POCT in coagulation

A. Demulder

CHU-Brugmann
Introduction

POC testing in coagulation is primarily focused on:

- Oral anticoagulation therapy (INR)
- Heparin monitoring (aPTT, ACT high and Low range)
- More specific applications (Thomboelastography)
- Diagnosis of PE and DVT (D-Dimer)
Oral anticoagulation

- Can certainly be improved in our country
- 66% of anticoagulated patients are inside their target INR +/- 0.75
- British guidelines recommand that at least 80% of the patients should be in their target +/-0.75 INR
- Incidence of bleeding is high 5.5/100 patient/year compared to other studies

Claes et al Huisarts Nu 2007:36:191-6
POCT and oral anticoagulation

- Technologies actually present on the market
- Reliability
- Usefulness /Anticoagulation clinics
- International use
- Use by Health care professionnal and patients (good practice-guidelines education)
- New anticoagulants
Main Coagulation POCT Devices
(Not exhaustive list!)

Roche/ Coaguchek series
ITC/ Hemochron signature series (Lameris)
ITC/ Protime (IL)
Abbott/ iSTAT
Hemosense INRatio
## Devices characteristics

<table>
<thead>
<tr>
<th>Type of Device</th>
<th>Thromboplatin</th>
<th>Sample type</th>
<th>End-point detection</th>
<th>iQC available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coaguchek S</td>
<td>Rabbit brain</td>
<td>10µl WB</td>
<td>Iron oxide particles</td>
<td>liquid</td>
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<tr>
<td>Coaguchek XS</td>
<td>Human recombinant</td>
<td>10µl WB</td>
<td>Electrochemical cleavage</td>
<td>onboard</td>
</tr>
<tr>
<td>Coaguchek X plus</td>
<td>Human recombinant</td>
<td>10µl WB</td>
<td>Electrochemical cleavage</td>
<td>Liquid and onboard</td>
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<tr>
<td>Hemochron signature series</td>
<td>Rabbit brain</td>
<td>50µl WB or CB</td>
<td>Electro-optical</td>
<td>liquid</td>
</tr>
<tr>
<td>iSTAT</td>
<td>Human recombinant</td>
<td>20µl WB</td>
<td>Electrochemical cleavage</td>
<td>liquid</td>
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<tr>
<td>Hemosense INRatio</td>
<td>Human recombinant</td>
<td>15µl WB</td>
<td>Electric impedance</td>
<td>onboard</td>
</tr>
<tr>
<td>Protime</td>
<td>Human recombinant</td>
<td>27µl WB</td>
<td>Electro-optical</td>
<td>Liquid and onboard</td>
</tr>
</tbody>
</table>
Whole blood tests for ACT+, ACT-LR (low range), PT (INR) and aPTT
CB: PT and aPTT
Roche Coagucheck series

CoaguChek System
- 1993 Germany
- 1994 US Professional

Low Volume (Mini) S Strip
- March 1998

CoaguChek XS System
- September 1999 Europe
- March 2001 US

XS Strip
- OBC
- Unsensitive to Heparins
- January 2006

CoaguChek XS Plus System HCP meter
- 2006 Europe

CoaguChek XS System Patient meter
- 2006 Europe
- 2007 USA and Japan
ITC Protime
Introducing inratio²

- 1 Minute Test Time
- 1 Button Operation
- 1 Step Auto-On with strip Insertion
- 200 Test Battery Life
- Larger LCD screen and digits
- Icon based interface
- On Board Quality Control
- Individually Wrapped Test Strips

And many other improvements!
Different pathway model of INR testing

*From laboratory to PoC testing*

- Routine Care/Usual Care
- AST: Alternative Site Testing: Testing by other Healthcare Professional
- PST: Patient Self-Testing
- PSM: Patient Self-Management
Usual Care

Venous sample draw → Sent to laboratory → Laboratory work done → Office contacted → Chart pulled

Results reviewed → Patient contacted (assumes patient reached on first call) → Intervention documented → Chart filed
Decentralized Coagulation Monitoring

AST Model

1. Fingerstick test
2. Results in one minute
3. Immediate patient consultation, therapy decision, and documentation
4. Chart filed
Decentralized Coagulation Monitoring

PST/PSM Model

• Patient trained to perform test (and possibly change his dosage if trained for PSM)
• Patients can test at any time, anywhere (e.g. vacation) and is more independent (no need to take a day off or travel to get tested)
• Ability of patient is required
• Still needs expertise of his physician in case of any doubt
POC INR testing

- Good performance has been demonstrated with commercially available POC in terms of accuracy, reproducibility and long-term reliability when used by selected patients and HCP

- PSM is better than poor-quality anticoagulation control (AC) provided by HCP and as effective as usual care of specialised clinics for AC

- Not all patients are capable of performing self-monitoring and some patients may find it unnecessary because of high quality care provided by existing AC

- The observed reduction in complications in some trials may be due to alternative explanations including education and patient empowerment.
Centralized vs. decentralized INR Testing

High variability among countries
Some countries, mostly in Europe and North America, are much more advanced in decentralizing INR testing:

- US: 30% (mostly AST, 1% PST)
- Germany 25% (mostly PSM)
- UK: 16% (mostly AST)
- France: starting in 2009 for children and teenagers
Reimbursement Situation in different countries
Cost effectiveness

- Must take account of
  - The cost of devices, strips and quality control
  - Cost of patient and HCP education
  - Cost of the administration and follow-up of the patient file/chart
  - Cost efficiency versus the usual care

- KCE report june 2009
PoC INR Testing

Cost efficiency vs. usual care (Germany)

Cost per Patient per Year [EUR]$^{(1)}$

-35% "Usual" Monitoring

Direct Costs for Therapy Monitoring

Cost for Treatment of Complications

Overall Cost

(1) Taborski et al., 1999 (Seminars in Thrombosis and Hemostasis, Vol. 25, No. 1: 103-107, 1999)
Cost-effectiveness

- German Cost efficiency study of relevance in Belgium?

- In the UK, PSM is unlikely to be more cost effective than the current specialised anticoagulation clinics and may represent an additional cost to the NHs

- Research is needed into the clinical effectiveness and cost effectiveness of patient and HCP education and training in long term anticoagulation therapy
Guidelines (UK) for PST/PSM

- Only patients with long-term indications for warfarin therapy should be considered for self-testing or management.
- Recommendations:
  - Training for HCP patient-trainers
  - 6-monthly assessment of patient’s POCT competence by a responsible HCP and patient should be reviewed every 6 months by the responsible physician
  - Routine internal quality control of POCT at regular intervals and also when a new batch of disposables (e.g. strips) is to be used
  - Regular quality control using the NEQAS system or by duplicate measures at reliable anticoagulation clinic
  - Retesting of unexpectedly high or low results
Clinical laboratory testing and *in vitro* medical devices — Requirements for *in vitro* monitoring systems for self-testing of oral anticoagulant therapy

*Laboratoires d'analyses de biologie médicale et dispositifs médicaux de diagnostic in vitro — Exigences relatives aux systèmes d'autosurveillance des traitements par anti coagulant oraux*
Internal Quality control (ISO 17593)

- Electronic IQC where available should be used each time the monitor is used.

- The IQC material should be analysed when introducing a new batch/lot number of test strips or when commencing use of newly delivered test strips (even when they are the same lot number as used previously), at the start of every clinic, and every 20 patients.

- The IQC material should be re-tested if an unexpectedly high or low result occurs.

- The IQC should be tested between 1 and 3 monthly, or with each test if the interval between testing exceeds 12 weeks.

- Patients who are self-testing should participate in at least one form of EQA

Semin Thromb Haemost 2008;34(7):647-662
• **External Quality control available for both health care professionnals and patients**

(a) Patients or professionals may participate in a formal EQA programme, or other accredited programme.

(b) The patients’ (HCP’s) monitor may be assessed in a centre that participates satisfactorily in an accredited EQA programme, such as NEQAS. In this case, the patient should test their own blood on their own monitor/test strips and the monitor/test strips routinely used in the clinic; the INR results should be within 0.5 INR units of each other.

(c) A venous sample may be collected at the same time as the POC test and sent to an appropriate hospital laboratory for analysis. This could be carried out every 6 months for stabilised patients. In this case, INR results are acceptable if within 0.5 INR units of each other.
ACT: activated clotting time
What is an Activated Clotting Time? (ACT)

Fresh Whole Blood
+
Activator
(Kaolin, Celite or Glass)

Time to Clot Formation
Activated Clotting Time (ACT)

Measures the intrinsic and common pathways of coagulation. Performed on freshly drawn whole blood. Activator added to blood to initiate Factor XII activation

- Lee and White Clotting Time (1913)
  - test tube based procedure for a whole blood clotting
  - glass walls of tube served as activator
- Celite activator introduced (1966)
  - Particulate activator
  - Accelerated clot formation

- Hemochron introduced first automated clot detection device for ACTs in 1969
Monitoring Heparin Therapy

- **aPTT**: monitoring of low-dose heparin (<1 U/ml)
  - In the central lab and as a POC test

- **ACT**: monitoring of high-dose heparin (1U/ml up to 6-10 U/ml)
  - Performed as a POC test in various clinical setting

- **Low ACT**: monitoring of low to moderate doses of heparin (0-3U/ml)
Variables Affecting an ACT

- Heparin
- Hemodilution
- Hypothermia
- Aprotinin
- Prekallicrein
- High MW kininogen
- Factors levels
- Ionic strength
- Histidine-rich glycoprotein
- Platelet factor 4
- Platelet count, function
- Calcium
- Temperature
- Antithrombin III
- Plasminogen
- Monocytes
- Tissue factor
- Protein C
- pH
- Activating agent
Main Coagulation POCT Devices (not exhaustive)

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<tbody>
<tr>
<td>ITC/ Hemochron signature series</td>
</tr>
<tr>
<td>Medtronic/ ACT II</td>
</tr>
<tr>
<td>Medtronic / Hepcon HMS</td>
</tr>
<tr>
<td>Abbott/ iSTAT</td>
</tr>
<tr>
<td>IL GEM® PCL</td>
</tr>
<tr>
<td>Actalyke</td>
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</tbody>
</table>
ACT II

Same cartridges/clot detection technology as ACT Plus

Why upgrade to ACT Plus

- End of Service Feb 1, 2007
- No QC or User lockout options
- No data management
- No memory
- All test information must be recorded manually
- ACT Plus makes it easier for customers to comply with regulatory requirements
Medtronic ACT Plus™

- Electromechanical real-time clot detection
- Large LED display and LCD interface
- Stores up to 500 test records, any mix patient and QC
- Duplicate channel testing
- Barcode Scanner Option
  - Cartridge/control lot and exp
  - Patient and Operator ID entry
- QC and Operator lockout options
- Download to floppy or serial port
Medtronic ACT Plus™ Cartridge

Two-channel measurement system provides extra confidence through duplicate results

First commercially available Kaolin activated clotting time

Activator is suspended in liquid for more consistent mixing and activation of sample

All mixing of blood sample and activator is performed by ACT Plus
Hemochron® Response

Mechanical clot detection
  - Celite and kaolin
Disposables same as 401/801
Additional tests and software for predicting heparin/protamine dose and verifying heparin neutralization
Heparin and Protamine response tests require multiple steps
ITC International Technidyne Corporation

Hemochron Signature series

Whole blood tests for ACT+, ACT-LR (low range), PT and APTT
CB: PT and aPTT
i-Stat®

Test menu (PT and ACT)

Celite and kaolin ACT activators

Endpoint uses synthetic substrate, not clot based

Electrochemical detection

i-STAT results are shorter than Medtronic ACT

Infra-red link for results transmission to portable printer or central data station
IL GEM® PCL

Add-on module for the Gem® Premier 3100

PT, APTT, HR and LR ACT testing

Clotting endpoint with optical detection

ITC Hemochron Signature technology
Actalyke

Actalyke Mini II and XL
Based on Hemochron tube technology

Multiple activators

Typically shorter clotting times
Internal Quality control

- Electronic QC where available should be used each time the monitor is used.
- The IQC material should be analysed when introducing a new batch/lot number of test strips or when commencing use of newly delivered test strips (even when they are the same lot number as used previously).
- The IQC material should be re-tested if an unexpectedly high or low result occurs.

- EQA?
Implementation of POCT at hospital level

• Establish a dialogue between
  • representative clinicians
  • laboratory representatives
  • nurses
  • hospital authority
  • medical informatics

• Make an inventory of already existing POC applications

• Draw conclusions

• Execute the plans and maintain the applications
Implementation of POCT for oral anticoagulation

- It is actually not clear if implementation of POCT alone will improve anticoagulant treatment if not coupled with education of HCP and patient.
- Self-monitoring may enhance the QoL for some patients who are on long term anticoagulation and find it difficult to go to a clinical lab.
- If a convention system is established, it should include the patient, the HCP, the clinical laboratory together with an educational program.
- Tracability and quality control of the results must be guaranteed.