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Guest: Dr. Yader Sandoval is a cardiologist at Hennepin County Medical Center and the Minneapolis Heart Institute at Abbott Northwestern Hospital.

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.

Improvements in the sensitivity of troponin assays have led to better management of patients presenting with chest pain and possible acute myocardial infarction. In addition, these newer generation assays have revealed populations with values above the 99 percentile upper reference limit who are at risk for myocardial injury even though their clinical features are inconsistent with traditional myocardial infarction.

Therefore, in an attempt to address this problem, the concept of type 2 myocardial infarction was introduced in the third universal definition of MI. Despite its specification as a condition, there is currently a lack of clarity and guidance in the diagnosis and management of type 2 myocardial infarction.

Thus, much debate has surrounded this subtype of myocardial infarction and its relationship with myocardial injury. This is the topic of a Review appearing in the January 2017 special issue of *Clinical Chemistry* which focuses on cardiovascular disease. Dr. Yader Sandoval the primary author of the review joins us for this podcast. Dr. Sandoval is a cardiologist currently specializing in interventional cardiology at Hennepin County Medical Center and the Minneapolis Heart Institute at Abbott Northwestern Hospital. He is an investigator at the Cardiac Biomarker Trials Laboratory where his research has been focused on the use of cardiac troponin assays.

Dr. Sandoval, the medical community including clinicians and laboratorians are certainly familiar with acute myocardial infarction, however, what is type 2 myocardial infarction?

Dr. Sandoval: Type 2 myocardial infarction was a concept that was originally introduced in the second universal definition of myocardial infarction in the year of 2007. As you know there has been three iterations of the universal definition of

myocardial infarction task force document, one in the year 2001, one in the subsequent second version in 2007, and the latter iteration in 2012. And it is the latter two documents that discuss this entity of type 2 myocardial infarction. There were five MI subtypes that were discussed at the time, with type 1 and type 2 myocardial infarction receiving most of the attention both due to their frequency as well as their prognosis.

And type 1 myocardial infarction is the more classical traditional acute coronary syndrome that clinicians and laboratorians are familiar with, which is that that occurs in the context of plaque rupture. Whereas conversely, type 2 myocardial infarction is myocardial infarction that occurs due to a supply and demand mismatch in the absence of plaque rupture.

Since the introduction of these two entities of these five MI subtypes, it has been as mentioned type 1 and type 2 are the ones that have been noticed of the high incidence in clinical practice and that has gained attention as to the importance of differentiating them and how to manage them.

Bob Barrett: And why is important for people to be aware of this condition?

Dr. Sandoval: For type 2 myocardial infarction, the importance at this point, relates primarily as mentioned, that it appears to be much more common in both clinical studies as well as in clinical practice. If you look at select studies, it can range from 1.6% in very select cohorts of patients that are from studies that were specifically in populations with coronary artery disease of acute coronary syndromes. However, this can range as high as 30%. And I can tell you that in some of our studies at our center, this could be at some point even 60% of all of acute myocardial infarction or more. So type 2 myocardial infarction is something that is frequently encountered in clinical practice. So, that is one aspect of it.

The second aspect of it is that in different studies, it has been shown to have a similar or if not, even a worse outcome, than type 1 myocardial infarction. And the main challenge has been not only that it is frequent and that it is associated with a poor outcome but furthermore, that at this point, we do not have any robust clinical practice guidelines to understand what is the best way to treat these patients that are having poor outcomes. And that is an area of very important ongoing study.

Bob Barrett: Going back, you said that this is frequently seen, just how frequent is this condition?

Dr. Sandoval: In clinical research studies, which have been the great majority of retrospective studies, the frequencies have ranged from as low as 1% to 2%, to as high as 60% to 70%. This is all very heterogeneous which is dependent on various factors. It can depend on what is the study population that is being examined. For example there are some of the studies that are post hoc analysis, as mentioned, of investigations that were focused on individuals with known coronary artery disease or presenting with acute coronary syndrome, and therefore there is already some selection via who is predisposed to have more type 1 myocardial infarction rather than type 2 myocardial infarction. And for that reason the reported incidence or rate of type 1 myocardial infarction is low.

However, in contrast there are other studies that are assessing all comers that come for example to the emergency department or at all comers that are in the hospital. And when one looks at more broad populations, that rate of type 2 myocardial infarction is much higher with some studies ranging from 20% to 30%. And in centers as mentioned for example in Minneapolis, we've seen that in some of our observational studies, this can at some points even reach 60% or more depending on how you look at it.

As I said there are various variables that play a role into why there is some heterogeneity in the frequency of type 2 myocardial infarction. One that is very important, as I have already mentioned, is the selected study population that is being examined. Second is sensitivity of the troponin assay that is being examined. So, assays that are less sensitive, you may have a lower rate, and with more high sensitivity assays in comparison to less sensitive, it is plausible that you could have even higher rates than in other studies.

And another aspect that is recently also gaining some attention, is what are the criteria that are being used to define type 2 myocardial infarction. So, there are some investigators that have used a specific criteria for type 2 myocardial infarction in which they use strict select criteria to determine what constitutes type 2 myocardial infarction. And with this strict criteria, you are also selecting a cohort of patients that have certain particular conditions. For example there is a study by Saaby et al in the *American Journal of Medicine* a few years ago that for example in order to define type 2 myocardial infarction, they look at predetermined criteria for what constituted a supply and demand mismatch. For example let's say a tachyarrhythmia lasting over 20 minutes, and you needed that criteria in order to have a type 2 myocardial infarction.

So as you see when you use this predetermined criterion, you're already looking at a more, let's say, more higher risk,

more preselected subset of type 2 myocardial infarction, and therefore the rate will be potentially plausibly lower.

However, in our studies and many other studies, folks have use a broad criteria to examine type 2 myocardial infarction, which some argued that it is more reflective of what clinicians do in clinical practice. And which is if there is, if there's a clinical context that is consistent with myocardial ischemia and there is supply demand mismatch that appears to be contributing to that clinical context, be that severe anemia or a significant tachyarrhythmia without a particular threshold, then you can invoke the diagnosis of type 2 myocardial infarction if there is thought to be no plaque rupture. And these are some of the very complex variables that play a role into why there are some heterogeneity in the frequency of type 2 myocardial infarction in various studies.

Bob Barrett: Doctor, besides distinguishing it from type 1 myocardial infarction, are there any other conditions that should be distinguished from type 2 myocardial infarction?

Dr. Sandoval: This is a very important question that you raise because certainly much of the emphasis over the past years has been to distinguish type 1 from type 2 myocardial infarction. However, increasing attention has been placed on the fact that there are also many challenges in distinguishing type 2 myocardial infarction from myocardial injury itself. That of course brings the question as to "what is myocardial injury?" So, myocardial injury is a concept that as of now is defined as an increased cardiac troponin concentration above the 99 percentile. And at least in our mind there are two ways that one could look at that.

One is you could define myocardial injury with necrosis and that would be consistent with any elevation above the 99 percentile, and if myocardial injury has the presence of overt ischemia such as ECG changes, symptoms reaching a wall motion abnormality, then you will invoke the diagnosis of myocardial infarction.

However, if you have absence of overt ischemia and you have isolated myocardial injury with necrosis with cardiac troponin concentrations above the 99 percentile, then you have a condition of isolated myocardial injury which is not myocardial infarction.

And one of the very important challenges and conundrums that we frequently face is how to distinguish folks that have type 2 myocardial infarction from those that have myocardial injury. There are several examples that we see both in clinical practice and research studies frequently, that indeed represent a significant challenge, be that patients

that have congestive heart failure for example, patients that have sepsis infection, critically ill patients or patients with renal failure. And much of the discussion of debate has been placed on how to categorize these patients. And it is has been at least our position that for example patients that have conditions, for example, such as renal failure, patients that have congestive heart failure, that do not have a significant presence of overt ischemia and do not have a dramatic rise and/or fall in cardiac troponin, be classified as myocardial injury rather than as type 2 myocardial infarction.

This is one of the very important conditions that needs to be differentiated. And of course as I already implied in some of the aspects that I've mentioned, a key aspect in differentiated injury from type 2 myocardial infarction will not only be the trend that cardiac troponin concentrations have but also the clinical context in which this occurs.

Bob Barrett: So what are the challenges for investigators and clinicians doing cardiac troponin diagnostic performance studies in regards to this classification?

Dr. Sandoval: This is a very important question as there are several challenges that we have been able to detect in studies assessing the universal definition of myocardial infarction. As already rephrased in some of the issues that we've talked about today, one very important aspect is well, foremost, how do we define type 2 myocardial infarction? And as already discussed beforehand, due to some of the outgoing dilemmas in how should we define type 2 myocardial infarction, it is certainly challenging then to have a consistent way to develop clinical research studies that can be replicated over time.

So, you can see that for example Group A of investigators can define type 2 myocardial infarction in a certain way, but Group B of investigators can define in another fashion. And this is partly due to some of the existing ambiguity in the latter iteration of the universal definition of myocardial infarction of how this condition is defined. And there is much expectation on how this would be further refined in the fourth universal definition of myocardial infarction in order to hopefully develop a more consistent way of performing clinical research that will allow to further understand who these patients are and how to improve their management and outcomes. That is one very important aspect.

The other aspect that is very important in relation to investigators, for example, using cardiac troponin it is that in studies assessing diagnostic performance of cardiac troponin assays, usually these studies will examine

diagnostic performance statistics, such as sensitivity, specificity, predictive values, negative and positive predictive values. And the question is, what is the endpoint that is being examined for these diagnostic performance studies? Prior to 2007 it was more straightforward in which these diagnostic performance statistics were calculated for the diagnosis of acute myocardial infarction.

However, nowadays the literature is somewhat clouded as there are some studies that focus on type 1 myocardial infarction alone, others claim to follow the universal definition of myocardial infarction subtypes. Yet there is no clear data as to whether the diagnostic performance studies included both type 1 and type 2 myocardial infarction. And there are some studies that have essentially, openly assessed diagnostic performance including both type 1 and type 2. Whether this influences or not significantly what is a performance of cardiac troponin studies, is not something that is yet clear, but it is something that I think it probably requires further attention, again particularly for the consistencies on how these studies are being performed.

The other aspect, as mentioned briefly before, was that moving forward, it will be also very important to ensure that we only not focus the attention in distinguishing type 1 from type 2 myocardial infarction, but also there needs to be measures on understanding what proportion of patients have myocardial injury and how was this defined.

Bob Barrett: Well finally doctor, let's look ahead, what is needed moving forward on this topic?

Dr. Sandoval: Several issues are needed. One, there needs to be a consensus on what we understand as type 2 myocardial infarction. As mentioned, as of now, type 2 myocardial infarction should be diagnosed when there is evidence of acute myocardial injury with necrosis, and this is confirmed when there is evidence of a rise and a fall of cardiac troponin with at least one value above the 99 percentile. And very importantly, this needs to be in a clinical setting consistent with overt myocardial ischemia. And there's needs to be an evident acute and/or sustained oxygen supply and demand imbalance in the absence of plaque rupture, plus at least one other MI criteria which is according to the universal definition of MI.

Moving forward it will be very important that we develop some guidelines as to how investigators and clinicians worldwide can develop some consistency in how this entity is being diagnosed and classified. Regardless of how we do it, I think it's probably fair to say that studies have shown us a signal that A, this is frequent and B, it is associated with a poor outcome. So in order for us to understand who

these patients are and understand how to better take care of them and improve their outcomes, it will be very important to define this clinical condition and refine the diagnosis of type 2 myocardial infarction.

Another aspect that has recently gained some attention, it is that type 2 myocardial infarction may occur with the presence or absence of concomitant coronary artery disease. There have been already a few studies that have raised some of the potential influence that coronary artery disease may have on the management and outcomes of these patients.

So further efforts are needed in understanding what is the frequency of underlying coronary artery disease in these patients and should that influence treatment, is something that will require attention. Right now as I've mentioned at the beginning, most of the studies that have been performed were on type 2 myocardial infarction are retrospective in nature.

So when they examine the incidence, the rate of coronary artery disease in type 2 myocardial infarction, there is some selection bias, and since these studies are retrospective, they are already assessing only those folks that were sent to coronary angiography clinical practice. So we don't really have a good understanding of what is the overall true rate of concomitant coronary diseases in patients with type 2 myocardial infarction. This is something that probably deserves more attention moving forward.

Lastly, a couple of issues that probably are very important, one is that of myocardial injury. Much more attention needs to be placed, that elevations above the 99 percentile are not synonymous with acute myocardial infarction. They did not equate such. Cardiac troponin elevation above the 99 percentile may be due to acute myocardial infarction or may be due to myocardial injury, and much of this distinction is done from a clinical basis. And this is something that will be important because it will influence how we take care of these patients and this is something that needs to be placed further attention, particularly with several cases that have already exemplified, such as patients that have renal failure, heart failure, that are often representing some conundrum as to why they are having myonecrosis and how should they be classified.

Lastly, I think that in regards to patients with type 2 myocardial infarction, studies have shown that there are signals that these patients have a similar or worse outcome than type 1 myocardial infarction which is in the context of rupture. However, it is very important to note that most of these studies have focused on all cause mortality rather

than cardiac mortality. So at this point, we do not understand well what is the mechanism for which these patients have a poor outcome. And it is very important that moving forward, we'd not only report why these patients are having a poor outcome, but ideally to understand what is the mechanism that leads to these patients having major adverse events, whether they are cardiac in etiology, are they having more myocardial infarction in follow-up, are there deaths of a cardiac nature or not. And this will be important so we can further understand what potential therapies and further steps may be needed to better define the risk and management of type 2 myocardial infarction.

Bob Barrett: Dr. Yader Sandoval is a cardiologist specializing in interventional cardiology at both Hennepin County Medical Center and the Minneapolis Heart Institute at Abbott Northwestern Hospital. He has been our guest in this podcast from *Clinical Chemistry* on type 2 myocardial infarction.

I'm Bob Barrett. Thanks for listening.