

PGM Guidelines for description of criteria and methods for testing of specificity of assay methods for quantities in the fibrinolytic system

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In this article

- In 1990 the Subcommittee of Fibrinolysis within the framework of the Scientific and Standardization Committee of the ISTH decided to point out a working group, which should study whether different commercial methods for measurement of plasminogen activator inhibitor activity and plasminogen activator inhibitor type 1 antigen produced results transferable from one laboratory to another

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1. Foreword

In 1990 the Subcommittee of Fibrinolysis within the framework of the Scientific and Standardization Committee of the ISTH decided to point out a working group, which should study whether different commercial methods for measurement of plasminogen activator inhibitor activity and plasminogen activator inhibitor type 1 antigen produced results transferable from one laboratory to another (1,2). The study documented that there was not consensus of the results produced by the different methods in different laboratories, and furthermore that some of the commercial methods might be characterized by a high imprecision and a poor accuracy (1,2). Subsequently, the Subcommittee of Fibrinolysis (Amsterdam, 1991) decided a further strategy to improve this situation, i.e. the introduction of reference measurement procedures as the most reliable approach to obtain accurate results in clinical laboratories for measurement of quantities in the fibrinolytic system. Such an approach makes use of the experience from clinical biochemistry (3).

To achieve this goal was more complex than originally anticipated and the involvement of various organizations and players in the field had to be defined and organized. However, in September 1995 a comprehensive procedure proposed by the

above-mentioned working group was accepted by the executive director of the SSC and started as a pilot project within the subcommittee of fibrinolysis.

The pilot project was run by a project group on methods (PGM) including Drs. T. Barrowcliffe, P. Declerck, C.W. Francis, P. Gaffney, J. Gram, J. Jespersen, C. Kluft (Chairperson).

Briefly, the procedure defines the role of the SSC and its subcommittees as experts on methods and materials in haemostasis; the NIBSC as the body produce and characterize standard materials, and the IFCC as the body to select and execute reference method procedures. The aim is to develop methods and materials in combination and coordinated in effort and time.

It was recognized that in order to provide a forum for selection of a reference method, the SSC should contribute with expertise by providing a platform of defining criteria for specificity and testing these criteria for methods of quantities in the haemostatic system.

2. Scope

Scientists and companies can document their methods according to the expert reports on criteria and test methods in order to obtain methods for determination of quantities in the fibrinolytic system with ensured day-to-day, intra- and interlaboratory consistency in clinical laboratories as well as research laboratories. The aim is to improve transferability of accurate data from one laboratory to another, from publications to daily laboratory work, and to obtain more clearly defined reference ranges and, if possible, decision limits for results of quantities.

A method fulfilling the said criteria should be characterized by high quality measure-

ment, which depends on detailed information on principle of reaction, method of measurement, preanalytical and analytical steps, data reduction, reliability characteristics, reference limits, and quality assurance.

The present guidance may not be applicable for description of all methods of fibrinolytic quantities. The structure of the present guidance is therefore optional, but the clauses included should be considered.

3. Written information

3.1. Format of the document

3.1.1. Title page

The title should be short and concise. Included in the title should be the name of the quantity being the objective of the measurement procedure. The name of the quantity should preferentially follow the latest edition from the International Union of Pure and Applied Chemistry (IUPAC) or otherwise a name officially accepted by ISTD (4).

3.1.2. Footnote

As a footnote to Title and Authors should be mentioned: This work was carried out by the authors as a working group within the frame-work of the Subcommittee on Fibrinolysis of the SSC of the ISTD. The report was approved by the Project group on methods and materials (Drs. T. Barrowcliffe, P. Declerck, C.W. Francis, P. Gaffney, J. Gram, J. Jespersen, C. Kluff (Chairperson) and a plenary session of the subcommittee.

3.1.3. Introduction

The document should include a short introduction which describes the use of the quantity in health care, general problems with measurement of the quantity in clinical laboratories, and the place of the recommended measurement procedure in a binary analyte reference system based on true values (when such exist) (5).

Molecular forms of the component which can occur in several body fluids, can occur in pathological conditions and during medical interventions, including quantitative information should be briefly summarized.

Explanation on which situation the selected analytical method can be applied and which molecular forms are addressed.

(Note: it is important to balance between completeness and practicability and it is possible to state that a limitation applies for example that total protein assay in blood plasma is aimed at and special molecular forms in extreme conditions such as polytrauma, lethal sepsis, and in rarely studied body fluids like liquor are not included).

Note: In principle, particular attention should be paid to blood, but study of other biological fluids can be included when information is adequate to decide so.

3.1.4. Principle of the assay procedure

The principle of the measurement procedure should be described.

It should be summarized which mechanisms are involved in the biological function of the component, and its appearance in blood, and on which information the method focuses. In case of an immunological method the fraction addressed or the total protein addressed should be explicitly defined.

In case of an activity assay the question should be addressed whether the method approaches closely the biological function and/or what has been excluded due to the principle of the assay method. The PGM favours for activity method procedures as complete as possible representing biological function, such as the clot lysis assay for plasminogen activators. This should minimize the risk that purified material is not representative and cannot be quantified at a higher metrological level by protein assay procedures such as amino acid analysis.

In relation to the assay principle interfering factors should be identified and listed for consideration.

3.1.5. Manuals

The working group can identify presently available manuals containing a prescription of the same method and comment upon the suitability or need for revision (ECAT book, Bergmeyer series, Methods in Enzymology, etc.).

3.1.6. Criteria for specificity

Based on the above considerations the working group defines a concise set of criteria.

3.1.7. Test methods for criteria

Based on the criteria set the working

group advises about techniques of testing a method for adherence to the criteria. This can be in the form of a set of clinical and manipulated samples that should be tested and have specific results (example depleted plasma should be zero; plasma spiked with excess of interfering factors should give the same answer as non-spiked plasma).

3.1.8. Standardisation and quality assurance

The working group should identify which available reference materials and standards (6) from NIBSC, WHO, or other sources are suitable or potentially suitable and define the status of the SSC secondary matrix sample. In addition the present activities of EQAS which include the analyte should be listed (7).

3.1.9. Remarks

This section can contain remarks on various aspects and include the following one when relevant.

3.1.9.1. Preanalytical factors

The document could describe potential preinstrumental sources of variation for the quantity to be measured.

3.1.9.2. Preparation of the patient

This sub-clause could contain brief information (preferably referring to appropriate source summary documents) on essential requirements for fasting, posture of the patient before sampling, which time of the day should the specimen be collected, time of rest before collection of samples, which specimens can be used, venipuncture techniques (e.g. two-tube techniques), and optionally, the physiologic effect of drugs (e.g. steroids, fish oil).

3.1.9.3. Preparation of specimen

This sub-clause could include information on site of blood drawing, which type of collection tubes and anticoagulants should be used, the addition to the sample of preservatives or stabilizers, storage conditions of the sample, storage conditions of the specimen, specifications of centrifugation procedures. It could be observed whether bilirubin, haemoglobin or lactescence of the samples interfere with the measurement procedure.

3.1.9.4. Description of materials

The degree of the necessary purity or source (recombinant?) of the reagents

used should be commented on when necessary. Trade names, systemic name or formula can be given. Similarly, the origin of calibration materials with information on purity, the procedure for preparation of calibrators with different concentrations should be detailed.

3.1.9.5. Instrumentation

It could be identified if the measurement procedure is dependent on specific equipment or alternatively, whether it can be applied with the use of equipment with similar measurement principles.

3.1.9.6. Genetic analysis

It could be identified whether presently genetic analysis of polymorphisms in the gene for the analyte is relevant to be included in view of composition of the analyte or in relation to its quantity.

3.1.9.7. Reference ranges

The reference ranges of the method should be reported according to accepted guidelines (8) and should be based on a sufficiently large study population (9). Possible sex and age differences or reference values should be described.

3.2.0. References

The references should be listed consecutively as listed in the text and follow the Vancouver declaration.

4. References

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