Guidance for laboratory testing of DOACs

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RCG Disclosures

Expert testimony for dabigatran and rivaroxaban testing

Speaker honoraria: Siemens Healthcare Diagnostics

Advisory boards: NovoNordisk, Roche Diagnostics

Consultant: Wilmer Hale law firm, Diagnostica Grifols, Siemens

Board member: NASCOLA and ICSH

ICSH: International Council for Standardization in Haematology

Initiated as a standardization committee by the European Society of Haematology (ESH) in 1963

Officially constituted by the International Society of Hematology (ISH) and the ESH in Stockholm in 1964.

The ICSH is recognised as a Non-Governmental Organisation with official relations to the World Health Organisation (WHO).

The ICSH is a not-for-profit organisation that aims to achieve reliable and reproducible results in laboratory analysis in the field of diagnostic haematology.

The ICSH coordinates Working Groups of experts to examine laboratory methods and instruments for haematological analyses, to deliberate on issues of standardization and to stimulate and coordinate scientific work as necessary towards the development of international standardization materials and guidelines.

Reinitiated interest in coagulation documents in 2016.

ICSH Lab guidance for DOAC measurement

AIM:

- **Intended as laboratory guideline**
  - **Not intended for, or recommending, whether patients should get tested while on DOACs**
- **Evidence based (peer-reviewed publications) or expert opinion with consensus**

ICSH DOAC Committee members

- Dot Adcock - USA
- Shannon Bates - Canada
- Jonathan Douxfils - Belgium
- Robert Gosselin – USA (Chair)
- Isabelle Gouin-Thibault - France
- Cecilia Guillermo - Uruguay
- Emmanuel Favalaro - Australia
- Steve Kitchen - United Kingdom
- Yohko Kawai - Japan
- Edie Lindhoff-Last – Germany

Over 100 DOAC related peer-reviewed publications by the committee members

ICSH Lab guidance for DOAC measurement

Document Objective

- Intended as laboratory guidance document
  - Address the three phases of DOAC (laboratory) testing:
    - Pre-analytical (sample acquisition)
    - Analytical (testing)
    - Post-analytical (reporting)
- Open access (free downloads)
- Not intended to address merits of patient testing

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- **Laboratory studies do not meet recommendations for clinical guidelines (e.g. GRADE), hence the term "guidance" document was adopted.**
- **Recommendations were based on (1) information from peer reviewed publications about laboratory measurement of DOACs, (2) contributing author's personal experience/expert opinion and (3) good laboratory practice**
- **Consensus recommendations indicate agreement by <u>all</u> contributing authors**
  - **Sticky points were sample stability, screening tests, EQA**

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Industry was supplied document prior to manuscript publication for input/comments

- **Pharma: Boehringer Ingelheim, Bristol-Meyers Squibb, Daiichi Sankyo**
- **IVD: Siemens Healthcare Diagnostics, Instrumentation Laboratory, Grifols, Diagnostica Stago, Sekisui**

Thromb Haemost 2018;118:437–450. Open Access

ICSH Lab guidance for DOAC measurement

International Council for Standardization in Haematology (ICSH) Recommendations for Laboratory Measurement of Direct Oral Anticoagulants

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Thromb Haemost 2018;118:437–450.

Abstract

This guidance document was prepared on behalf of the International Council for Standardization in Haematology (ICSH) for providing haemostasis-related guidance documents for clinical laboratories. This inaugural coagulation ICSH document was developed by an ad hoc committee, comprised of international clinical and laboratory direct acting oral anticoagulant (DOAC) experts. The committee developed consensus recommendations for laboratory measurement of DOACs (dabigatran, rivaroxaban, apixaban and edoxaban), which would be germane for laboratories assessing DOAC anticoagulation. This guidance document addresses all phases of laboratory DOAC measurements, including pre-analytical (e.g. preferred time sample collection, preferred sample type, sample stability), analytical (gold standard method, screening and quantifying methods) and post analytical (e.g. reporting units, quality assurance). The committee addressed the use and limitations of screening tests such as prothrombin time, activated partial thromboplastin time as well as viscoelastic measurements of clotting blood and point of care methods. Additionally, the committee provided recommendations for the proper validation or verification of performance of laboratory assays prior to implementation for clinical use, and external quality assurance to provide continuous assessment of testing and reporting method.

Keywords
- direct oral anticoagulants
- laboratory measurement
- laboratory guidance
- recommendations

received
August 28, 2017
accepted after revision

DOI https://doi.org/10.1055/s-0038-1627480.
ISSN 0340-6245

ICSH Lab guidance for DOAC measurement

Background and DOAC description

- **Drug details (indication, dose, bioavailability, etc)**
- **Anti-factor IIa DOAC (Dabigatran)**
- **Anti-Factor Xa DOAC (Rivaroxaban, Apixaban, Edoxaban)**
  - **Acknowledged recent approval of betrixaban but noted lack of data related to laboratory testing.**

ICSH Lab guidance for DOAC measurement

General patient recommendations:

- **If non-emergent testing is necessary, recommend trough drug level assessment.**
- **Recommend DOAC levels be reported in ng/mL units.**
- **Recommend a comment with each reported DOAC result to indicate lack of DOAC 'therapeutic ranges', but cite expected trough levels (correlating with dose) for DOAC-treated patients from published studies.**
  - **Usefulness in randomly (emergent) collected samples?**

ICSH Lab guidance for DOAC measurement

Sample requirements for DOAC measurements

- Plasma prepared from3.2% sodium citrate can be used for quantitative and qualitative clot-based and chromogenic assays. Liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) can use serum or plasma.
- Citrated whole blood samples should be processed within 4 hours of collection.
- Plasma samples for dabigatran that cannot be tested within 24 hours of collection should be frozen (stability of 14 months or greater if maintained at 20°C or colder) using monitored freezers or dry ice
- For thrombin time testing (dabigatran), plasma samples are stable for 4 hours at room temperature.
- Plasma samples for anti-FXa DOACs that cannot be tested within 8 hours of collection should be refrigerated (stability of 48 hours) or frozen (stability of 30 days or greater if maintained at 20°C or colder) using monitored freezers or dry ice.
- Data would suggest that at least three freeze–thaw cycles could be performed without significant loss of activity.

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Qualitative assays for DOACs

Consensus screening assay recommendations:

- **The PT and/or APTT may not be reliable to detect the presence of 'on-therapy' concentrations of all DOACs.**
- **PT and APTT are not responsive to 'on-therapy' apixaban levels.**
- **The PT and APTT should not be used to quantify DOAC concentration.**
- **In a patient with known DOAC exposure, a prolonged PT or APTT should be considered secondary to drug effect until proven otherwise, and in emergent or life-threatening conditions, tests for quantifying DOAC should be performed to aid in patient management**

ICSH Lab guidance for DOAC measurement

Consensus screening assay recommendations, con't:

- **A normal TT excludes the presence of significant dabigatran concentration.**
- **At the time of writing this article, there is not enough clear data to support the use of TEG or ROTEM for detecting DOAC anticoagulant activity.**
- **Nonspecific POCT methods may not have sufficient responsiveness to detect DOAC presence.**
- **Urine DOAC screening tests may provide a rapid assessment (qualitative and semiquantitative) of recent DOAC exposure, but may not reflect circulating drug presence or concentration.**

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Quantitative Assays for DOAC Measurement

Consensus LC-MS/MS recommendations:

- **LC-MS/MS should be considered the gold standard test for measuring DOAC concentration.**
- **A suitable internal standard for each DOAC is mandatory.**
- **DOAC metabolites, that are pharmacologically active, should be reported.**

ICSH Lab guidance for DOAC measurement

Other Methods for Quantifying Anti-FIIa (Dabigatran)

- **Demonstrated to be comparable to LC-MS/MS, drug-calibrated DTT, ECA, ECT and anti-FIIa chromogenic methods are recommended as suitable methods to provide rapid quantitation of dabigatran**

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Other Methods for Quantifying Anti-Xa DOACs

- **Demonstrated to be comparable to LC-MS/MS; drug-calibrated anti-FXa is recommended as suitable methods to provide rapid quantitation of anti-Xa DOACs.**
- **Antithrombin supplemented anti-FXa methods should not be used for DOAC assessment, as these methods tend to overestimate drug concentration and are not validated by the manufacturers.**

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POCT and assays in development

- **No recommendations, but alerted readership to current (at time of writing) studies.**

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Quantifying DOACs:

Assay Validation or Verification of Performance:

- **Method validation or verification of performance is required before assays are used for clinical reporting.**
- **Prior to performing method validation or verification, a plan (protocol) should be written that describes how the validation will be conducted and acceptance criteria.**
- **Method validation studies should include precision, accuracy, linearity, determination of LLOQ, LLOD and reportable range and may include stability studies.**
- **Method verification of performance studies should include precision, accuracy and possibly linearity**

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DOAC External Quality Assessment/Assurance

Consensus DOAC EQA recommendations:

- **Each laboratory must enroll in an EQA program specific for the DOAC being measured.**
- **EQA should be at a minimum two samples per dispatch, with at least two dispatches in a calendar year**

ICSH Lab guidance for DOAC measurement

Limitation(s)

Laboratory guidance – no method descriptions

Gosselin RC, Douxfils J. Measuring Direct Oral Anticoagulants. Methods Mol Biol. 2017;1646:217-225.

Document is fixed, whereas the field is fluidic and changes rapidly

- New drug approvals (betrixaban)
- Minimally addressed impact of secondary drugs on DOAC testing results (e.g. LMWH and anti-Xa DOACs)
- Absence of addressing reversal strategies and impact on DOAC testing (Praxbind, AndexXa)
- New or modified (existing) measuring methods or techniques

DOAC measurements using POC

- **Microfluidics**

  Bluecher, et al Thromb Haemost 2017; 117: 519–528

- **Quartz Crystal Microbalance with Dissipation (QCM-D)**
  Hussain, et al Biosens Bioelectron. 2018;104:15-20.

- **Dry spot blood collection for mass spec testing**

  Foerster, et al 2018 Anal Chem

- **2018 SSC Dublin**
  - **Numerous novel POC methods with increased specificity**
  - **Modification of existing methods**
  - **Dusting of older methods**

ICSH Lab guidance for DOAC measurement

ICSH proposal for update on DOAC guidance document

- **ICSH board approved**
- **Updates to be submitted**
  - **~1.5 years (if necessary)**
  - **Short communication format**
    - **~1500 words**
- **Committee agreed to premise and format**
- **Planned document update for early to mid-2019**

ICSH Document Committees in progress

- **POC INR and D-dimer – David Fitzmaurice, chairperson**
- **Coagulation Preanalytical variables – Steve Kitchen, chairperson**
- **Factor VIII+IX inhibitor assays – Piet Meijer, chairperson**
- **APTT mixing studies – Dot Adcock, chairperson**
- **ADAMTS-13 testing – Ian Mackie, chairperson**
- **Coagulation critical values – Bob Gosselin, chairperson**

Submitting ICSH coagulation document proposals

- **Formalized mechanism in progress**
- **ICSH Administrator**
  - **Mr Terry Fawcett (admin@icsh.org)**

Thank you