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Rapid Rule-Out of Myocardial Infarction Using a Single High-Sensitivity Cardiac Troponin I Measurement Strategy at Presentation to the Emergency Department: The SAFETY Study

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Guest: Dr. Fred Apple is the Medical Director of the Clinical and Forensic Toxicology Laboratory and Principal Investigator of the CLIA-certified Cardiac Biomarkers Trials Laboratory at the Hennepin Healthcare Research Institute in Minneapolis, Minnesota.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the American Association for Clinical Chemistry. I'm Bob Barrett. Consider a patient who presents to the emergency department with chest pain and shortness of breath. Does she need to be admitted for further evaluation and treatment of myocardial infarction? Or is her risk so low that she can be safely discharged?

As emergency department overcrowding becomes a challenge at many hospitals, a rapid test to rule out myocardial infarction shortly after presentation would be immensely valuable, helping to improve patient satisfaction and conserve healthcare resources. High-sensitivity cardiac troponin assays have been evaluated for this purpose, but appropriate thresholds to rule out myocardial infarction at presentation remain to be determined.

A new research article appearing in the June 2023 issue of *Clinical Chemistry* addresses this question by establishing a single measurement rule-out threshold with high sensitivity and negative predictive value for myocardial infarction, as well as 30-day adverse events. In this podcast, we are excited to welcome back the article's senior author, Dr. Fred Apple. Dr. Apple is the Medical Director of the Clinical and Forensic Toxicology Laboratory and Principal Investigator of the CLIA-certified Cardiac Biomarkers Trial Laboratory at the Hennepin Healthcare Research Institute. He is also a member of the 'Universal Definition of Myocardial Infarction and Myocardial Injury' Global Task Force. Dr. Apple, could you please start this out by talking about the clinicaltrials.gov SAFETY study?

Fred Apple: So, the SAFETY study was an investigator-initiated study, which I received funding for from Siemens Healthineers. The acronym SAFETY stands for Use of High-Sensitivity Cardiac Troponin In Ruling Out Emergency Patients With Acute Myocardial Injury and Infarction. It was a study that I designed and we participated enrolling patients from October of 2020 through January of 2021.

Bob Barrett: So why is it important to derive assay-specific thresholds for each assay used to rule out myocardial infarction?

Fred Apple: Well, the SAFETY study was one of many studies that was looking to derive a cutoff threshold at a lower limit to safely consider sending patients home from the emergency department, in this case using a single sample at presentation. The importance of deriving assay-specific decision concentration is: the world knows that cardiac troponin assays, whether we're looking at the high-sensitivity assays of troponin I or the high-sensitivity assays of cardiac troponin T, they are not harmonized and they are not standardized. Therefore, since a cardiac troponin result from one assay will not be the equivalent, or the same, as a troponin assay from another assay, it's critically important that each assay on their own goes through the process of a clinical study or trial and derives the optimal threshold cutoff, mostly based on to make sure there's patient safety at the end of the day, if the clinicians consider sending patients home.

And the one point I want to make here, just to conclude this answer, is we all need to keep in mind that troponin itself is just a test. It's not a standalone test. It's another tool for clinicians to use, with their clinical judgment and other tools like imaging or EKGs, to assess the ability to send a patient home early from an emergency department.

Bob Barrett: Okay. Dr. Apple, your study evaluated consecutive enrolled patients and measured troponin in fresh samples. Why is this more appropriate than using frozen, biobanked samples?

Fred Apple: So, our lab has always tried to address this type of observational study using fresh samples because it's more representative and reflective of what the troponin was at the time before a sample was handled, frozen, and then stored away and pulled out of a freezer, weeks, days, or even years later. Fresh specimens often and sometimes measure differently after freeze-thaw cycles. And therefore, the ideal world is you want to mimic what happens in the clinical world, where we draw specimens from patients they come to the lab. And in a research study, if you can accommodate the use of measuring fresh samples, it's one less concern of having a sample that may have showed some kind of discrepancy due to the processing and freezing of a sample.

Bob Barrett: So how do the results of your study compare to other US and European studies that have addressed single measurements at presentation?

Fred Apple: So, when we designed this study, we took a very, well, I'll say aggressive metric to define our threshold. It was

predicated on deriving a cutoff that was based on a concentration that gave a 99.5% negative predictive value and a 99% sensitivity.

Because in the field, cardiologists and emergency medicine physicians are often looking at patients who come a little differently as far as ruling in or ruling out. But safety is the number one thing. So, when we looked at our studies and this comparatively to, let's say, other US and European studies. First in the US, our study is really the only study based, and this is on the Siemens Atellica IM High-Sensitivity Cardiac Troponin I assay. It's the only study in the US that actually has done consecutive enrolled patients using fresh specimens. The only other US study was not really a clinicaltrials.gov study. It was a study done by Siemens. It was called the High US Study that was utilized to use for data submission to the FDA for 510(k) approval.

And the things that sometimes when you do a study that is not consecutive, there are sometimes the patients, just the patients are not necessarily focused the same way you would see on a patient who would come into the emergency department that's getting a troponin order based on clinical indication. Often the FDA studies are more focused on patients with high suspicion of myocardial infarction, specifically type 1. And that's true often for the European studies. There's two other European studies based on the Siemens assays, and they also more or less focus on patients that are at higher risk, patients with, who say, often use the term chest pain. We often enroll patients with symptoms suggestive of ischemia.

So the concepts of the study are the same. But we felt the design of the study we used being consecutive, being fresh samples, was the most ideal, and being in an inner city where this study was carried out. And that is also one of the limitations; it's a single site study, but being in an inner city in the US. When we looked at this type of single sample rule-out, you're seeing patients maybe with not insured, first time they showed up in the hospital, there's greater chance that we see more ethnicity, more diversity in race, more comorbidities, and actually a greater percentage of women that we observed in our population.

Bob Barrett: Well, looking ahead, let's put on our prediction caps and do you think future laboratory test reporting will include a risk assessment?

Fred Apple: One of the things I think that the people listening to this podcast should look at, I'm just going to point you towards one table. Excuse me, look at figure number 1. And I call this figure, I call it the Mills model figure. And this is the important thing to think about. This is the way we present our data. I

did mention our goals were 99.5% negative predictive value and 99% sensitivity. But what we did here, is that we started at the limit of detection of the assay, and then we ramped it up one nanogram per liter of high-sensitivity cardiac troponin at a time. And we present data that shows how the sensitivity and negative predictive value changes over that one nanogram change.

And you do, what we do is we picked the optimal cutoff, in this study was less than 10 nanograms per liter. And why that is important, because that's the cutoff we're going to look at then to say 'what is the risk safety assessment?' There's two things to think about here. Number one, in the US, the FDA does not allow laboratories to report results below the limit of quantitation, which is a 20% imprecision value. Yet the data would show that even imprecisions that are slightly higher than 20% do add great value to clinicians to use as a tool for the possible assessment of sending patients home.

Second, what we've learned is when you are in the inner city and the rapid EMS services we have, is that you do get a large percentage of patients that are early presenters. Right? And the early presenters in our study, we had about 1100 patients in our study. In our early presenters, we had 122 patients that showed up within 2 hours. And that concept is important when you think about risk, because the early presenters, they're so early, they might not have had time to allow troponin to increase in those that had possible injury.

So taking all that into account, when we look at our data, we find that in our inner city single sample population, we were very successful at identifying 46% of patients that were potentially able to be sent home at great cost savings to an institution. Now, when we look at those, that's a good number if they go home. But then we have to then go downstream and say, what's the 30-day risk? Ideally, we'd like to have 180-day or a year risk. But we looked at the 30-day risk, and we used the concept of 1% or less should be at risk of a 30-day adverse event.

And what our data showed was only one patient would have been missed in this population, looking at someone who had an NSTEMI, we had one patient that we would have missed that had an adverse cardiac event. And that's very powerful type of information when you're looking at risk. So what comes from this is that down the line, in future, we will develop odds ratios. There'll be assay based odd ratios with confidence intervals because you just can't use a single number because there's a wide range of confidence intervals. Again, if you look at Figure 2, it'll show those confidence intervals. We want the clinicians to get the full idea, even though we may say it's a 99.5% negative predictive value, depending on the prevalence of disease, if the confidence

intervals goes down to 90%, maybe a clinician won't want to use that number, and they might choose a lower number for clinical utilization.

Bob Barrett: Okay, well, finally, Dr. Apple, what's the key message you'd like readers to take away from this study?

Fred Apple: The key message is all laboratories, number one, should be transitioning to a high-sensitivity assay. Choose the assay that works. Number two, you should invest time partnering the lab, partnering with emergency medicine and cardiology, to develop an algorithm that could be used either as a single sample rule-out like this safety paper does, or in the group of patients that involve, let's say, a questionable early rule out uses maybe a 0/2-hour sample monitoring to develop a value for rule out. Because at the end of the day, if we can send, in this case, 40% to 50% of patients home safely, the amount of institutional savings, the personnel that have to see and touch patients, will be a great savings to our healthcare system. Plus, patients don't want to stay in the hospital if they don't have to.

So if we can allow the patient to go home, feel safe, and if necessary, the clinician will say, we'll follow you up with your primary care physicians for further evaluation. I don't know anyone that I've ever known that would rather spend the night in their own bed than have to spend the night in a hospital bed.

Bob Barrett: That was Dr. Fred Apple from Hennepin County Medical Center. He published a new research study on the use of a single high-sensitivity troponin I result to rule out myocardial infarction in the June 2023 issue of *Clinical Chemistry*, and he's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.