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Can High-Sensitivity Troponins Help to Level the Playing Field in Cardiovascular Disease Prevention between Women and Men?

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Guest: Dr. James de Lemos is University of Texas Board of Regents' distinguished teaching professor and holds the sweetheart ball Kern Wildenthal distinguished chair in cardiology at UT Southwestern Medical Center.

Bob Barrett: This is a podcast from *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett. Unfortunately, gender differences persist in the prevention and management of cardiovascular disease. Improved risk-based treatment algorithms may help to reduce these gender disparities by facilitating the targeting of prevention and treatment strategies to those high-risk women who are more likely to benefit. However, to accomplish this precision medicine goal, objective tools are needed to better characterize cardiovascular risk in women. An important paper in the October 2021 issue of *Clinical Chemistry* adds to a growing body of evidence supporting high sensitivity troponin I and T for risk assessment of women in primary care practice. That paper by Dr. Dorien Kimenai and her colleagues in the United Kingdom was the subject of an editorial in that same issue by Dr. Rebecca Vigan and Dr. James de Lemos.

We are pleased to have Dr. de Lemos as our guest in this podcast. He is University of Texas Board of Regents' distinguished teaching professor and holds the sweetheart ball Kern Wildenthal distinguished chair in cardiology at UT Southwestern Medical Center. His primary research interests are in the early detection, risk assessment, and management of cardiovascular disease with a particular focus on the role of cardiovascular biomarkers. So, first of all, Dr. de Lemos, what are some of the gender differences and disparities and cardiovascular disease that our listeners should be aware of?

James de Lemos: Well, women tend to be diagnosed later and less often with cardiovascular disease than do men. For example, in the setting of a heart attack, women get less aggressive treatment. They go to the cath lab less often, and they go later than do men. When you think about women with suspected coronary disease, they get less testing than men do. And when they get diagnosed, they receive fewer treatments than men do. For example, they get treated with statin agents at a lower rate than do men. And the reason for these disparities is multifactorial. Part of it is that women do have lower rates of all cardiovascular disease as compared with men, particularly at younger ages (at an older ages they

tend to catch up). But there also maybe issues including bias of medical practitioners that lead to less aggressive diagnosis and treatment of women.

Bob Barrett: Please tell us a bit about the paper, your editorial covers. Were there any surprise findings?

James de Lemos: This is a really interesting paper from a group evaluating a large cohort of individuals in Scotland where they evaluated high sensitivity troponin T and I measurements and associated those with cardiovascular outcomes over long-term follow-up. And the focus of their paper was comparing outcomes associated with abnormal troponin levels in men and women in the general population; and the big news here is that the predictive value of troponin both high sensitivity troponin I and T was greater in women than men. And I'd say that's unexpected in one sense. On the other hand, it has been reported in a couple of other papers before. So -- but it is still a bit of a surprise because I don't think people would have assumed that from a pathophysiology standpoint before these studies were done.

Bob Barrett: So, why do women have lower circulating concentrations of troponin than those found in men?

James de Lemos: Well, that's an interesting question and one that probably I can't completely answer. We know that in multiple studies, including the one that was reported in this issue of *Clinical Chemistry*, women have levels of circulating component that are considerably lower than do men and that leads to suggestions that if we're using troponins for heart attack diagnosis that the threshold to diagnose a heart attack should be lower in women than men. The reasons for this are multifactorial. Part of it is that women have smaller hearts than men on average. And so, that's a part of it. There's been a lot of speculation that differences in sex hormones may contribute to differences in troponin levels that estrogens may be protective, androgen may be harmful in terms of cardiac injury. But in point of fact, when you account for menopausal status, the sex difference doesn't go away including when you also account for cardiac size. So, there are some factors like smaller heart size and sex hormones that contribute, but other factors that we haven't fully delineated. And I had pointed out that the paper in this issue of *Clinical Chemistry* really can't help us understand that because they didn't do the kind of detailed imaging measurements and assessments of sex hormones that we need to understand this better.

Bob Barrett: You mentioned that troponin may level the playing field between women and men for risk prediction. Could you expand on that? What do you mean by that?

James de Lemos: Well, the interesting thing again here is that most predictive tests are demonstrated to be of potentially more value in men than women because women have lower rates of heart disease. And here, in this study, the opposite is shown. And if you drill deeper into the findings -- so, the finding here was that the predictive ability of troponin T and I was greater in women than men and they assessed this both by looking at the area under the receiver operating characteristic curve which is the measure of discrimination.

But also, the adjusted hazards for a certain threshold of troponin, and they see that the hazard is higher with a higher level of troponin in women than men. And really the question is, is that because high troponins are worse in women or because low troponins are better in women? And this study doesn't actually provide the data to get at that. But prior work from Torbjørn Omland and his group in Norway suggest that the real difference is that low troponin levels where non-detectable troponin in women is associated with extremely good outcomes in very few cardiovascular events. But then, in men, low troponin isn't completely protected. The flip side is that troponin is high, the absolute risks appear to be quite similar in men and women. So, what troponin seems to do is if it's abnormal, level the playing field and associate with very similar absolute risks in men and women. The flip side is that when it's undetectable in men, the hazard of being male still persists so that men with an undetectable troponin may still have some risk for cardiovascular disease.

The interesting thing is this is actually been seen in other disease states. For example, when you look at the benefits of invasive therapies for patients with acute coronary syndromes, they don't do as well in women than men. But if you look at women specifically, that have abnormal troponins which is a relatively smaller proportion of women, the risk associated with that is the same in after heart attack in women and men and the benefit of invasive therapies appear to be the same. So, this might be a paradigm that extends across multiple different cardiovascular disease states in the study that we're talking about today, it's risk prediction of the population. But that's also been shown. For example, in the emergency room in a hospital among women with chest pain symptoms who have abnormal troponins.

Bob Barrett: Well, finally, Dr. de Lemos, look ahead. What do you believe are the implications of these findings and how can they be translated into practice?

James de Lemos: Great question. I think the implications here are that women with abnormal troponin levels are at substantial risk for future cardiovascular events. This study focused on atherosclerotic events. But in fact, the greatest predictive value of troponins in the population isn't for atherosclerosis; it's for heart failure

events. And I would expect the findings to be mirrored if one looked at heart failure. And it can be difficult for practitioners to accurately evaluate risk in women, and this study clearly shows that troponins are a valuable tool to help identify women at the highest risk for vascular events and those women should be targeted with the therapies that we know are already beneficial, things like statins, blood pressure lowering therapies and such.

But in the future, really, this biomarker paradigm that can really identify women and men at high risk who might not otherwise be recognized based on traditional risk factors is one that's really important. But the next steps really have to be to translate this from a lot of consistent epidemiology data to clinical trials and then eventually to clinical practice. And I think our group and many others are very interested in getting this sort of risk prediction using biomarkers in addition to the traditional risk factors into the electronic medical record, and providing that information to practitioners in their prevention visits so that they might identify individuals at unexpected risk -- and in this case, women at unexpected risk, and target them for more intensive preventive therapies and prevent some of these future vascular events and heart failure events that we know occur in the setting of an abnormal troponin level.

Bob Barrett: That was Dr. James de Lemos, professor and chair in cardiology at the University of Texas, South Western Medical Center. he has been our guest in this podcast on how using high sensitivity troponins help to level the playing field in cardiovascular disease prevention between men and women. His editorial, as well as an original scientific paper examining sex differences in cardiac troponin I and T and the prediction of cardiovascular events, appears in the October 2021 issue of *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.