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Interpreting Cardiac Biomarkers in the Setting of Chronic Kidney Disease.
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Guest: Dr. Christopher deFillippi is the Vice Chair of Academic Affairs at the INOVA Heart and Vascular Institute in Fairfax, Virginia.

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.

Chronic kidney disease is a common disorder whose prevalence increases with age. Patients with chronic kidney disease frequently undergo testing for troponins and natriuretic peptides, since many have cardiac comorbidities and acute or chronic symptoms that may represent heart failure or an acute myocardial infarction. The interpretation of cardiac biomarker results in such cases is challenging. This potentially results in missed opportunities to direct appropriate treatment. The January 2017 special issue of *Clinical Chemistry* features a Review intended to improve understanding of this issue.

Dr. Christopher deFilippi joins us for this podcast to describe the importance of summarizing the literature base that has developed specifically around interpreting cardiac biomarkers in patients with chronic kidney disease. Dr. Christopher deFilippi is the Vice Chair of Academic Affairs at the INOVA Heart and Vascular Institute in Fairfax, Virginia which is part of the INOVA Health System in Northern Virginia. His research and clinical interests are focused on the interaction of renal and cardiovascular disease, and on how renal disease influences the interpretation of cardiac biomarkers. So Dr. deFilippi, let's start with this, why write a Review about cardiac biomarkers in patients with chronic kidney disease?

Dr. deFilippi: Well, it's important for everyone to recognize, and I think most of your readers do, that renal disease is more than a niche topic, that simply confounds the interpretation of cardiac specific biomarkers. But it's a common comorbid condition that's present in a large minority of patients with or without symptomatic heart disease. For example, it's estimated at 30, and up to 50% of patients with heart failure also have some element of impaired renal function. Impaired renal function is often defined clinically as an estimated glomerular filtration rate less than 60 mls per minute. And the first part of the review that's being published outlines the epidemiology of chronic kidney

disease and its association with higher cardiovascular morbidity and mortality.

Bob Barrett: Okay. Before we get into the weeds here, let me get your opinion on, if elevated biomarkers in patients with chronic kidney disease who are asymptomatic are the result of decreased renal clearance or increased production?

Dr. deFilippi: Yeah. So there's been a lot of controversy over the years when looking at common clinical cardiac specific tests, and these included the cardiac troponins and the natriuretic peptide tests. My reading of the literature and findings around research is that there are strong associations with biomarker levels and cardiac comorbidities. And this is less so an issue of, really, renal clearance of these proteins. And in the Review by Dr. Herzog and myself, we discuss cardiac pathophysiology that is often unique to patients with renal disease, so it's important for readers to recognize that renal disease tracks with a lot of the same cardiovascular risk factors. And the severity of renal disease is often associated with disparity of traditional risk factors but also there are unique pathophysiologies related to renal disease such as higher calcium phosphorus product, deposition of calcium, and acceleration of atherosclerosis and cardiac fibrosis.

Bob Barrett: So is it just that renal disease is associated with systemic diseases like hypertension and diabetes that are cardiac risk factors, or does renal disease convey independent aspects to cardiovascular disease that would be reflected by elevations in cardiac biomarker levels?

Dr. deFilippi: We think that there are unique aspects. And that you don't have to be a patient on renal replacement or in dialysis to have the influence by the unique aspects of impaired renal function. Let's say just hypertrophy, left ventricular hypertrophy is very common in patients with all levels of renal impairment. Hypertrophy is associated with cardiac fibrosis and risk for sudden death as well as vascular calcification, increased risk of ischemic heart diseases, myocardial infarction, unstable angina.

Bob Barrett: Are there any caveats that need to be considered when using cardiac troponin assays to diagnose some myocardial infarction in patients with chronic kidney disease?

Dr. deFilippi: You know, there are. I think since the mid-2000s when there came to be a recognition that both whether you're using cardiac troponin I or cardiac troponin T, that there can be elevations of these symptomatic patients, yet these are relatively uncommon in patients who are not receiving renal replacement therapy. That's going to change tremendously in United States, as has already been seen in Europe and throughout much of the rest of the world with the addition

of these high sensitive troponin assays. In fact, a publication which we review that was published about a year ago in *Circulation* demonstrates that most of the commercially available high sensitive troponin assays, whether it's troponin T or troponin I from a number of vendors, will represent values in asymptomatic renal disease patients who are not on dialysis that are above the 99% cutoff when they're asymptomatic.

So what needs to be done is carefully follow the universal definition for myocardial infarction, and look for that rise and fall, as well as other findings that might be associated such as electrocardiographic changes or new imaging changes.

Bob Barrett: We're anticipating a transition to high sensitive troponin assays in the U.S. in 2017. What can we anticipate with respect to diagnostic accuracy from myocardial infarction with these assays compared to the sensitive assays now used in clinical practice?

Dr. deFilippi: As I have just mentioned, we can anticipate that the majority of patients with chronic kidney disease will have a value above the 99 percentile, what we define as normal in a healthy general population. However, the caveat is that the overall accuracy of the test is still about the same as the sensitive test that we now use, with the recognition that we need to look at that rise and fall and look at serial biomarker levels and never rely on a single measure that's elevated.

There may also become a time where we begin to identify that patients who do have impaired renal function, we might want to use a higher cutoff value, since so many of them who are asymptomatic do have elevated levels. But we shouldn't expect that to be in the FDA package insert, and it may be something that evolves with time.

Bob Barrett: Let's move on and talk about natriuretic peptides. What can you tell us about their accuracy for the diagnosis of heart failure in patients with chronic kidney disease? Are there differences with respect to diagnostic accuracy for B-type natriuretic peptide or the amino-terminal pro-BNP?

Dr. deFilippi: Comparable perhaps to the troponin study. There's been a lot of confusion or consternation about the use of the natriuretic peptide assays maybe N-terminal pro-BNP a little more so than BNP, with respect to trying to make the diagnosis of heart failure and a patient who presents with shortness of breath. So these values are often somewhat elevated in patients with chronic kidney disease. However, they remain still extremely accurate. What do we mean by that? The areas under the curve for let's say all comers

would be on the order of about .90 to .92 for either natriuretic peptide.

And when you look at patients just who have impaired renal function, now excluding those on dialysis but with eGFRs less than 60, one can anticipate still a very good diagnostic accuracy with the area under the curve of about .88 to .9. So, what has been done is that with the use of BNP often, we'll say the most accurate cutoff should be doubled from that of 100 to 200 or perhaps even a bit higher, and for N-terminal pro-BNP, age specific cutoffs have been identified as perhaps being most accurate and when you utilize these age specific cutoffs, initially identified through the ICON Study a decade ago, that often accounts for some element of renal impairment which is more common in older patients so you don't need to make any specific adjustment for it to retain its accuracy.

Bob Barrett: Well finally, doctor, given that natriuretic peptides are often elevated in patients with chronic kidney disease, does this still provide prognostic information in the setting of chronic kidney disease?

Dr. deFilippi: Yeah. In fact, it's extremely important. It's important to recognize that the natriuretic peptides in patients who are not on dialysis, their clearance isn't significantly impaired across the spectrum of renal function going almost all the way down to an eGFR of 15. So an elevated level represents cardiac pathology, whether that is increased intracardiac pressure, left ventricular hypertrophy, or other cardiac comorbidities. So it's shown in patients who present with heart failure in the presence of an elevated natriuretic peptide.

In this case, in one study for example, done through the ICON cohort, a value when patients presented with decompensated heart failure above the median, which I believe was about 2,700 picograms per milliliter, combined with evidence of diminished renal function, an eGFR of less than 60, was associated with the substantial increased risk of mortality over the next 60 days. And interestingly, the presence of just one of those two factors, whether it be just the high natriuretic peptide in the presence of normal renal function, or just impaired renal function without the elevated natriuretic peptide level, conveyed just as good a prognosis as somebody who had neither.

So there's quite a bit of synergy prognostically with respect to impaired renal function, and an elevated natriuretic peptide level in someone with heart failure should be taken quite seriously.

Bob Barrett: Dr. Christopher deFillippi is the Vice Chair of Academic Affairs at the INOVA Heart and Vascular Institute in Fairfax, Virginia. He's been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.