Clinical Chemistry Trainee Council
Pearls of Laboratory Medicine
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TITLE: Implementing High Sensitivity Cardiac Troponin Assays Into Practice

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Slide 1: Title Slide
Hello. My name is Dr. Fred Apple. I am Medical Director of Clinical Laboratories at Hennepin County Medical Center in Minneapolis and Professor of Laboratory Medicine in Pathology at the University of Minnesota, School of Medicine. Welcome to this Pearl of Laboratory Medicine on "Implementing High Sensitivity Cardiac Troponin Assays Into Practice."

Slide 2: How to sell a high-sensitivity cardiac troponin assay
High-sensitivity (hs) cardiac troponin assays for I and T will soon be FDA-cleared for clinical use in the United States. At present, Roche Diagnostics markets an assay designated hs-cTnT. Peer-reviewed literature will be necessary to provide the evidence for essential analytical characteristics including limit of detection (LOD), concentrations with imprecision (%CV) at 10% and 20%, and the 99th percentile value of a presumably healthy (reference) population.

Slide 3: High-sensitivity assays: looking forward and status today of analytics
hs-Cardiac troponin assays will be judged by their ability to obtain a measureable concentration in normal, reference subjects. A Task Force of the IFCC has deemed that to be considered a high-sensitivity assay, $\geq$50% of the reference subjects should provide a measureable concentration greater than the LoD. Gender-specific cutoff concentrations will need to be determined also. In addition, an imprecision at $\leq$20% at the 99th percentile will be essential for use in clinical practice.

Slide 4: Biomarker Guidelines
A list of published papers provide an overview of the evolving process, from 1999 through 2012, demonstrating the overwhelming acceptance worldwide of cardiac troponin as the sole definitive biomarker to be utilized to detect an acute myocardial infarction.

Slide 5: Universal definition of myocardial infarction
The Third Universal Definition of Myocardial Infarction has again supported cardiac troponin as the sole biomarker for AMI detection, predicated on a rising and/or falling pattern in the clinical setting of ischemia. Timing and serial sampling over a 3 to 6 hour period will provide optimal diagnostic accuracy. Assay imprecision is ideal at < 10%CV at the 99th percentile, but clinically acceptable at <20%CV.

Slide 6: Being rational about imprecision
The evidence-based literature supports the use of cardiac troponin assays that have an imprecision <20% CV at the 99th percentile. This has been revised since the 2007 NACB and the 2nd Universal Definition of MI guidelines. Assays with imprecision >20%CV should not be used in clinical practice.

Slide 7: Cardiac troponin epitope regions used for a majority of assays in the marketplace
This slide shows the similarities and the differences for both capture and detection antibodies used in the design of contemporary and point-of-care cardiac troponin assays. Because of the differences in antibody configurations and without a primary reference standard, standardization of assays is unlikely. Assay to assay differences in increased cardiac troponin concentrations will therefore be observed. There is no correction factor that can harmonize all cTnI assay results.

Slide 8: Cardiac troponin epitope regions used for a majority of assays in the marketplace
This slide shows the analytical characteristics of both cTnI and cTnT assays used for testing in the central laboratory. Due to the lack of assay standardization, substantial differences are found between assays for the limit of detection, 99th percentile, and imprecision of %CV at the 99th percentile value.

Slide 9: Cardiac troponin epitope regions used for a majority of assays in the marketplace
This slide describes the analytical characteristics of both FDA-cleared and other cTnI and cTnT point-of-care (POC) assays. Due to the lack of assay standardization, substantial differences are found between assays for the limit of detection, 99th percentile, and the imprecision at the 99th percentile value.

Slide 10: Nomenclature
The journal *Clinical Chemistry*, as published in an editorial by Apple and Morrow and a mini-review by Apple and Collinson in the January 2012 special issue, has taken the position that the novel, analytically sensitive assays will be designated as 'high-sensitivity.' Further, the use of whole number reporting in 'ng/L' will be required in all future articles published in the journal. The authors support international acceptance of these 2 proposals.

Slide 11: High-sensitivity cardiac troponin assays
This table demonstrates the analytical characteristics of the hs-assays. Improvements are observed in lower LODs and optimal %CVs (<10%) at the 99th percentile values.

Slide 12. Cardiac troponin assay scorecard criteria
This slide shows the criteria proposed by Apple regarding designation of assays according to a) imprecision at the 99th percentile value and b) measurable concentrations within the reference populations used to determine a 99th percentile value.

Slide 13. High-sensitivity assay scorecard
This slide demonstrates that all 5 hs-cTnI assays qualified as a level 3 or level 4 assay according to the scorecard. However, the hs-cTnT assay, even with the calibration readjusted assay, is designated as a level 1 (not a high-sensitivity assay) due to the fact that <50% of normal subjects have measureable values.

Slide 14: Reference interval portioning factors
How studies define what a normal, presumably, healthy reference population is will be important as for determining criteria for enrolling subjects into normal range studies. Studies have now demonstrated that 99th percentile values for men are higher compared to women.

Slide 15: Schematic of multiple cardiac troponin assays in healthy population
This figure, recently published (Clin Chem 2012), demonstrates the diversity of each assay's ability to a) measure concentrations within a normal population and b) the assay to assay variability at the 99th percentile value for high-sensitivity, contemporary, and POC assays.

Slide 16: Histograms of high sensitivity assay vs. contemporary assay by same manufacturer
The representative histograms using the Abbott Architect assays, as an example, show the near Gaussian distribution utilizing the hs-assay with 96% of subjects measureable, compared to only 1.7% with the current FDA-cleared contemporary assay by the Abbott Architect.

Slide 17: Biological variation of high sensitivity cardiac troponin assays
With the novel high-sensitivity assay's ability to measure cTn concentrations within the normal reference population, biological variability can now be determined for these assays. This may assist in clinical interpretations for determining analytical/biological noise for real, evolving changes from injury to the heart.

Slide 18. Points considered
This final summary slide overviews the "pearls" of investigational, published data for the high-sensitivity cardiac troponin assays that are expected to be FDA-cleared sometime in 2013.

Slide 19. References