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HOPEing That a PEACEful Resolution for the Clinical Utility of High-Sensitivity Cardiac Troponin in the Ambulatory Setting Will Improve Laboratory Testing

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Guest: Dr. Peter Kavsak from McMaster University and the Hamilton Regional Laboratory Medicine Program, based at the Juravinski Hospital and Cancer Centre in Hamilton, Ontario.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett.

High-sensitivity troponin has firmly established itself as the go-to laboratory test when evaluating myocardial infarction in patients presenting to the emergency department with chest pain or other suggestive symptoms. Some have advocated expanding its use even further to predict cardiovascular events in healthy asymptomatic outpatients, but the literature is plagued by contradictory information.

Can high-sensitivity cardiac troponin predict cardiovascular events in the outpatient setting? Are troponin T or I assays preferred, or do they provide equivalent information? If they can be used in this context, do currently available assays exhibit the necessary imprecision? How should results be reported to clearly communicate patient risk? Finally, what practices should laboratorians adopt to ensure adequate analytical performance at this low concentration range?

A new editorial, appearing in the June 2025 issue of *Clinical Chemistry,* summarizes a meta-analysis published in the same issue comparing high-sensitivity troponin assays for the prediction of cardiovascular events in outpatients and highlights what laboratorians can do to support this testing.

In this podcast we welcome the article's author. Dr. Peter Kavsak is a Professor in the Department of Pathology and Molecular Medicine at McMaster University and a Clinical Chemist at the Hamilton Regional Laboratory Medicine Program based at the Juravinski Hospital and Cancer Centre in Hamilton, Ontario. His research focuses on cardiac and cancer-related laboratory diagnostics, particularly high-sensitivity cardiac troponin assays.

So Dr. Kavsak, you've chosen an interesting title for this editorial: HOPEing That a PEACEful Resolution for the Clinical Utility Of High-Sensitivity Cardiac Troponin in the Ambulatory Setting Will Improve Laboratory Testing. Where did the inspiration for this title come from?

Peter Kavsak: Yeah, well, it's not necessarily *War and Peace*, but there's two great *New England Journal* publications named--studies, clinical studies, the HOPE study and the PEACE study. Why I have inspiration on them is those two studies were actually pretty game-changing in regards to clinical medicine.

In brief, the HOPE study published 25 years, in 2000, really demonstrated that in high-risk individuals for cardiovascular disease, treatment with a statin would reduce cardiovascular death, MI [myocardial infarction], and stroke, and it was a really powerful finding in that the American Heart Association decided to amend their guidelines to say that for secondary prevention patients should be on ACE inhibitors, and that's what the HOPE study demonstrated, and the HOPE study stands for Heart Outcomes Prevention Evaluation.

Fast forward four years later, the PEACE study was done and it was trying to assess if this added benefit of ACE inhibitors would also be translated to a lower risk population. And PEACE was an acronym and the long title is Prevention of Events with Angiotensin Converting Enzyme Inhibitors. In actual fact that study didn't show the same type of benefits. And so, it's really important because all these studies had samples collected and the investigators from these studies then started to probe high-sensitivity troponin in those populations to assess whether or not it had added utility for risk stratification.

And why I say that is that the fundamental differences on HOPE and PEACE relate them to the patient population, a high risk versus a lower risk population, and so the findings of both those studies when we actually applied high-sensitivity troponin test to them were a little bit different. And so that's why it's not *War and Peace*, but I'm more hopeful that looking now at the latest data, that there could be a better understanding on how to use cardiac troponin in the non-acute setting, and that's where the title came from, hoping that there's now a peaceful resolution to high-sensitivity because that's what's happened with the latest publication in *Clinical Chemistry*. At least, that's my feeling on the matter.

Bob Barrett: What does the paper you describe in the editorial tell us about the differences between cardiac troponin I and cardiac troponin T outside of the emergency setting?

Peter Kavsak: Yeah, yeah. I alluded to a part of this before and the fact is that the findings of the utility of high-sensitivity in the HOPE study and in the PEACE study populations were a little bit different. Briefly, the HOPE population demonstrated that high-sensitivity troponin could actually be predictive of future MI for both troponin T and troponin I.

Whereas the PEACE Study just indicated that it was really just troponin I with the high-sensitivity assays that could predict future MI. And the actual fact for the, I'm assuming 12+ years, there's many, many studies that were trying to understand differences between cardiac troponin I vs cardiac troponin T for future cardiovascular risk stratification. Is it just for heart failure or is it for MI? Could it be for both? And are there really differences between cardiac troponin I and cardiac troponin T?

And the sum of it, this large meta-analysis that was done and it was published in *Clinical Chemistry*, in over 250,000 patients where they were able to assess MI, and why I stress that is, that was the outcome that was different. Lot of groups said MI is only going to be able to detect a troponin I and not troponin T, whereas others said, well, maybe both assays could do. And I think with this large meta-analysis, which is really the only way you can do that, I mean they screened over 5,000 studies. They narrowed down to 50, which is the nature of these meta-analysis, so 1% of the studies, but from them what they found was that there's no difference, that the risk stratification ability for future MI outside of, and in fact, even in, but in this population, which is community ambulatory population, it was the same if you used high-sensitivity troponin I or high-sensitivity troponin T.

And I think that's a really important finding because now we can move past these discussions and these arguments and these debates to see, are there differences between the two? And of course there's always going to be differences between proteins and analytical assays, but overall they're actually very similar. And in fact, to quote the late Maya Angelou, "in minor ways they differ, but in major ways they're the same," and I think that's what this meta-analysis has indicated, that we can use these tests outside of the hospital setting in the same manner and I think that's really a powerful message and I hope will push the field further.

Bob Barrett: That's very interesting. How do you think laboratory testing using the high-sensitivity cardiac troponin assays will improve?

Peter Kavsak: Yeah. So I really think that what is really important for laboratory medicine is that we'll see changes once there becomes clinically utility. And right now there's been a real understanding that a very low cardiac troponin concentration, at least in the emergency setting and the hospital setting, can be used to perhaps identify people at low risk for immediate MI, and so that's where our focus has been on and we're trying to understand better ways to understand that, to utilize that, to monitor that in the laboratory.

But that's not where it ends. The story actually starts to begin outside of the hospital setting is that we need to really be monitoring these assays at the slow end if we're really looking at for risk stratification. And right now there's a little bit of a gap in that we're not really able to have really good documentation or evidence to use. What are the right quality control materials at the lower end? What's important for risk stratification? How do we know if the assay is in control versus not control? And a lot of our information on this has really been done at the emergency setting to rule in and rule out an MI. But I think that will change once we start to use these assays in the setting as what the paper mentioned as well as other studies to date to say outside of the hospital setting and the ambulatory population. For providing information on risk stratification, we better be sure that we're providing reliable and accurate results at that low end because people's management and treatments may change depending on that.

Bob Barrett: Tell us, are there any gaps for implementing testing in this area?

Peter Kavsak: Yeah. And I mentioned this a little bit briefly in the previous response, but I would just want to maybe expand on the comments is that the IFCC and what was formerly AACC, but ADLM, produced a document in 2018 on some recommendations, laboratory recommendations on monitoring high-sensitivity troponin assays, and it was really important because it highlighted the fact that we really wanted to monitor the quality control, the precision, or imprecision below the 99th percentile, the "normal range."

Well, if we're going to start to apply these assays for further risk stratification in that "normal range," what we need is we need to develop different quality control, or different ways to assess quality control, in that low range and possibly within the single digits. It's not enough to say "oh, well, I have a quality control, my assay is working well below the 99th percentile." We may actually have to start to monitor assays at clinically important cutoff concentrations down low where we know that those elevations above a certain threshold portend a higher risk for patients and perhaps would necessitate different types of interventions and further assessment.

So, I think we'll need to advance our understanding of cardiac troponin, especially quality control, at the lower end. Depending on clinical utility we may need to expand the quality control measurements, the metrics that we use currently, so that we're able to provide reproducible and robust information to clinicians and patients, as patients are more owners of their health information so that they're able

to be informed on what their values are and what they can do with those.

Bob Barrett: Well, finally Dr. Kavsak, let's look ahead. What do you think the future will hold for testing high-sensitivity cardiac troponin in the ambulatory setting?

Peter Kavsak: I mean this is interesting because this concept, back in 2007 we published a paper in *Clinical Chemistry*, it was actually on long-term outcomes on "normal concentrations" and not with a high-sensitivity assay. And I remember back then receiving a message from a patient understanding, they're talking with their cardiologist to figure out how do we interpret this? What should we do? I'm at higher risk but how do I interpret that? And now I look and almost 20 years later, I think some of those questions still exist, and I think that's what we need to do. So the future we'll hold is that we need to actually start to relate risk to concentrations of cardiac troponin and really for the most part numerical cutoffs right now, a lot of the studies say higher or lower values. What we really need is cutoffs. I know really exciting to have a continuous variable, but we still want to look, maybe should we develop assay-specific cutoffs for this?

But perhaps what's probably more exciting is perhaps the integration of cardiac troponin into further risk stratification. And there was just a publication in *JACC, Journal of the American College of Cardiology,* in April of this year that looked at that ability, looking at high-sensitivity, and this was in over 60,000 patients, where they were able to see the addition of high-sensitivity troponin, either I or T, so consistent with these meta-analysis findings in *Clinical Chemistry*, but if you added these to standard lipid and cardiovascular risk measurements, it actually improved risk stratification for those that are at intermediate, they reclassified into higher risk. And that's really important because they lay the groundwork: how do you start to build testing of cardiac troponin outside of the obviously hospital setting for further risk stratification?

And I think that's what the future holds is that: how do we integrate high-sensitivity troponin results at the lower end so that they encompass risk with other clinical and biochemical factors for sure, and how do we in the laboratory maintain that we're provided robust, reliable, and accurate results?

And so, 20 years ago I couldn't even tell the patient how to think of this, and I remember writing my message back trying to be as eloquent as possible, saying like this is just the start and there's going to be more research here. I mean again in 20 years, and obviously I mean the authors of the meta-analysis looked at over 5,000 papers just on high-sensitivity, and over 250,000 patients, and even more than that, there's

even publications that look at 160,000 individuals with high-sensitivity, and that was published in *JAMA* last year.

So now the wealth of information and knowledge that we've gained here, really I can see in the not-so-distant future a proper way to start to report risk with high-sensitivity assay, and what I really hope is that it won't take another 20 years before this becomes a meaningful test to be used for patients outside of the hospital setting.

Bob Barrett: That was Dr. Peter Kavsak from McMaster University in Hamilton, Ontario, Canada. He wrote an editorial in the June 2025 issue of *Clinical Chemistry* describing high-sensitivity cardiac troponin measurement in the outpatient setting. He's been our guest in this podcast on that topic. I'm Bob Barrett. Thanks for listening.