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Early rule-out and rule-in strategies for myocardial infarction

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Guest: Dr. Louise Cullen is a Senior Staff Specialist in the Department of Emergency Medicine of Royal Brisbane & Women's 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.

Chest pain with suspected heart attack or acute myocardial infarction is a common reason patients present to emergency departments. These cases typically involve extensive work up and play a major burden on healthcare resources. Clinicians are challenged to accurately identify patients with acute heart disease while balancing the need to safely and rapidly reassuring discharge those without serious conditions.

Therefore, physicians need ways to safely and rapidly identify those with and without acute myocardial infarction. A review in the January 2017 special issue of *Clinical Chemistry* summarizes the current evidence on accelerated strategies for the rule in and rule out of acute myocardial infarction. The authors focused their discussion on optimal use of troponin results. The review's first author, Dr. Louise Cullen, joins us for this podcast.

Professor Louise Cullen is a Senior Staff Specialist in the Department of Emergency Medicine, Royal Brisbane & Women's Hospital, and an active clinician-researcher with particular interests in acute cardiac diseases, syncope, and cardiac biomarkers. She is widely published in numerous peer-reviewed journals including the *Lancet*. Her mantra is "You do not do research for research's sake" and as such, clinical redesign and translational research is a key part of her endeavors.

So Dr. Cullen, there is a lot of interest in rapid assessment strategies for patients who present with suspected heart attack or the more accurate medical term, "acute myocardial infarction." Why is this the case, and are there any issues about this that clinicians need to understand in the application of such protocols?

Dr. Louise Cullen: Yeah, look. It's a very important question, Bob. What we know is that the burden of assessing patients with chest pain and other symptoms of a potential heart attack or

acute coronary syndrome in emergency departments is large and it doesn't matter what part of the world that you are in, this is a significant problem. It's also the most common or the second most common reason that they will present in the emergency department and it makes up between 5% and 10% of all the presentations in adult hospitals.

The challenge for us as clinicians is to accurately identify those that do have an acute coronary syndrome or who are at risk in the short term, but we've also got to balance the need of safely and rapidly reassuring and discharging those patients who don't, and the vast majority of patients thankfully don't have an acute coronary syndrome.

So that's really why there's been a lot of attention at this point in time. It's problematic. What we are trying to do, we're assessing patients with acute coronary syndrome is walk a tightrope between not missing those people within the infarct, because their risk of if we miss this, of some serious harm is quite significant. But equally, we don't want to be over investigating or harming patients by doing unnecessary things to them who ultimately don't have the disease.

So it's been increasingly recognized that we need to refine our system processes and that probably clinical gestalt is not appropriate in this area to try and optimize the assessment process in the emergency department.

In terms of your second question, in terms about are there any issues about that clinicians need to understand in the application of such protocols, there's a number of different strategies that are out there at the moment. It's a really exciting time to be in this area in acute cardiac care, because we have got a number of different alternative options.

When people are looking at implementing one of these strategies, it could have us think quite seriously about the situation, the clinical system that they work in at this point in time, because you'll find that some of the studies that are out there focus very much on just the identification of acute myocardial infarction, while others have looked for the broader outcomes of acute coronary syndrome, that also includes of course, unstable angina which is the troponin-negative or the biomarker negative condition. And we do know that patients with unstable angina or significant underlying coronary artery disease may also come to some harm.

There are different approaches and what we find is that for some systems that have got very strong outpatient services,

it might be appropriate just to rule out acute myocardial infarction, knowing that these patients will be able to be discharged and picked up very quickly in an ambulatory setting and have the final assessments needed to rule out significant underlying coronary artery disease.

While there are other systems that have got very much a hospital-based approach, and so some of these are focused more on trying to complete the assessment process early for the full spectrum of the acute coronary syndrome as well.

One of the other things though that this is in these protocols is also the consideration of what's an acceptable niche for events. Now there's absolutely enough -- you mentioned this perfect. And one of the things that we know is that there will be times because of the nature of this disease that we fail to detect the patients. And so, different strategies have got different sort of acceptable risk thresholds, and people need to read these and think about their own clinical context and their own personal tolerance of risk to also identify what might be appropriate for them as well.

And probably the third point about the different protocols that's the most important is the troponin assay that's used. All of the different accelerated strategies at the moment are very much focused on troponin, but there's a very big difference in how the assays perform from contemporary or sensitive assays through to the highly sensitive troponin assays. And unless clinicians have got a good understanding of what their local assay is, they won't be able to work out which of the different protocols are appropriate for incorporation in their own practice.

Bob Barrett: So why are there so many different strategies in use? What's the difference between sensitive or contemporary assays and the high sensitivity assays for troponin?

Dr. Louise Cullen: Well firstly, the reason why we've got so many strategies, there are really probably two reasons at this point in time. And it's interesting that around the same time around the world, a number of different groups started investigating in this area at the same time. And because of that, different strategies have developed that were relevant to the local context, as some of them were very much reliant on new biomarkers. Others of them looked at other strategies and incorporated some clinical features into risk stratification as well.

I guess the big reason why there are so many different strategies is because of the different troponin assays that exist, and that of course depends on where you live and what you've got access to. So, for example, at the moment in United States, there are no highly sensitive troponin

assays that have been approved by the FDA. So it alters the alternatives that might be appropriate in that setting.

And equally, there are places which will never have access to essential lab troponin tests because of regional remoteness, and so they're reliant on point-of-care assays. And so, clinicians that work within those sorts of areas need to understand what strategies might be actually acceptable and what are evidence-based in that context.

In terms of your question about the different assays, what we know is that in a contemporary sensitive assay, you can't safely rule out any presentation, and so, all of their international guidelines continue to recommend serial troponin testing which, of course often means admission to hospitals or placement into emergency observation units.

Highly sensitive troponin assays have got excellent precision at very low concentrations, and they permit the accurate quantification of troponin in the majority of healthy people. These assays are the ones that have the potential to transform the assessment of patients, which has been coming to the emergency department and have allowed us to investigate a number of different safe and effective strategies to rapidly rule in or rule out acute myocardial infarction.

Bob Barrett: We have seen reports in *Clinical Chemistry* and other journals about a single test being used to rule out acute myocardial infarction. Is this a safe strategy or should clinicians be cautious in circumstances?

Dr. Louise Cullen: This is a really exciting area that's emerging now. We're beginning to know more and more that people, whether they are in the community or presented in the emergency department with some symptoms of possible acute coronary syndrome, if they have a very, very low circulating values of troponin at that first instance, that the risk of coming to harm over the next 30 days or even up to one year is incredibly low, and it's exciting to think about potentially our ability to stop at as a single blood test or single blood draw when they come to the emergency department. There is a great study by the authors of the TRAPID-AMI study that analyzed their big databases and suggested that if you combine a normal ECG and troponin T concentrations of less than 5 milligrams per liter, you can rule out an infarct with very high negative predictive value very, very safely.

It rules out a fairly significant proportion of patients, so up to about 45% of patients, and with the advantage of doing a single test rather than more -- within the literature at the moment, most of the strategies involve serial testing. Equally in the *Lancet*, Nick Mills and his group have looked

at the values using High Sensitive Troponin-I of less than 5 nanograms per liter, again, with exquisitely sensitive negative predictive values, so it gives us a confidence that it's safe with similar sorts of proportions of patients that might be able to be ruled out in a single blood test. Now this is really exciting because the opportunities then to send patients home from the emergency department reassures there's an early time point and stop unnecessary healthcare utilization is phenomenal. But we've got a little bit of a way to go and I don't think it will be long before we get the evidence here about how this might actually work in real practice.

A lot of these have been observational trials and so, we really need to see what it might be when we've put it into a perspective validation.

Equally, I think there's an important caveat that very early presenters, that those patients who present it potentially within one, two or maybe up to three hours of their onset of symptoms, we may not be able to say that this is as safe as it is of course for those patients who have some delay in their presentation, and time will tell.

So, this is a very rapidly evolving area that's really exciting to see but there are some caveats at the moment and I think within the next 12 months, it will be much clearer about the safety of such a strategy and I suspect that there will be people that will be adopting this strategy, but give us a bit more evidence first.

Bob Barrett: Some protocols emphasize the use of risk stratification on electrocardiograms in addition to measuring troponin. Now why is this?

Dr. Louise Cullen: Yeah. Believe it or not, I think it's fair to say that all of the accelerated strategies really incorporate the ECG criteria and this is sometimes lost in translation. When you look at the studies, many of the studies have actually excluded people that have got ST Segment Elevation Myocardial Infarction or STEMIs on their ECG or any other signs of ischemia. And so, people often just look at the troponin values and things not realizing that ECGs have already been incorporated in the very beginning of it. But there are some other strategies that talk a lot more about risk stratification processes, and then sometimes it's evolved because of the use of less sensitive assays that have been used in the actual clinical trials, or because their endpoint was not only acute myocardial infarction but a broader category of ACS. Equally, there are some strategies being focused on picking up patients that are at high risk, not only just for the acute coronary syndrome but those patients that have got

significant underlying coronary artery disease or other complaints.

And so, there is some difference data at the moment, and I think there are reasons why there are differences. It again highlights that there's no perfect answer for everyone. What we need to do when we look at these protocols is actually contextualize it on what you've got access to and what's relevant to you in your clinical practice for you to move ahead with.

Bob Barrett: Well finally, doctor, looking ahead, are there any novel biomarkers that are currently being investigated that may change our approach the patients with possible acute myocardial infarction?

Dr. Louise Cullen: There are a lot of great interests in this area. And in a world searching for the golden chalice, at the moment troponin is a fantastic biomarker looking for evidence of myocardial necrosis, and so, the other ones that are emerging are up against a stronger competitor. Even though using a highly sensitive troponin assay, the concentrations for troponin in the setting of an acute myocardial infarction might actually take a few hours to increase. And so, there's that period in the first year after onset where the troponin values are rising but not necessarily identified as abnormal which is the time and the space that people are looking to see whether novel biomarkers might actually work.

There have been two biomarkers that have been investigated very heavily in this, and one is the H-FABP which is a cytoplasmic protein that is involving fatty acid transport within the myocytes themselves, and we know that it rapidly appears in the plasma after a myocardial ischemia.

It's looked as if it had some promise. It's been helpful for example for prognosis in patients with chest pain and there's been some combinations in the use of both sensitive and highly sensitive troponin assays, but unfortunately when you use it with a high sensitive troponin, it probably only marginally improves the diagnostic performance when you look at things like area under the receiver of characteristic codes. And there's a particular strategy called MACS, or The Manchester Acute Coronary Syndrome, which is incorporating clinical information, ECGs with H-FABP and highly sensitive troponin assay, that this actually might allow us to identify patients early more quickly. But we're looking more towards -- you know, there's a randomized controlled trial that's being conducted at the moment -- it would be interesting to see how that performs.

The other assay is copeptin which is a prohormone or vasopressin. It's attracted a lot or interest at the moment. It has been shown to have some incremental value when you use it with troponin for ruling out ACS in the setting of using a contemporary or a sensitive troponin. When we look at it with patients with highly sensitive troponin assay where we're still trying to investigate how it will perform. There's been a randomized controlled trial that it's actually looked at in-patients who didn't have troponin elevations and they incorporated copeptin to help guide their care. This is the standard of care, and there have been some studies that have shown or a study that has shown that the use of copeptin significantly reduced the median length of stay within the hospital.

This particular study was a non-inferiority trial. It was only powered to demonstrate the incidents of most and was no more than 5% higher in the copeptin group. We really need some larger study still. Clinical implementation is a challenge when we've got to say that you need not only troponin, but you need additional biomarkers as well. And so, there are a few places within the world that I'm aware of that you utilize either a H-FABP or copeptin but it hasn't had wide uptake.

In terms of other things on the horizon, there's a number of different things that are being looked at. But at this stage, I don't think any of them are progressing towards this, seriously considering the clinical implementation. As I said, they're up against a really good biomarker, and so we got to see a significant incremental benefit to make things a bit more complex by adding a second biomarker either to see whether or not that will actually be able to transform patient care.

Bob Barrett: Dr. Louise Cullen is a Senior Staff Specialist in the Department of Emergency Medicine of Royal Brisbane & Women's Hospital. She has been our guest in this podcast from *Clinical Chemistry.* I'm Bob Barrett. Thanks for listening.