Clinical Chemistry

Association of Growth Differentiation Factor-15 with Coronary Atherosclerosis and Mortality in a Young, Multiethnic Population: Observations from the Dallas Heart Study

Bob Barrett: This is the podcast from *'Clinical Chemistry'*. I am Bob Barrett. Growth differentiation factor-15 is produced by cardiomyocytes in atherosclerotic lesions under stress conditions. High concentrations of growth differentiation factor-15 are associated with many abject cardiovascular conditions, but the relationship of GDF-15 with atherosclerosis had yet to be defined.

In the January 2012 issue of *'Clinical Chemistry'* Anand Rohatgi, an Assistant Professor of Medicine at the University of Texas Southwestern Medical Center and his team of researchers examined data from the Dallas Heart Study, a probability based population sample of ethnically diverse adults collected between 2000 and 2002, and concluded that higher concentrations of growth differentiation factor-15 is independently associated with subclinical coronary atherosclerosis and mortality, and its potential role for risk stratification in the general population merits further evaluation.

Dr. Rohatgi is our guest in this podcast. Doctor, what is GDF-15 and why is it important in cardiovascular disease?

Dr. Anand Rohatgi: Growth differentiation factor-15, it's a protein that's the member of the transforming growth factor superfamily. It's similar to TGF-beta and it's produced by a number of tissues in the body including the heart, inflammatory cells like macrophages, endothelial cells, vascular smooth muscle cells and adipocytes among other cells.

It's important in cardiovascular disease because investigators have found that it is expressed in the heart muscle after it's been injured. So during periods of ischemia, it's secreted and expressed to the heart muscle, and has a protective effect on the heart. It can prevent the heart from developing hypertrophy and other types of damage.

Bob Barrett: Put your study findings in the context of what's known now about GDF-15 and other cardiovascular biomarkers such as troponins and natriuretic peptides.

Dr. Anand Rohatgi: It's a good question. So a number of investigators have measured GDF-15 in various populations and tried to correlate them with cardiovascular outcomes, but the first initial sets of studies looked at GDF-15 levels in older patients and in patients with heart failure. And they found that levels of GDF-15 were elevated in the people with heart failure and the people with the highest levels of GDF-15 in particular greater than 1800 nanograms per liter had worse outcomes. They were at increased risk of dying.

And then other investigators extended those observations to people who were being admitted for acute coronary syndromes, both non–ST and ST elevation MIs, coming into the emergency room with chest pain. In all of those cohorts, elevated levels of GDF-15 on presentation were correlated with increased risks of dying primarily.

Some studies have correlated relationships within GDF-15 and nonfatal myocardial infarctions, but those findings have been somewhat inconsistent. The more consistent and robust findings have been with elevated levels of GDF-15 and increased risk of mortality and death.

More recently the Rancho Bernardo Study investigated GDF-15 in an older community-dwelling population. So these were healthy people but they were older, mean age of about 70. And they also measured GDF-15 in these people and found that those with higher levels had an increased risk of all-cause deaths, cardiovascular deaths, and non-cardiovascular death as well.

So our findings add to that literature in a number of ways. One is most of these studies were not population-based studies. They were people with disease presenting to a hospital or some type of cardiovascular disease at baseline. Our population is a healthy population from Dallas County and much younger than most of the other population studies. Our age was a median age of 44, and it was ethnically diverse. Like other markers, most studies of markers in cardiovascular disease have been studied in mostly Caucasian subjects, and mostly male subjects and 50% of our dataset was African-African and 50% were women.

So our findings were extended to those populations as well, and we found similar relationships with increasing GDF-15 levels with increased risk of death, cardiovascular deaths, and interestingly, atherosclerosis.

So GDF-15 had not really been explored all that well in prior studies with actual coronary atherosclerosis. Very few studies have actually found that association. But we found an association with coronary artery calcium measured by CT scan, so that those with the highest GDF-15 levels had a two-fold increased risk of coronary calcium in their arteries. That was a new finding as well.

Bob Barrett: And do you anticipate clinical applications of using GDF-15 measurements in patients with cardiovascular disease?

Dr. Anand Rohatgi: That's a great question. Right now, there have been very few markers that have been studied, that have made it to

clinical application in cardiovascular disease, and among them, the ones that we do use are the troponins, markers of myocardial necrosis, both to diagnosed heart attacks, acute coronary syndromes and for prognosis, and the natriuretic peptides, BNP and NT-proBNP. And those markers also are related to increased risk of heart failure and increased risk of death, both the troponins and the natriuretic peptides, and they are used clinically.

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They complement each other, the troponins and the natriuretic peptides. They measure different things, but in general that are structural disease markers and markers that damage to the heart muscle in some way.

GDF-15 is very interesting, because it's also a similar marker in the sense that it's a marker of damage to the heart muscle, but it's reflecting something different because in our study even when we adjust it for BNP and troponin, the relationship between GDF-15 and death was still there, and others have shown the same thing that even when adjusting or accounting for troponins and natriuretic peptides, BNP and NT-proBNP, these associations between GDF-15 and increased mortality persist.

So because of the number of investigations that have had such a consistent finding between GDF-15 and death just like the troponins and the natriuretic peptides, I do think that as part of a multimarker panel, GDF-15 is a very likely contender to be part of that panel, just because of its prognostic ability apart from the troponins and natriuretic peptides. So I think there is a potential there.

Bob Barrett: So Doctor, what's next? Given these findings what's the next step in your research?

Dr. Anand Rohatgi: Well, in the Dallas Heart Study, what we have done is with the leadership of James de Lemos and others here, we have assembled a host of markers that have been measured in the Dallas Heart Study in an effort to find the ideal markers or set of markers to predict cardiovascular disease, and through that, we investigated GDF-15 among some other markers.

So our next step is to see just like what I have mentioned before, see what the potential of GDF-15 is as part of a multimarker panel that will likely include the troponins and the natriuretic peptides, and perhaps some other novel markers to see if putting GDF-15 in the multimarker panel will really improve our ability to predict cardiovascular disease outcomes, and particularly, cardiovascular deaths.

And we have now had over 2,000 of our participants come back for serial follow-up in terms of imaging for atherosclerosis, and all of our participants, over 3,000 participants have been followed for cardiovascular outcomes including death. And so what we are now in the phase of doing is assembling strategies, assessing multiple markers including GDF-15 to see if there is a role for multimarker panels to predict risk.

Bob Barrett: Dr. Anand Rohatgi is an Assistant Professor of Medicine at the University of Texas Southwestern Medical Center. He has been our guest in this podcast from '*Clinical Chemistry*'. I am Bob Barrett. Thanks for listening!

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