even a increased troponin with not an MI.

And, what we're going to learn with these high-sensitivity assays including the gender-specific, lower cut-off for women and higher cut-off for men is we're going to be using this to determine acute myocardial infarction in these patients who may have type 2 MIs. And the power of this will be to allow, not only for that diagnosis but we've learned that patients who are not categorized an ACS type of MI, but some of these non-ACS type 2 MIs are not given the same appropriate therapy, because these therapies out there are not uniformed and are not managed the same way patient-to-patient because the ideologies of the pathologists are different.

And we've learned that an increased troponin, in these populations if not managed appropriately, have a significantly worst short-term and long-term outcome for mortality and its data growing for even major adverse cardiac events. So as we move into these gender-specific cut-offs, there's going to be a wealth of studies that need to be performed and need to be evaluated, unfortunately; but fortunately on an assay-to-assay basis, company A: Abbott, company B: Siemens, company C: Roche; we will have to not generalize but utilize each assay to develop outcome based-evidence for risk stratification. Because what I would love to see in our future as we talk about deltas or gender-specific cut-offs, that we will develop hazard or odd ratios based on that presentation of a troponin in these patients that will help put a person into a level of care that'll get someone's attention, whether it's a cardiologist or if a neurology person is taking care some of closed head trauma with a troponin increase secondary to that injury. I think it'll be vitally important that a team approach, based on a biomarker gets into play.

Dr. Allan Jaffe: Yeah, I know I agree wholeheartedly and one of the points to make is that, say type 2 MIs tend to have less marked elevations of cardiac troponin. So there is a circumstance in which one may well have many more differences than in the type 1 MIs which tend to be bigger events and therefore, may manifest for most, if not all patients, large changes and large values for troponin. And the same thing is the case for individuals who may present -- who may not have an acute myocardial infarction at all or may have some other disease process, or may just simply be in the community if one begins to look at community screening.

There are tremendous data out there now to suggest the importance of low levels of troponin increases, and their ability to predict who is at risk for the development of heart failure and there's a growing number of epidemiologic studies that suggest that we now can identify patients who might be at risk subsequently for the development, let's say, of heart failure particularly. It'll be terribly important and very likely that in that circumstance, the use of gender-specific cut-offs would be even more important.

So not only are there another subset of acute diagnoses where gender-specific cut-offs would be important, but there is this screening in the community effort for which troponin are going to be terribly important and subsequently for risk stratification in a variety of diseases where it will be important as well. Let me just use one example. There are very nice data now that have evolved suggesting that the use of high-sensitivity troponin will markedly improve the ability to detect who is at risk when patients have atrial

fibrillation, whether they come in acutely or more chronically to a doctor's office.

And utilizing high-sensitivity troponin, one can then go and risk-stratify not only for mortality but interestingly enough for the frequency of embolic events in these individuals. No one has looked yet in the published literature at the gender-specific cut-offs and the need for them, but it's very likely that there, in that circumstance, will be the need again because women have lower values at baseline, different values to optimize the ability to make those critical distinctions. And there are a large number of additional ones that I would argue are likely to evolve over time.

Dr. Fred Apple: So, you got to make a promise to me then that by the time my daughters have to be evaluated in 40 years, 50 years, 60 years, you'll be around to optimize the therapy based on gender-specific cut-offs, can you do that?

Dr. Allan Jaffe: Well, as you know, whenever your daughter needs something, I will take care of it.

Dr. Fred Apple: Okay.

Bob Barrett: Dr. Allan Jaffe is from the Cardiovascular Division and Department of Laboratory Medicine and Pathology at the Mayo Clinic. And Dr. Fred Apple is from the Department of Laboratory Medicine and Pathology, Hennepin County Medical Center in Minneapolis. They have been our guests in today's podcast from Clinical Chemistry.

I'm Bob Barrett, thanks for listening.