Is standardisation in coagulation feasible?

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In the hierarchy of standardization, an unbroken traceability chain of standards and methods is needed with definitive methods and primary standards at the top, reference methods and secondary standards in the intermediate part and field methods and working standards at the end of the chain. Coagulation tests are often functional field methods.
Current EQA-programs for coagulation evaluate the performance of field methods and working standards. In order to move to type 1 or 2 EQA-programs, which allow trueness verification of test results and monitoring of interlaboratory variation, commutable and value-assigned EQA-materials are needed (1). To that end, ECAT installed a working group which explored the feasibility of enhancing the evaluation capability of its EQA-program using antithrombin (AT) as an example.
As AT has multiple proteoforms, it was decided to set up a mass-spectrometry based Candidate Reference Method, using a bottom up quantitative proteomics approach. Selection of peptides in antithrombin not affected by known mutations in type II antithrombin or variation in glycosylation will provide a general method for all antithrombin. Specific peptides which discriminate between α (4 CHO antennas) and β (3 CHO antennas) AT allow detection of these subtypes of AT. The progress on this endeavour will be shown.
The consequences will be significant, as ECAT will be able to distribute samples which have been value assigned for α- and β-antithrombin. From the moment that target values are available, scoring of lab performance can be done against target values and no longer against consensus values. Secondly, standardization of field methods can be improved once a reference measurement system is in place. To that end, field methods can be tested for selectivity, because selective functional methods for β-antithrombin and insensitive to type II slow AT are desired.
The working group also further developed methods for beta antithrombin (using high salt) and insensitive and sensitive to type II slow AT (using short and long incubation). Validation with patient samples is planned.
We conclude that with the introduction of MS-based quantitative proteomics, standardisation of coagulation tests will become feasible. For multiple molecular forms or mutants of proteins, such as for antithrombin, the challenge lies further in the development of field tests which measure well defined, clinically relevant proteoforms.

References
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