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Chest Pain Assessment: What Is Our Endgame?

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Guest: Dr. Louise Cullen is a Staff Specialist in emergency medicine at the Emergency and Trauma Center Royal Brisbane and Women's Hospital and the Faculty of Medicine at the University of Queensland in Brisbane, Australia.

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.

Cardiac troponin testing is crucial in assessing patients with chest pain and other acute anginal equivalent symptoms. The latest definition of myocardial infarction recommends the use of troponin to identify patients who may benefit from targeted therapies.

Developments in immunoassays for cardiac troponin I and troponin T, many published in *Clinical Chemistry*, and the subject to previous podcasts, have resulted in highly sensitive assays with improved ability to detect and quantify troponin concentrations. Each cardiac troponin assay has its own analytical characteristics and clinical approaches need to be tailored to the analytical characteristics of each new assay.

Two papers appearing in the February 2022 issue of *Clinical Chemistry* add to our understanding of troponin assays and how they should be used in assessing for acute coronary syndromes. These two papers were the subject of an editorial in that same issue titled "Chest Pain Assessment: What Is Our Endgame?"

The lead author of that editorial is Dr. Louise Cullen. She is a Staff Specialist in emergency medicine at the Emergency and Trauma Center Royal Brisbane and Women's Hospital and the Faculty of Medicine at the University of Queensland in Brisbane, Australia. We are pleased to have Dr. Cullen as our guest in this podcast.

So, first, Dr. Cullen, can you explain why there has been so much research into this one biomarker and methods to measure it.

Louise Cullen: Yes Bob. It's really interesting, isn't it? But troponin has overwhelmed us in terms of the volume of different articles that are valuable. It is incredibly important biomarker clinically in allowing us to identify patients who have an acute myocardial infarction. And for a substantive dose, that is those people who got a type 1 or coronary artery occlusion event and identifying these patients that benefit from

therapies like thrombolytic therapies or percutaneous integration, PCR.

So, it really gives us the evidence for us to drive and support patients having fairly aggressive therapies if they have type 1 myocardial infarction. The other thing that's really interesting about this is that as an immunoassay, different manufacturers assays have different analytical characteristics and they all perform differently. There is no standardization or harmonization of these assays, which means that for each assay we actually need to evaluating the right clinical context.

So all of these different aspects to it have meant that we've got a lot of information that's come out. Troponin has been around now for about 20 years and the evolution of assays has driven the research and of course, therefore, the publications as well, about how we can continually improve and maximize the information that we can get from these assays.

So that's from the third aspect that has meant that we have an awful lot of information that is out in the literature. It's exciting but it can be overwhelming particularly as a clinician trying to interpret the information of therapy.

Bob Barrett: Well, your editorial focuses on methodological and reporting aspects of both trials. Why was this the case?

Louise Cullen: So, first and foremost, I'm an Emergency Physician and I'm very lucky to be a clinical researcher. But as a clinician, I know that I read the literature trying to identify new strategies that I might be able to implement that will improve patient care, that will improve the health systems that we work within it.

And I find that in this particular area that is all the publications and biomarkers, the information can be different subtly. Now, it's a big thing just in the first instance for clinicians to understand that different troponin assays perform differently. That's one aspect to it. But then trying to ensure that the information that I'm reading is applicable to my cohort of patients; for example, emergency patients who present with chest pain and potentially acute myocardial infarction, and then trying to see whether or not what's being reported is something I could then adopt in that sort of for that cohort of patients is challenging.

When people then talk about what's the best aspect or the best assay to use or the best strategy to use, you've got to have an understanding about the nuances which are being proposed. That is the differences in the assay types. The differences potentially in the cohort that they're being evaluated in, the differences in what they've included to

evaluate is important; and we'll get onto that hopefully in just a moment. So I think that's really, really interesting.

And then also things like differences in serial timing. So it's a challenging area to synthesize things and I think it's very easy to get lost and not appreciate that there are significant differences in some of the publications that are proposed.

And so, I thought for this particular editorial with these two fantastic papers in *Clinical Chemistry*, highlighting the differences in them is just a way to make people aware that they should also look for these differences in other journal articles that they might actually read into to work out how to interpret it for their own use.

Bob Barrett: Doctor, can you tell us a bit about the influence of including different clinical diagnosis in the main outcomes for each paper?

Louise Cullen: Yeah, I can Bob and thank you. This is a really interesting aspect. We have a number of different diagnoses that are important when we talk about an acute coronary syndrome. And so acute coronary syndrome in the broadest context involves unstable angina and acute myocardial infarction. And you can see from the colleagues in literature from Norway, they have included unstable angina as part of the primary outcomes.

Now, unstable angina is a really challenging diagnosis, objectively, in the sense that it is a condition where by definition the troponin the biomarker is not elevated, but it is in the context of myocardial ischemia. And when we look at the Fourth Universal Definition of acute myocardial infarction, one of the characteristic features that they talk about for myocardial ischemia symptomatology or chest pain or chest discomfort that is in keeping with this.

Unfortunately, people with acute myocardial infarction can present with a variety of different symptoms and describe their symptoms differently. So it's a little bit subjective in about trying to ascertain if this is something that should be included with evidence of no elevation of the troponin as a diagnosis of acute myocardial infarction.

And also it's a bit of a stretch to think that for people that don't have a troponin elevation but may have evidence on some sort of objective testing for example that they've got myocardial ischemia, the symptoms they've got are directly related to that and not something else.

So it's a hard thing to include because of the lack of an agreed objective finding. The other thing though that's interesting in this space is when we talk about myocardial infarction and

again, the Fourth Universal Definition talks about a number of different types of myocardial infarction.

In the emergency setting, we see commonly both type 1 and type 2, so they are a currently inclusive one and then we also see the type 2, the supply-demand mismatch in a variety of causes. Often in papers when we report primary outcomes, it's just acute myocardial infarction which includes both type 1 and type 2 and that's actually pragmatically very sensible in the sense that at the front door in the ED, it is often very difficult to truly tease out which is type 1 and type 2, and it's not until further investigation, sometimes angiography is performed, so we might actually be able to classify people into different groups.

The problem with this though is that there's a lot of heterogeneity in the treatment that is required for type 2 acute myocardial infarction and the ED focuses very much trying to identify those people with that type 1.

They're the ones that we want to expedite care under our cardiologists and as I said, potentially need some sort of coronary artery opening therapy, whether it be license or PCR, to enable them to get the best outcomes.

So putting it all together under the banner of acute myocardial infarction makes sense. But I do think within the papers with reporting, it'd be lovely to see additional information about type 1 only to give us some identification about the different strategies and the performance of the different strategies that we have within the ED.

So there's nothing wrong with different ways, it's just providing I guess more information whether or not you include unstable anginas well, and clearly identify how you've defined that, including both type 1 and type 2, but also having another secondary analysis. Looking at type 1 alone, I think then gives people the most information that they can then pull out and contextualize it for their local practices, their local EDs.

Bob Barrett: In your editorial, you put out a call for consistency and evaluation of outcomes. Can you explain for us what would be your ideal targets for assessment of emergency patients with suspected acute coronary syndromes?

Louise Cullen: This is another really interesting aspect because we see a lot of studies as I said about this, which is fantastic. The more information we get, the better it's going to be, but I think it's important when we try to look at comparisons to make sure that we are looking at the same metric.

So, when we're looking for an ED cohort of patients who present with suspected acute myocardial infarction, I think the key aspect from an ED perspective is the rule out. So I will speak to that one first of all, and that's identifying these patients who don't have acute myocardial infarction or at low risk for some complication.

And if we set targets, for example, about negative predictive value or NPV, greater than or equal to 9-9.5% and take that as our first instance. That means you will have a missed rate of about 1 in 200 patients for that which is acceptable. That should be our first assessment or a rule out strategy.

I don't think it's although just about that point estimate. We need to also look at the confidence intervals and of course, if you've got these smaller studies the confidence intervals can be really wide.

So, I think we need to look at what's the lower acceptable estimate of how it performs. And maybe we set our confidence interval to a lower margin of that at 99% for example, because I don't think that anyone would accept even if you had a point estimate of 99.5% if the lower confidence interval was about 70%. I don't think anybody is going to be accepting or missing that many corrections with acute myocardial infarction.

So, I think the NPV is the way we start. I think we then need to also with all the values. So that would be recorded for a troponin value for example or X nanograms per liter. I think we need to then go and report the sensitivities as well in the papers. There's been some reported evaluation that was acceptable miss rate for AMI and from an ED sort of physician's concord it's about one in 100.

So again, we should be setting our sensitivities high as well, up around 99%, but you might accept our confidence interval down as low as 90 or 95%. What they need to do in the third part of that, is look at the proportion of any patients that are ruled out utilizing different values that give you those metrics. And I just think it's really important for that to be transparent for everybody to read.

What we do know is that the prevalence of acute myocardial infarction differs in different in cohorts and around the world it's probably because we've got primary care physicians in some countries that are doing a lot more evaluation than in others where it's very much a hospitalize-based assessment for people with chest pain. So, I think it's important to have both negative predictive value which will be influenced significantly by the prevalence of disease sensitivity, and options ruled out over what the recommended value should be but also potentially values above and below that so that

people can take on board what might be relevant in their own context and utilize it.

The same can be said, then, for specificity and PPV and you find that, like in these papers, a lot of the criteria or a lot of algorithms have been evaluated using PPVs of 70 or 75% and above. And I think it's important that we have some sort of standard that's out there so we can compare things with transparent recording.

I'm very happy and love to see great supplemental material. I realize this is a lot of information to go out there. But having it accessible even in supplementary materials in journals helps us as clinicians to make decisions for how we utilize this rich information that's provided to us by this good studies.

Bob Barrett: Finally, Doctor, how do you think clinicians should proceed with new information about troponin assays, especially if they're wanting to make local changes in their assessment practices?

Louise Cullen: Firstly, I'd encourage people to continually evaluate whether or not there's other opportunities out there and definitely not get stuck in a rut of always done it this way around here. And I think when you're looking at ED assessment practices for patients with potentially acute myocardial infarction, the first thing to do is to setup a case or more group of people that will work with you. And in this context, it's going to involve cardiologists, emergency physicians, and also lab-based experts as well because it's defining what I see you using at the moment and then looking at potentially what might change.

I'd recommend firstly, pulling all of the published data around how a particular assay performs in the group that you want to evaluate it in. So that is for example, all of the emergency reports or reports on emergency patients with one particular assay. Talk amongst your local colleagues about what's an acceptable risk. When I was talking before about the importance of patients ruled out and negative predictive value and things like that, there will always be different risk thresholds in different populations. And it's important to have that understanding from your local context. Have you got an incredibly cautious group? Have you got access to great outpatient services that can happen in approximate time? These sorts of factors will influence what you think might be relevant for use in your own style.

And I guess the other key thing is that if you're going to make a change evaluating what the impact might be to see if there is benefit for you to do to make that change. So, look at your own system and the proportions of patients that may be impacted particularly exciting for again, for emergency

clinicians is numbers of people that we can rule out rapidly and potentially not need to admit to the hospital.

If you can identify ways to do this that are safe from the data that we can find in great which to such as in *Clinical Chemistry*, then this really helps support change within a local sort of setting. So do a context assessment in your own area to evaluate it. But I guess to do this, this is why I'm so keen about having some consistency in the metrics that we report, at the moment there is great variability. So, it does take attention and detail to looking at the methodology of each of the studies that are reported to identify whether or not it can truly campaign and how relevant they will be for your context.

So, it's a great initiative to change or be involved in lots of changes locally. I'd encourage people to do it, but I think you go through it in the right steps to ensure that everybody is happy with the outcome.

Bob Barrett: That was Dr. Louise Cullen, a Staff Specialist in emergency medicine at the Emergency and Trauma Center Royal Brisbane and Women's Hospital and the Faculty of Medicine at the University of Queensland in Brisbane, Australia. Her editorial titled "Chest Pain Assessment: What is our End Game?" appears in the February 2022 issue of *Clinical Chemistry* along with the Regional Research papers discussed in that editorial. I'm Bob Barrett. Thanks for listening.