Guest: Dr. Joan Voltaire is from the Departments of Internal Medicine and Cardiology at the University Hospital Basel, Switzerland.

Bob Barrett:	This is a podcast from *Clinical Chemistry,* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.
	Coronary artery disease is the most common cause of death and morbidity in developed countries, resulting in substantial healthcare costs. The early detection of this disease and identification of patients at risk for myocardial infarction has enormous medical and economic value. The introduction of high-sensitivity cardiac troponin assays has revolutionized early diagnosis of myocardial infarction, but what about their use for identifying patients at risk with stable coronary artery disease?
	A recent study to address that issue as well as a comparison of high-sensitivity cardiac troponin I and troponin T assays appeared in the November 2018 issue of *Clinical Chemistry.* The research was done in both Swiss and German laboratories and we are pleased to have one of the authors from Basel, Switzerland, as our guest in this podcast. Dr. Joan Elias Walter is a resident and research fellow at the Departments of Internal Medicine and Cardiology of the University Hospital Basel and examines biomarkers in relation to coronary artery disease. So, Dr. Walter, what was the overall aim of the study that you and your co-workers recently published?
Dr. Walter:	Yeah. Well, it is pretty straightforward actually. The aim of the study was to directly compare high-sensitivity cardiac troponin I and T in the detection of functionally relevant coronary artery disease, and as you know, both high-sensitivity cardiac troponin I and T are already an integral part in the workup of acute coronary syndromes. But evidence is increasing that they might also be helpful in the risk stratification of patients with suspected functionally relevant coronary artery disease which is manifoldly more common presentation.
	As an example, last year, we published in *Clinical Chemistry* a work on a rule out strategy for functionally relevant coronary artery disease based on an ultrasensitive cardiac

troponin I assay. And also cardiac troponin has been identified as a robust event marker by many research groups. Nevertheless, there were several clinical questions that needed to be addressed before considering the transition to clinical practice. First, do high-sensitivity cardiac troponin I and T as currently in use, provide comparable diagnostic accuracy in the detection of functionally relevant coronary artery disease? Second, does a sex-specific approach provide higher diagnostic accuracy? And third, do the cardiac troponins I and T provide comparable prognostic accuracy for future cardiac events? In our study, we addressed these questions.

Bob Barrett: So, both high-sensitivity cardiac troponin I and troponin T assays seem to have provided only modest diagnostic accuracy for functionally relevant coronary artery disease. Is this enough to make them clinically relevant?

Dr. Walter: This is a key question, and I think in this context, it is important to assess the present situation. The clinical course of coronary artery disease is highly variable and it is extremely common when applying the conventional anatomical definition. At the moment, pretest risk stratification based on symptoms and patient characteristics alone is far from perfect. More and more cardiac imaging techniques are used in patients with very low pretest probability and it was found that about one-third of cardiac imaging stress tests are potentially inappropriate. This causes annual costs of more than 500 million U.S. dollars in the United States alone. Though we also saw in this study that the clinical assessment of the treating physician, that integrated all medical information available before stress testing, actually had a relatively poor diagnostic accuracy. And by the way, also significantly lower than high-sensitivity cardiac troponin I or T alone.

And what I'm trying to say is that there is a rather large room for improvement in the pretest risk stratification of patients with coronary artery disease. And when considering the huge population at risk, I think that despite the modest diagnostic accuracy of high-sensitivity cardiac troponins, it can actually yield a clinically relevant improvement. And I also want to point out that we explicitly focus on functionally relevant coronary artery disease. In other words, inducible ischemia due to coronary artery disease as our outcome and not just on pure anatomically coronary artery disease. And in that sense, high-sensitivity cardiac troponin as the marker of cardiac ischemia can directly reflect the pathophysiological process which really strengthens the position.

Thus, high-sensitivity cardiac troponin as the marker of cardiac ischemia can directly reflect the pathophysiological

process which really strengthens its position as a potential risk stratification tool. Lastly, already in current clinical practice there are patients with available, but unused high-sensitivity cardiac troponin concentrations. In patients presenting with angina to the emergency department and after acute myocardial infarction has been ruled out using high-sensitivity cardiac troponins, stable angina might be considered during further workup. With high-sensitivity cardiac troponin concentrations already available, why not utilize them?

Bob Barrett: Doctor, your study noted a clear difference between the high-sensitivity cardiac troponin assays risk stratification based on the limits of detection and on the 99th percentile of the population. How do you explain this?

Dr. Walter: Well, we noted that the LOD of the high-sensitivity cardiac troponin I assay provided a sensitivity of around 95% for a safe rule out of functionally relevant coronary artery disease, but the LOD of the high-sensitivity cardiac troponin T assay, on the other hand, only provided about 80% sensitivity for the rule out. While this can certainly be explained by the assay's differences in analogical sensitivities, there also were significant differences for the 99 percentile as you mentioned. And the I assay's 99 percentile provided about 95% specificity for the rule in while the T assay's 99 percentile only provided around 80% to 90% specificity. And at least to some extent, these differences could reflect that the assays' 99th percentiles are actually not biological equivalent, and in that context, our group previously found that with the use of these approved clinical decision values, almost one out of five myocardial infarction patients had inconsistent diagnosis between T and I.

So, also for patients with suspected functionally relevant coronary artery disease, simply using the LOD in the 99 percentile is not advisable at all, and the cutoffs need to be tailored.

Bob Barrett: Your group has previously published on uniform rather than sex-specific cutoffs for patients with suspected acute myocardial infarction, but in this study, you suggest that sex-specific cutoffs may be preferred for functionally relevant coronary artery disease. Why the difference?

Dr. Walter: Well, the emergence of high-sensitivity cardiac troponins provided a new diagnostic window. When enabling the measurement of very low circulating cardiac troponin levels, far below the 99 percentile and consistent to prior work, we found in our study that high-sensitivity cardiac troponin I and T levels were higher in men than in women, and this might be due to differences in comorbidities. But studies

also suggest that the larger male heart size and thus, the corresponding higher number of cardiomyocytes undergoing apoptosis and renewal is responsible for this observation.

Now, in case of suspected functionally relevant coronary artery disease, the concentrations of interest are often closer to the LOD and sometimes even lower. In other words, they are in the range which is currently defined as healthy. Thus, even slight systematic differences between men and women can have important implications as we have seen in our data. In case of acute myocardial infarction, the concentrations of interest are generally around the 99 percentile. And also, it was shown that women and men with an acute myocardial infarction have actually comparable high-sensitivity cardiac troponin concentrations.

Bob Barrett: Finally, doctor, let's look ahead, what's the next stage of your investigation and what do you see as its potential impact on coronary artery disease?

Dr. Walter: Yeah. As also noted in the editorial by Dr.s Adamson and Mills, there is a stacking amount of evidence that high-sensitivity cardiac troponins provide important and robust information regarding pathophysiological processes in the cardiovascular system, but the appropriate clinical application of this information needs to be further elucidated.

I think we need to consider that, as I mentioned before, there are already patients with suspected angina and unutilized but available high-sensitivity cardiac troponin concentrations in current clinical practice.

Dr. Walter: I also think it is important to note that the current risk stratification approach to suspected coronary artery disease is far from perfect. Having the high and increasing prevalence of coronary artery disease in mind, this puts a tremendous strain on any healthcare system aside of potentially putting patients at risk. Any improvement of the current coronary artery disease workup could have really a great impact as such at the Cardiovascular Research Institute in Basel, we believe that blood biomarkers and potentially their combination but also for instance the further improvement of stress ECG evaluation, could have a significant clinical impact. Point of care testing, proteomics, machine learning for ECG analysis are all aspects that we are exploring.

And for short-term, I think the integration of currently employed cardiac biomarkers and well-established anatomical coronary artery disease pretest risk scores, so that the scores can also predict the functional relevance,

would provide physicians with a really important insight. In the end, no available piece of information should be discarded unnecessarily, but there needs to be an evidence-basis for the appropriate use.

Bob Barrett: That was Dr. Joan Elias Walter from the Departments of Internal Medicine and Cardiology at the University Hospital Basel, Switzerland. He has been our guest in this podcast about the latest published research in high sensitivity cardiac troponin assays and coronary artery disease. That article is in the November 2018 issue of *Clinical Chemistry*.

I'm Bob Barrett, thanks for listening.