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This is the podcast from *Clinical Chemistry*. I am Bob Barrett. Women, blacks, and individuals living in the south-eastern United States, the so-called "stroke belt" where stroke mortality is approximately 50% higher than in other parts of the country all have a higher prevalence of increased high-sensitivity C-reactive protein, or CRP.

A report published in the September issue of *Clinical Chemistry* showed that all studied vascular risk factors as well as lower socioeconomic status were associated with increased serum concentrations of CRP. But these variables did not explain the observed differences, especially for blacks and women.

Dr. Mary Cushman, is the lead author of the report, and a Professor of Medicine at the University of Vermont in Burlington, where she is Director of the Thrombosis and Hemostasis Program of the Hematology/Oncology Unit, and she is our first guest in this podcast.

Dr. Cushman, what were the major findings of your study, regarding the prevalence of elevated C-reactive protein?

Dr. Mary Cushman: Well, when we use the standard clinical cutpoints that are used in practice, which is a CRP greater than 3 milligrams per liter being elevated, and our study which was a general population sample of people, 40% had high levels. And these high levels were seen more commonly in women, 47% of them and in African-Americans where 48% had high levels.

These rates are higher than has been seen previous studies, and this could be for many reasons. It might be that our study included people who were more like the average population than other studies, because of the way we've recruited people. And it could also be that they were more recently recruited, and because of that, they have higher obesity rates than has been seen in other studies.

We know that obesity is a major cause of elevated CRP. So, this may be part of the explanation for that.

Host:

So what risk factors were related to high CRP?

Dr. Mary Cushman: Well, as I said, obesity was important, and it was the strongest determinant of CRP elevation. Fully 56% of the people who were obese had elevated CRP. However, all of the standard cardiovascular risk factors and most demographic factors were related to high CRP level. Even things like lower income level, and lower educational status are related to higher levels.

When we looked closely at the prevalence of higher CRP, we were interested in the differences by ethnicity, comparing blacks to white, and comparing men to women. And we evaluated this in great detail, and what we showed is that levels were higher in African-Americans and in women, but only part of that difference was explained by accounting for the differences and other characteristics of people.

So it makes a certain amount of sense that African-Americans would have higher CRP, because we know they are at higher risk of vascular events like stroke and heart-attacks. But it makes less sense for women to have higher levels compared to men, because women tend to have a lower risk of stroke in MI compared to men, except when they get to very older ages.

Host: What exactly did you find when evaluating the potential practice implications of these findings?

Dr. Mary Cushman: Well, the correct guidelines for using CRP in practice suggests that practitioners measure CRP in certain patients to reclassify their predicted risk of cardiovascular disease. For example, you might calculate a score called the Framingham Risk Score, which will place each person into categories of low, medium, or high level of predicted risk. CRP is then used to attempt a better classification of those people, into low, medium, and high levels of risk, and usually we are talking about predicting the ten-year risk of heart disease or stroke.

So, for example, if a person is at medium risk, based on their Framingham Risk Score and then CRP is measured and found to be elevated, this would move that patient to the next higher level of risk or to the high level of risk. And that might change the treatment regimen for prevention of cardiovascular disease. For example, it might reinforce the idea of treating a person with a statin for hyperlipidemia or aggressive blood pressure management.

So, if you apply this logic, which is what we did in our study, and to our study population, we found that more African-Americans than whites, and more women than men would move to a higher level of predicted risk.

So, for example, among women, who were at medium baseline risk, based on their Framingham score, 61% of black women and 56% of white women would be moved to the high level of risk. This is a huge number of people. Among men at medium risk, less people moved. So 38% of black men, and 31% of white men would be reclassified to a higher level of risk.

Now these sorts of reclassifications may or may not be appropriate for the women especially, since they tend to have lower risk of disease than men. It's important to recognize that in the current study which was a cross-sectional study, we can't yet evaluate whether this sort of reclassification is important clinically until we have the outcome events available for analysis.

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At that time, we'll be able to test whether these reclassifications are correct or not correct. And then in addition, as we've pointed out in editorial to this paper by Drs. Albert and Cook, the classification based on the standard risk factors will also need to be recalibrated for our population, because scores like the Framingham score might not work correctly in our population. So, the impact of the risk factors that contribute to that score will have to be sort of recalibrated to our population. And once we have enough vascular outcomes in the study during the follow-up phase, we will be able to do those important analyses.

Host: Well, what about region? It's been reported that the REGARDS studies assessing why stroke mortality is higher in the Southeast states, did CRP differ by region?

Dr. Mary Cushman: Yes, it did. So, people who live in the Southeastern stroke belt states, what they are called have nearly a two-fold higher risk of dying of stroke, than people living in other parts of the country. And one of the main purposes of the regard study is to determine why this is. And we previously reported that differences by region in the major stroke risk factors only explains about one quarter of this expected difference in risk of stroke by geographic regions.

So, here we showed that elevated CRP was more common in the stroke belt states. Now, there were differences in the other risk factors related to CRP, like diabetes and obesity. So, when we accounted for the geographic differences and all of those risk factors, it turned out that there was a 10% higher chance of elevated CRP in the stroke belt states compared to the rest of the country. This difference wasn't as great as the difference comparing African-Americans to whites, but it could play a partial role in explaining the geographic patterns of stroke mortality. And we won't know for sure about this, until we have the follow-up outcome events in the study where we'll be able to evaluate stroke outcomes by regions and see if CRP is playing any role in explaining this.

Host: An editorial in the September issue of *Clinical Chemistry* suggests that from a pathological perspective race and ethnic differences in cardiovascular risk require further

examination. Co-author of the editorial, Dr. Nancy Cook, suggests that only when we have data regarding cardiovascular endpoints, can we be certain of the causes for the excess stroke mortality among U.S. blacks, women, and people living in the stroke belt.

Dr. Cook is an Associate Professor in the Division of Preventive Medicine at the Brigham and Women's Hospital in Boston, Massachusetts, and she is also our guest in this podcast.

Tell us Dr. Cook, why is it important to look at CRP or other markers among blacks and residents of the so-called "stroke belt"?

Dr. Nancy Cook: Well, it's known that blacks in particular and also residents of the stroke belt have higher rates of cardiovascular disease, and they don't seem to be explained by lipids or other traditional risk factors. Among blacks in particular, there are complex relationships among these things. They seem to have less plaque and lower CAC scores. But their lipid levels aren't that different from whites, and their rates of cardiovascular disease are much higher.

So, while some of the differences might be explained by hypertension, for example. It doesn't seem to be all explained by those other factors. So, inflammation as assessed by CRP may explain some of the relationship, and the explanation for the differences.

Host: So, could CRP be the explanation for the differential risk based on data from the REGARDS study?

Dr. Nancy Cook: Well, the REGARDS study did find that CRP levels were elevated among blacks and among those in the stroke belt, so it's about 30-40% elevated among blacks to the smaller elevation about 10% among those in the stroke belt. So, this could potentially be the explanation for the increased risk.

Host: Does the elevated CRP directly translate into increased risk for cardiovascular disease?

Dr. Nancy Cook: Well, that's difficult to say. You can't directly compare scores as they have. They look at assessment of risk based on the Framingham Risk Score and the Reynolds Risk Score. The Framingham score does not include CRP, and then Reynolds risk score does.

However, those scores were developed on different populations with different baseline risks of disease. In addition, and primarily the outcome used was different in the two scores. The Framingham score even for

cardiovascular disease included softer endpoints, such as angina, TIA, and intermittent claudication, while the Reynolds score just included MI stroke, revascularization, cardiovascular mortality.

So, the rates are much higher in Framingham. And when you compare these scores, it looks like people are being classified downwards, even though they have high CRP. But that's mainly due to a different in scores.

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Host: Well, with that in mind, what else is needed to answer the question?

Dr. Nancy Cook: Well, first of all you need to compare scores developed on the same data. For example, scores with and without CRP, such as was used in the Physician's Health Study or the Women's Health Study. They also need to look at rates of CVD by information. These authors did not have CVD outcomes. However, they are planning to collect them, and then in the future that will be very important information, and then they can look at the rates, in blacks and whites, see if they differ by CRP, and see whether CRP can explain some of the differences in rates by race.

Another point is that these scores are generally not available among blacks. They are developed among largely white populations. So they may not offer the same level of risk prediction in another population if directly applied there.

Host: What do other data show that high CRP being associated with higher risk?

Dr. Nancy Cook: There are a lot of studies that show that CRP is associated with higher risk of cardiovascular disease. They are at least ten other studies that show that risk increases as CRP goes up.

The question is, whether this can translate into a clinical utility for risk prediction, and several studies now have shown that that's true. At least in U.S. populations, the Women's Health Study, the Physician's Health Study, and the Framingham Heart Study have all shown that including CRP and risk prediction model will improve risk stratification, and in the sense of getting more accurate estimates of predicted risk.

Host: There is even some controversy about CRP and whether it's a causal factor for cardiovascular disease. What do other data show?

Dr. Nancy Cook: Well, whether or not CRP is causal and whether it actually causes disease has been part of the controversy. But some studies have suggested that it's not causal, mainly studies that use so-called Mendelian Randomization, which look at genetic effects. However, there are a lot of questions and controversies regarding those studies, and I don't think you can definitively exclude CRP as a causal risk factor.

However, even if CRP is not causal itself, it looks like it's an important marker for inflammation, and inflammation might be the underlined cause of the disease, which is then reflected in the CRP levels. So, while the CRP molecule may or may not be causally associated or in the pathway, itself inflammation seems that it is. And in fact the JUPITER study show that among those with high CRP, lowering it with statin did lead to greatly reduced rates of cardiovascular disease.

So, it looks like CRP plays some role, whether it's just providing an indication of information or whether it's causally related itself, it does seem to have some importance in development of cardiovascular disease.

Host: Dr. Mary Cushman is a Professor of Medicine at the University of Vermont in Burlington. Dr. Nancy Cook is an Associate Professor in the Division of Preventive Medicine at the Brigham and Women's Hospital in Boston, Massachusetts. They've been our guests in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thank you for listening!

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