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The Slow Progress in Developing Better Long-Term Cardiovascular Risk Assessment in Women Continues

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Guests: Dr. Allan Jaffe and Dr. Leslie Donato from the Mayo Clinic in Rochester, MN.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. Heart disease remains the leading cause of death in both men and women, and substantial effort has been focused on identifying factors that increase one's risk, enabling early intervention. As we've learned more about the causes of heart disease, it's become apparent that risk factors are different in men and women, a finding that has gone largely overlooked in historical disease prevention programs.

Another limitation of the current risk prediction algorithm is a relatively short time horizon, only ten years, which is inadequate to support disease prevention programs in younger individuals. Fortunately, both of these shortfalls are being addressed, highlighted by a recent research paper using data from the Women's Health Study, in which novel cardiac biomarkers were used to estimate risk over a 30-year time period.

A new perspective article, appearing in the May 2025 issue of *Clinical Chemistry*, places this article in the context of previous work, summarizes the new findings, and describes how a new approach could revolutionize cardiovascular disease prevention in women. In this podcast, we are pleased to speak with the article's lead and senior authors. Dr. Allan Jaffe is a Professor in the Departments of Cardiovascular Medicine and Laboratory Medicine and Pathology, and holds the Wayne and Kathryn Preisel Professorship for Cardiovascular Disease Research at the Mayo Clinic in Rochester, Minnesota. Dr. Leslie Donato is a clinical chemist and Associate Professor in the Department of Laboratory Medicine and Pathology, also at the Mayo Clinic, and Dr. Donato, let's start with you. Let's get basic first. What exactly does cardiovascular risk mean, and why is it important to assess in everyone?

Leslie Donato: Well, thank you for the question, and thank you for having us. I would like to just start by thanking the research group, Dr. Ridker and his colleagues, who published this influential study, which is really just part of a long line of important studies in this field. So, to answer your question of what does cardiovascular risk mean, we are talking in the context of primary prevention, which means it's the risk of developing

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cardiovascular disease, such as a heart attack or a stroke, or peripheral artery disease in a person with no previous history of this disease. The reason why it's so important to assess that risk is that in any given individual, several interactions such as dietary and lifestyle modifications or pharmacotherapy can be started in that patient that will ultimately lower that risk of developing the disease, and the earlier you identify a high-risk patient, the earlier those interventions can be initiated.

Bob Barrett: So, Dr. Donato, how is cardiovascular risk typically assessed in primary prevention?

Leslie Donato: Well, the initial evaluation includes patient-specific data such as the patient's BMI, their diet and activity lifestyle, their family history of developing disease, and things like that. Additionally, one of the major tools physicians will use to assess cardiovascular risk is by using one of the many cardiovascular risk disease calculators that have been developed. These calculators use patient-specific data, which is taken by the calculator, and then a background algorithm is used to calculate the probability that that person will develop cardiovascular disease within the next ten years of their life. Inputs to that calculator are things that the patient can't control, such as the patient's age or sex, but additionally, modifiable risk factors such as total cholesterol, HDL cholesterol, blood pressure, and even smoking status. So, these risk calculators have been typically used in clinical practice will estimate a person's risk over the next ten years of their life, which is good information to have, but ultimately may not be long enough to assess whether a young individual is at risk during their entire lifetime.

In addition to those risk calculators, physicians can use additional biomarkers that have been tested and are known to directly contribute to cardiovascular risk. There are many biomarkers that a physician can use, but the ones that are really important for the study we are talking about today are three biomarkers. So, those are a low-density lipoprotein cholesterol, or LDL cholesterol, high-sensitivity C-reactive protein, or hsCRP, and thirdly, lipoprotein little a, or Lp(a). These three biomarkers are really important and have a long history of data in the literature showing that they are directly responsible and contributory to the initiating events of atherosclerosis progression that initiate cardiovascular disease.

Bob Barrett: And just to follow up one more time on this, why is early intervention so important?

Leslie Donato: So, you can think of cardiovascular risk in terms of lifetime exposure to disease-causing agents. And I like to think of this is similar, in similar terms to the concept that we are probably

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all well aware of, the concept of pack-years of smoking. So, in lung disease, if a person is a smoker, we know that the number of years a person spends as an active smoker is directly proportional to their risk of developing lung disease. We know that that's the case because the more years of smoking and the lungs being exposed to those damaging agents, the more disease that is formed afterwards throughout the patient's lifetime. The same concept applies to cardiovascular risk assessment. The longer a person lives with elevated lipids or lives a sedentary lifestyle, et cetera, the more likely they are to develop atherosclerosis, the progenitor of cardiovascular disease. So, the earlier those contributing factors for cardiovascular disease can be mitigated within a patient's lifetime, the more benefit can be realized for lowering that risk and preventing cardiovascular disease, and we all know that changing those lifestyles, dietary lifestyles, activity lifestyles, and implementing healthier lifestyles is easier in young people than it is an older people.

Bob Barrett: Well, Dr. Jaffe, let’s bring you into the conversation. What is novel about this Ridker study in terms of improving cardiovascular risk assessment?

Allan Jaffe: Thank you, Bob. There are several aspects that are really important to understand. The very first one is that it focuses on risk in women. Many previous studies have used exclusively male populations, or women have often been underrepresented, if indeed women are included at all. Despite that, we know that the risk in women is unique in many ways. For example, women develop cardiovascular disease later in life compared to men, and there are many biologic factors in women, such as variable hormone expression, bile acid and lipid profiles, proteomic expression profiles, that are strikingly different, and all can significantly affect a woman's risk for developing cardiovascular disease. So, doing a study on women is really unique and important.

Secondly, it’s a very long-term study, 30 years, and it suggests that in a very early stage, because these women were relatively young in their early 50’s as a mean age when the study started, that one is able at an early point in time to identify factors that might lead to cardiovascular disease long before its overt, and then looking out 30 years, it does predict what’s going on. Finally, it does in a graded fashion. We look at the overall results and we say they’re predictive, but if you look at each quintile, for every quintile that one is in, in terms of risk, the risk is higher than the preceding one. So, many of these values are not values for high-sensitivity CRP or LDL or Lp(a) that would mandate therapy, but when you put them all together, they end up with the profile that is compelling from the point of view of someone who’s interested in

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prevention, of leading one to really strongly consider treatment at an earlier point in time.

Bob Barrett: So, what did this study find?

Allan Jaffe: Well, what it found was that after 30 years of follow-up, those three biomarkers that are well known in the primary prevention category of LDL-c, high sensitivity CRP, and the Lp(a), are all predictive both individually and together synergistically. That means that the inflammation is additive at least, and it means that looking at all three of these, because they represent different biologic contributions, is important. They did additional analysis to make sure that the analysis of the biomarkers was not confounded by the use of things like hormone replacement therapy, body mass index, and renal function, and it wasn't. As I indicated earlier as well, there was a graded response across quintiles and as the values increased, so did the risk, but I would argue, and we'll talk about this later, that if one is interested in prevention, that one can make a compelling case for moving these thresholds further and further down to end up helping women by starting preventive therapies at an earlier point in time, as Dr. Donato so nicely outlined.

Bob Barrett: Well, Dr. Donato, tell us, how will the results of this study improve patient management?

Leslie Donato: So, the results of this study are important because physicians can be confident that measuring these well-known cardiovascular risk contributing factors early in a patient's life can effectively predict the onset of cardiovascular disease up to 30 years in the patient's future. That's huge. That's a really long time and will be a really powerful tool, and we're talking about a one-time measurement, which is again really, really impressive. A lot of cardiovascular risk mitigation involves patient buy-in to conform to those healthier lifestyles that we talked about before. So, agreeing to take risk-lowering medication, or you know, modifying a diet, or increasing activity levels. We know that when these risk-lowering tools are implemented earlier in life, like these healthy habits, are easier to maintain and the risk-lowering benefits are realized for a longer period of time. So, the concept is that the earlier interventions are adopted, the fewer years the patient spent in pro-atherogenic conditions. So, going back to our early correlation to those pack-years of smoking and lung disease, we're effectively reducing the pack-years of smoking, but in terms of lowering cardiovascular risk exposure.

Bob Barrett: Well, finally, Dr. Jaffe, what additional questions might be explored next, and are there any final thoughts you would like to share?

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Allan Jaffe: Well, I think one of the important concepts here is that often we tend to underestimate risk, especially in the younger individual, and there have been several initiatives that have been stimulated in our society and one of the primary advocates for these has been Valentin Fuster's what's called "primordial risk prevention." That is to say, emphasizing to all of us at the time from birth on about healthy eating, healthy habits, exercise, diet, and the like. What this study suggests is, that if you look at markers which often represent markers of some of the conditions that come when one doesn't have such a healthy lifestyle, that they're very, very predictive of long-term events. So that it fits nicely into this idea primordial prevention and I would argue that it suggests that even at values that are lower than conventional data that we use to decide when treatment should start, when these markers are additively increased, all right, even modestly, that that makes a pretty good argument for starting therapy earlier versus later. I think this study also has probably, over time, additional samples, and it would be helpful I think for this team to remeasure those samples serially, because for example, if a given marker was sort of on the cusp of kind of, "Gee, I'm not sure" and the clinician is unsure whether or not to treat, looking again downstream in five years or eight years, or even ten years, and saying they're going up, is very likely another clue that clinicians could use to again, become more aggressive about this preventive approach. So, I think that the bottom line for clinicians is that we have been under-aggressive, need to be more aggressive in looking at these things, considering lowering our cut-offs, and embracing primordial prevention.

Bob Barrett: That was Dr. Allan Jaffe and Dr. Leslie Donato from the Mayo Clinic in Rochester, Minnesota. They authored a perspective article in the May 2025 issue of *Clinical Chemistry,* summarizing advances in the prediction of cardiovascular risk in women, and they have been our guests in this podcast on that topic. I'm Bob Barrett. Thanks for listening.

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