Clinical Chemistry

Optimizing Early Rule-Out Strategies for Acute Myocardial Infarction: Utility of 1-Hour Copeptin

Article:
P. Hillinger *et al*.
Optimizing Early Rule-Out Strategies for Acute Myocardial Infarction: Utility of 1-Hour Copeptin
Clin Chem 2015;61:1466-74
http://www.clinchem.org/content/61/12/1466.abstract

Guest:
Dr. Petra Hillinger is from the Department of Internal Medicine at the University Hospital Basel in Switzerland.

Bob Barrett: This is a podcast from *Clinical Chemistry*, sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I am Bob Barrett.

Symptoms suggestive of heart attack were among the leading causes of presentation at emergency departments. The rapid identification of acute myocardial infarction as a life-threatening disorder is important for the early intervention of appropriate therapy and treatment.

Since the introduction of high-sensitivity cardiac troponin assays, myocardial infarction can be diagnosed earlier and with greater sensitivity. However, a safe rule out of AMI is still time-consuming, especially in patients who present early after symptom onset.

A promising strategy to accelerate rule out of AMI is the combination of high-sensitivity cardiac troponin and copeptin measurements at presentation. The December 2015 issue of *Clinical Chemistry* published a multicenter study regarding optimizing early rule out strategies for acute myocardial infarction.

The lead author of that paper is Dr. Petra Hillinger from the Department of Internal Medicine at the University Hospital Basel in Switzerland. She is our guest in today's podcast.

Dr. Hillinger, tell us something about acute myocardial infarction and why an early rule out of AMI is important in routine emergency medicine management?

Dr. Petra Hillinger: There are several reasons why early rule out of acute myocardial infarction is relevant for emergency medicine practice. First of all, chest pain and other symptoms suggestive of acute myocardial infarction are among the leading causes for presentation at the emergency department. Around 10% of all patients presenting to the ED have chest pain as the chief complaint and about 50% of all patients presenting with chest pain are finally admitted as inpatients.

As chest pain is a very common clinical feature at the emergency department, it is important to rapidly identify patients who eventually suffer from acute myocardial infarction as it is a potentially life-threatening disorder. Although management and therapy has improved over the last decades, AMI is still a leading cause of morbidity and mortality.

When rapidly identified, appropriate and evidence-based therapy can be initiated early, thus leading to better outcomes.

The diagnosis of acute myocardial infarction is based on three cornerstones. First, clinical assessment, including the patient's history and detailed description of the chest pain characteristics, the 12-Lead Electrocardiogram and especially biomarkers of myocardial necrosis, and if it's possible, cardiac troponin. Because the vast majority of suspected acute MI patients eventually do not suffer from acute myocardial infarction, rapid and safe rule out is very important to prevent delayed consideration of alternative diagnosis and expensive overcrowding of the emergency department. So correct management decisions are also of great economic importance.

Bob Barrett: There has been a lot of activity in medical diagnostics regarding cardiac markers. Can you tell us something about the latest advances to help establish early rule out of acute myocardial infarction?

Dr. Petra Hillinger: Due to the delayed increase of troponin after onset of myocardial ischemia, serial measurements are mandatory to diagnose or exclude acute myocardial infarction as the conventional troponin markers lack sensitivity within the first hours, the so-called troponin line periods.

High-sensitivity cardiac troponin assays allows to diagnose AMI earlier and more frequently; nonetheless, it's really time-consuming to safely rule out acute myocardial infarction, especially in patients who present early and very early after symptom onsets.

A promising new strategy to facilitate rule out of AMI is the combined measurement of troponin and copeptin at presentation. Several studies have shown that copeptin is really universally elevated in the first hours of the night and that biomarker of endogenous stress provides substantially incremental value for the early rule out of acute myocardial infarction when using conventional, less sensitive cardiac troponin assays.

So what's copeptin exactly? It's the C-terminal part of the vasopressin prohormone and it can be used as a stable surrogate marker for the unstable and rapidly cleared arginine vasopressin.

Copeptin and arginine vasopressin are both synthesized in the hypothalamus and then both released into the circulation from the neurophysin.

AVP helps to regulate osmotic and cardiovascular homeostasis, and has been observed that concentrations are increased in acute medical conditions like septic shock, stroke, heart failure or myocardial infarction, and copeptin seems to be associated with increased mortality.

There are at the moment conflicting data on the incremental value of copeptin when using high-sensitivity cardiac troponin. Accordingly, copeptin is recommended in conjunction to troponin whenever high-sensitivity cardiac troponin is not available.

With high-sensitivity cardiac troponins the time interval to the second cardiac troponin measurement can be shortened to 3 instead of 6 hours.

For some high-sensitivity cardiac troponin assays a 1-hour approach has been validated. This algorithm is recommended in the recently published guidelines of the European Society of Cardiology for the management of acute coronary syndrome in patients presenting without persistent ST-segment elevation.

High-sensitivity cardiac troponin is a continuous arrival and the probability of acute myocardial infarction increases with increasing levels of high-sensitivity cardiac troponin. Early absolute changes of the levels within 1-hour can be used as surrogates for absolute changes over 3 or 6 hours.

It's important to consider that the cutoff levels are assay-specific. When using any algorithm, there are several conditions to consider.

First of all, algorithms should only be used in conjunction with all available clinical information, including chest pain characteristics and electrocardiogram.

And second, in patients who present very early after chest pain onset, a second cardiac troponin level should be obtained at 3 hours, if it's a high-sensitivity cardiac troponin level. If not, if it's conventional, at 6 hours later, as late increases in cardiac troponin has been ascribed in the small subgroup of patients.

Serum cardiac troponin testing should be continued if the clinical suspicion of acute MI remains high or in the setting of ongoing or recurring chest pain.

Bob Barrett: Doctor, what are the advantages of the dual marker approach using both copeptin and high-sensitivity cardiac troponin, and are there any shortcomings to this approach?

Dr. Petra Hillinger: So a dual marker approach with high-sensitivity troponin and copeptin has been shown in some studies to have higher negative predictive value for the rule out of acute myocardial infarction, but not in all studies.

So as I said before, there are conflicting data and results about it, the combination of copeptin and high-sensitivity cardiac troponin, and further studies are needed to really prove this hypothesis for both markers in conjunction.

What we know is that copeptin has been shown to rise immediately after acute myocardial infarction and it declines over the next hours. So it's a very useful tool in the early diagnosis of acute myocardial infarction.

The exact release pattern of copeptin during the initial hours of spontaneous acute myocardial infarction was until now relatively poorly investigated. So it's unknown whether acute MI patients missed by copeptin measured at presentation could be detected by obtaining a second measurement at 1-hour to accelerate the rule out of acute myocardial infarction.

So our main field of interest are patients with negative high-sensitivity cardiac troponin concentrations but elevated copeptin concentrations at presentation. As there is evidence that these patients are at higher risk of acute myocardial infarction, our hypothesis was that a second copeptin measurement 1-hour after presentation could facilitate the assessment of these intermediate risk patients and thereby improve the diagnostic accuracy and reduce the time to rule out acute myocardial infarction.

Contrary to our hypothesis, a second copeptin measurement did not significantly increase the negative predictive value of patients in the rule out setting and the negative predictive value for patients in the intermediate risk setting was not increased either. So therefore we cannot recommend fewer copeptin measurements for diagnostic purposes.

Bob Barrett: Well, finally doctor, what do you see is the current major gaps in evidence and knowledge in the diagnosis and early rule out of AMI?

Dr. Petra Hillinger: First of all, the incremental value of copeptin over high-sensitivity cardiac troponin assays remains to be further investigated and fully proven.

Another very important topic is the 1-hour algorithm with high-sensitivity cardiac troponin to rule in and rule out acute myocardial infarction. So in patients presenting with chest pain to the emergency department, this algorithm has been validated for some assays, but has not yet been tested within a randomized controlled trial.

With this new accelerated rule out option, with this 1-hour algorithm there is a clinical need to further investigate the best management of patients assigned to the observational zone according to the 1-hour algorithm.

Bob Barrett: Dr. Petra Hillinger is from the Department of Internal Medicine at the University Hospital Basel in Switzerland. She has been our guest in this podcast from *Clinical Chemistry*.

I am Bob Barrett. Thanks for listening!