Clinical Chemistry

Temporal Biomarker Profiling Reveals Longitudinal Changes in Risk of Death or Myocardial Infarction in Non–ST-Segment Elevation Acute Coronary Syndrome

Article: Mark Y. Chan, et al.
Temporal Biomarker Profiling Reveals Longitudinal Changes in Risk of Death or Myocardial Infarction in Non–ST-Segment Elevation Acute Coronary Syndrome.
Clin Chem 2017;63:1214-26.
http://clinchem.aaccjnls.org/content/63/7/1214

Guest: Dr. Mark Chan is a senior consultant cardiologist at the National University Heart Centre, Singapore, and an associate professor at the Yong Loo Lin School of Medicine, National University of Singapore.

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.

It is well-known that circulating concentrations of N-terminal pro–B-type natriuretic peptide, or NT-proBNP, and high-sensitivity C-reactive protein, hs-CRP, reflect levels of hemodynamic stress and systemic inflammation. When measured during acute events, increased NT-proBNP is associated with risk of heart failure and mortality, while increased hs-CRP is associated with increased risk of myocardial infarction. We don't know whether monitoring longitudinal changes in these biomarkers after a patient is stabilized has prognostic significance in their long-term dynamic risk for cardiovascular events.

An original article published in the July 2017 issue of *Clinical Chemistry* investigated this question. The article's primary author, Dr. Mark Chan, joins us for this podcast. Dr. Chan is a senior consultant cardiologist at the National University Heart Centre, Singapore, and an associate professor at the Yong Loo Lin School of Medicine, National University of Singapore.

Doctor, your study quantified changes and commonly used biomarkers over time, and associated those with risk for cardiovascular events in patients with non-ST segment elevation acute coronary syndrome. So, why did you decide to investigate the time-based changes in NT-proBNP and high-sensitivity-CRP in this group of patients?

Dr. Mark Chan: The motivation for this study really first grew out of what I've thought was an unmet need in the clinic when managing patients with non-STE acute coronary syndrome, so non-STE ACS. When we monitor these patients in the clinic, we would measure their blood pressure, and lipid profile and again, diabetic. We measure their glucose levels but these are really just looking at the risk factors. We don't really have any quantitative or objective way to tell if the patient is going to get another acute coronary syndrome or end up with death from an acute coronary syndrome.

So, I was looking for an objective means of, preferably, some blood-based, easily accessible, easily measurable biomarker that could be used in the clinic that we could give as a better idea of what would be happening down the road at six months after a heart attack or acute coronary syndrome. Would that patient be at risk of having another acute coronary syndrome in the future? So, that was the key motivation. And our group is not the first group that has investigated, looking at repeated measurements of biomarkers to monitor the progress of patients with non-STE ACS.

A number of other groups have done a very good work on this topic. The one particular study that was, I would say, a benchmark, a definitive study, was actually done by one of the associate editors of *Clinical Chemistry*, Dr. David Morrow, who in 2004 looked at how changes in BNP, B-type Natriuretic Peptide, may confer a change in the prognosis of a patient with non-ST ACS if that BNP level either went up or came down over an eight-month period from the time the patient had the first event to eight months later when the BNP test was remeasured.

So, that was really the first paper, first analysis that showed that measuring the BNP once would not necessarily be the final answer as to what the patient's long-term prognosis would be. But that, by remeasuring the patient's BNP, we would know whether the patient's prognosis would be altered whether the patient may actually be doing better depending on how the BNP measurements changed over time.

One of the key things I found in that study, kind of take that study further was to try to look to see whether the change over time could be analyzed more quantitatively. In Dr. Morrow's paper, he looked at BNP levels going from baseline to eight months above and below a threshold of 80 picograms per milliliter. But this was really a dichotomous way of looking at changes in BNP measurement over time.

We wanted to see basically if there was a better way of quantifying the change over time to see if greater changes over time would confer a much better or, potentially, much worse prognosis depending on the direction of change of the biomarkers over time.

Bob Barrett: Okay, so what were the key findings in this study?

Dr. Mark Chan: So, the key findings in this study were that, first, this is a population that had non-ST ACS but were uniquely managed in that they were managed medically without any upfront revascularization. And this is a less commonly encountered population, but it is a very useful population for such a

study because this is really the kind of natural history of non-ST ACS.

So, this was a unique opportunity and I'm grateful to the TRILOGY trial investigators and the study sponsors of giving this opportunity to answer this question with this clinical trial population but, essentially, in 1,550 or so subjects with non-ST ACS, we measured NT-proBNP which is the N-terminal peptide, the pre-peptide of BNP, in all patients and we measured them not just at baseline but also at 30 days and at 6 months after the non-ST ACS.

We also measured the high-sensitivity CRP or C-reactive protein at the exact same time points, baseline, 30 days and 6 months. And we found that with NT-proBNP, it was interestingly not just predictive of what happened to the patient three years later, it was also the change in NT-proBNP between time points that was incrementally predictive of what would happen to the patient. And the interval of change that was required to signify a significant improvement of the duration and prognosis was an increase or decrease in NT-proBNP of 40% between the baseline measurement and the six months measurement.

Now, if your BNP went up by 40% from the time you had your non-ST ACS to six months later, it doesn't increase over that six-month period, you were at a 14% increased risk of cardiovascular death up to three years compared to another patient whose NT-proBNP levels had not changed over that six-month period. Conversely, if your NT-proBNP came down by 40% over that six-month period, you'd then be at 14% lower risk of dying of cardiovascular death event compared to another patient whose NT-proBNP level had not changed by that extent over the six-month period. And that is similar to what Dr. David Morrow showed in his seminal paper in 2004.

So, here, we took it a step further, we looked to see what would happen if the BNP levels went even higher, if the change over that six-month interval was even higher either in an increasing fashion or a decreasing fashion. And we found that when we looked at BNP changes over time in such a quantitative fashion, that there was actually an incremental risk of cardiovascular death if your BNP increased in increments of 40%. So, for example, if your BNP increased by 80% over a six-month period, your risk of a cardiovascular death event would then be around the region of 28%. And if your BNP went up even further to 240%, you would then be at 120% increased risk of cardiovascular death, up to three years. And this quantitative association was also preserved for patients whose BNP came down over time. So, if your BNP levels came down by 120% over a six-month period, you would

then have a 70% lower risk of having a cardiovascular death event at three years after your initial non-ST ACS.

Now, we then analyzed the high-sensitivity C-reactive protein levels in the same way. And we found a similar relationship but the CRP in this case was predictive of recurrent myocardial infarction events, but not cardiovascular death events.

The hs-CRP level of 40% increase over six months was predictive of a 10% increased risk of myocardial infarction up to three years after the initial non-ST ACS. And likewise, with increasing levels of hs-CRP over a six-month period, for example, if your hs-CRP increased by as much as 240% from the initial amount over the six-month period, you would then have close to an 80% increased risk of another heart attack, or myocardial infarction, at three years after the initial non-ST ACS. Likewise, if your hs-CRP came down over that six-month period, if it fell by 40%, you were then at 10% lower risk of recurrent myocardial infarction, up to three years. And if the patient's hs-CRP fell by 120% over a six-month period, that patient would then be at a 80% lower risk of having a myocardial infarction event up to three years.

Those were essentially the findings that showed that time-based changes in NT-proBNP and hs-CRP were quantitatively associated with the changes in the risk of cardiovascular death and myocardial infarction events respectively wherein patients are followed up over three-year period.

Bob Barrett: So doctor, how are these results applicable in the clinical care, and could they change the way patients are managed?

Dr. Mark Chan: I think these results are applicable to clinical care in a number of ways. We have NT-proBNP and hs-CRP available in many labs, they are almost now universally available and they cost very little to do. So, going back to original motivation for performing the study, we have really no tools that we can use to monitor if a patient is going to do badly. We do not know if the patient is going to have another ACS or the patient is going to die from an ACS or some other cardiovascular event.

And this is really a major challenge, a major unmet need in the management of non-ST ACS patients. It really feels that there is a lack of monitoring biomarkers when we, say, compare ourselves to the oncologist, an oncologist or cancer specialist who's managing a patient with colon cancer can measure the patient's carcinoembryonic antigen, CEA levels, over time regularly at each visit. And when the levels go

up, then the oncologist would suspect that the patient may be having a recurrence of the cancer.

However, we, until now, don't really have such tools in clinical practice. And I think this study, our team has demonstrated two very readily available tests in almost any hospital's laboratory, can now be used to monitor our patients with acute coronary syndrome that we can use this to give us an idea or glimpse into the future by simply measuring these readily available biomarkers at any of the follow up visits with such patients.

I don't think that these tests need to be repeated regularly, multiple times, necessarily at every single follow up visit. I do think that if we do want to measure the test in a serial way, in a repeated way, to get answers about whether the patient's prognosis changes over time, then based on the results of our study, it would be most useful to measure these biomarkers at around the time the patient is hospitalized for the non-ST ACS and several months later, six months later, not thirty days later, but to allow at least a period of four to six months before the repeat measurement is made. That's probably when you think that to get a good idea of whether the patient has stabilized your initial treatment and whether the outcomes are going to be moving in the right direction. So, that's how I think our results can be applicable to the way we manage patients.

Bob Barrett Okay. Well, finally, Dr. Chan, what other research questions remained to be answered related to this work?

Dr. Mark Chan: I would say that this work is just one of a few early steps in developing monitoring biomarkers to evaluate long-term progress and prognosis of patients with non-ST ACS.

If we look at the incremental predictive value of NT-ProBNP and hs-CRP compared to other clinical risk factors, we found that by measuring the changes in NT-proBNP and hs-CRP over time, these changes only offered quite a modest improvement or increase in the prediction of risk. They were incrementally predictive over common available clinical risk factors, but they were not very, very incrementally predictive.

So, I think that the search is still on for better biomarkers out there. There will be such biomarkers available in the future. I'm confident of that because there are so many augment technologies that now allow us to discover many potentially prognostic biomarkers that we weren't able to discover previously.

The other important question to answer is that, once we have established such biomarkers that change over time, I

think the next point we need to try to address is to see if changes in treatment can actually modify the levels of these biomarkers to see whether we are actually making a difference to the patient.

Bob Barrett: Dr. Mark Chan is a senior consultant cardiologist at the National University Heart Centre, Singapore and an associate professor at the Yong Loo Lin School of Medicine National University of Singapore. He has been our guest in this podcast from *Clinical Chemistry*. I'm Bob Barrett. Thanks for listening.