Clinical Chemistry

The Challenges and Concerns Companies Face Pertaining to the US Food and Drug Administration 510(k) Process for Cardiac Biomarkers

Bob Barrett: This is the podcast from '*Clinical Chemistry*'. I am Bob Barrett.

The cardiac troponins have been internationally recognized as the standard biomarkers for the detection of myocardial injury, the diagnosis of myocardial infarction and risk stratification of patients presenting with symptoms of acute coronary syndrome.

Several organizations have endorsed the use of the 99th percentile value of troponin which is derived from a referenced non-diseased population as the medical decision-making cut-point.

There is now a significant body of literature describing new high-sensitivity assays of both troponin I and troponin T assays that are marketed outside of the US, but are not yet cleared by the US Food and Drug Administration.

Manufacturers are facing new challenges in bringing to market new assays that use the 99th percentile as the cut-point value for medical decisions. The January 2012 issue of '*Clinical Chemistry*' featured a question and answer session with several industry leaders on the challenges of obtaining approval from the US Food and Drug Administration for high-sensitivity cardiac troponin assays and other issues involved in making these tests an integral aspect of diagnostics.

Joining us in this podcast is Dr. Christian Zaugg from the Medical and Science Affairs Division of Roche Diagnostics in Switzerland who participated in the question and answer session.

Dr. Zaugg, what new analytical challenges are presented to implement these assays into your current instruments and platforms?

Dr. Christian Zaugg: So in contrast to most other biomarkers at the precision range for troponins is really near to lower analytical limits off the assays. So this poses challenges to the signal to nodes ratio and potential interferences and another major challenge certainly is to reach a high-sensitivity and precision at the lower concentrations across all assay versions and platforms. And moreover the assay really needs to provide low imprecision at the lowest concentration range that is also below the 99th percentile cutoff down to the limit of detection, because this range is not only necessary and important for risk stratification of patients, particularly non-ST elevation ACS, it is also important for the correct diagnosis of acute myocardial infarction according to the universal definition of MI, because according to this definition only one value need to be

evolved in 99th percentile out of two -- at least two zero troponin values.

So in other words, one of two zero troponin values maybe below the 99th percentile, therefore, values below the cutoff provide useful information. For instance, there is a major difference where the rise is from 13 to 15 or from 5 to 15 picograms per ml. Therefore, this rise and fall criterion needs to be as precise as possible. It is clear that minimal change values for rise and fall criterion of troponins are still a matter of debate.

According to the recent publications also absolute delta changes need to be superior to relative changes and any rise and fall criterion will critically depend on the assay precision around the cutoff value, and will therefore be assay-dependent and this as a consequence validated assay-specific algorithms will therefore likely be a necessity to assist clinicians in the routine use of high-sensitivity troponin assays.

Bob Barrett: Doctor, what do you think is the greatest potential barrier facing diagnostic manufacturers who are looking to introduce new troponin assays?

Dr. Christian Zaugg: The major barrier to introduce these new troponin assays is related to the new regulatory expectations and to a lack of guidance, and this is a consequence of lack of expert consensus. Again, this leads to sharply rising development timelines, cost and risk, and this is again predominantly due to new regulatory expectations as well as lacking expert consensus and FDA guidance on critical aspects of high-sensitivity troponins. Increasing costs and risks as well as continuing pressure to reduce the price of diagnostic tests in general will eventually undermine the return of investment, and it may cause manufacturers to rethink development of new troponin assays.

Bob Barrett: What do you hear from your customers? What kind of feedback? What's their major issue regarding current commercial assays for troponin?

Dr. Christian Zaugg: Well, customers have not been reporting really major concerns related to contemporary troponin T assay that is the fourth generation assay, and the high-sensitivity troponin T assay, the fifth generation, was developed really to meet the requirements of universal definition of myocardial infarction, and as a result of improved sensitivity as it is true for all tests, the diagnostic specificity of high-sensitivity troponin assays has decreased and accordingly reduced specificity and the increased numbers of positive troponin testing has been the major concern with customers, particularly in the phase of right ask of the

conversation from the conventional to the high-sensitivity troponin T assay.

Still these concerns quickly could be and can be adequately addressed by preparation and education of clinicians and laboratory physicians about non-acute coronary syndrome etiologies and troponin elevations, and about importance of rise and/or fall in serial troponin values, and also by the fact that troponin testing should not be used like any other biomarker without clinical context. And accordingly, the high-sensitivity troponin assays are now recommended by the European Society of Cardiology Guidelines for non-ST elevation acute coronary syndrome.

Bob Barrett: Okay. Well, let's look ahead. What do you see is the future for additional development for troponin and other biomarkers?

Dr. Christian Zaugg: We think that a future helpful tool or instrument in the daily clinical routine will likely consist of algorithms for rapid and optimized differential diagnostic performance in ruling in and out of acute myocardial infarction and transferring patients, presenting to the emergency department. These algorithms should provide rapid rule-in or out and improve the specificity and such algorithms will likely be assay-specific and must each be supported by solid clinical evidence.

First algorithm for rapid rule-out of acute myocardial infarction within one to two hours after admission to the emergency department has been shown for the high-sensitivity troponin T assay. And of course these assays on algorithms need to be a post-active map elevated in large clinical trials.

We also believe that the introduction of high-sensitivity troponin assays has really left very limited room for auto-biomarkers in the diagnosis of acute MI or recurrent infarction.

There is clearly more room for additional prognostic biomarkers given that they provide incremental information to reclassify patients, and that is useful to guide therapy in meeting higher risk non-ST elevation ACS patients.

Bob Barrett: Dr. Christian Zaugg is from the Medical and Scientific Affairs Division of Roche Diagnostics in Switzerland. He has been our guest in this podcast from '*Clinical Chemistry*'.

I am Bob Barrett. Thanks for listening!

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