Update on cardiac troponin standardization

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DEVELOPMENT OF A REFERENCE MATERIAL (RM) FOR COMMON CALIBRATION OF THE DIFFERENT ASSAYS FOR CARDIAC TROPONIN I (cTnI) DETERMINATION

So far, there is no consensus standard for cTnI; manufacturers prepare their own, so that different purification procedures and type of calibration antigens (purified free cTnI or cTnI complexed with troponin C or T) are employed. This leads to an important source of disagreement between assays. To decrease the discrepancy between existing assays, it is matter of importance to calibrate assays against the material representing the natural form of the antigen, i.e. the binary or the ternary complex. Interesting results were produced by HyTest scientists (1): Six different forms of cTnI were evaluated as possible common calibrator of six different assays: a natural free form, a recombinant free form, recombinant binary and ternary complexes, an 'in vitro' obtained ternary complex, and a native ITC complex purified from human cardiac tissue. The lowest between-assay bias in a serum sample was observed when native ternary ITC complex was used for the calibration of the systems. This important study demonstrated that it should be possible to achieve a considerable degree of method harmonization for cTnI by the use of an appropriate common calibrator material. The Committee for cTnI standardization of the American Association for Clinical Chemistry (AACC), having as primary mission the development and the characterization of a consensus RM for cTnI to minimize between-method variation, started a similar protocol, involving the evaluation of ten different candidate RMs, consisting of human native and recombinant protein, free and complexed, in liquid-frozen and lyophilized forms. The IFCC Committee on Standardization of Cardiac Markers (C-SMCD) cooperates since its creation with the AACC Committee.

Preliminary characterization studies to verify the material composition were conducted at National Institute for Standard and Technology (NIST). A round robin study, involving 8 participating manufacturers/13 analytical systems, using the 10 selected candidate RMs was later performed (Spring 2000), with the purpose of objectively identify a feasible number of RMs. This excercise targeted three RMs as preferable to move on to the next evaluation stage. Data from this study have recently been published (2). The next step (Spring 2001) will be a second round robin study, including serum pools for comparison and a preliminary evaluation of commutability of the three candidate RMs. It is hoped that the obtained results will allow initial harmonization of cTnI results in the short-term, so that all methods can achieve a degree of comparability.

Further developmental work to allow more rigorous, scientific standardization is however required. In fact, true standardization and traceability of measurement require a complete reference measurement system, employing purified complex as primary RM, a matrixed (serum-based) secondary RM, and a reference method needed to perform the value assignment to the secondary RM and to evaluate the analytical performance of the field methods (3).

DEFINITION OF QUALITY SPECIFICATIONS FOR TROPONIN ASSAYS

cTnI standardization is not only the process of realizing traceability by the creation of a reference system, but also the attempt to reduce the sources of variability of immunoassays. On this particular topic, an IFCC document was recently prepared by C-SMCD for publication (4). Goals of this document are that:

a. Manufacturers endorse or at minimum address the enclosed recommendations.

b. All package inserts and instructions for use of troponin immunoassays include adequate information on method design, as well as on preanalytical and analytical performance characteristics as outlined in the document itself.

c. Research projects that consider the definition of the issues addressed in the document are selected with priority and appropriately designed.

With regard to the last point, C-SMCD is preparing a protocol to evaluate the analytical imprecision of commercially available troponin assays around the decision limit for myocardial infarction, through the definition of the imprecision profile for each assay. Manufacturers of troponin assays will be invited to directly participate to this study.

REFERENCES

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