Point-of-Care Testing for Coagulation: Limitations and Challenges

Russell Higgins, MD, FCAP
April 17, 2013
Today’s Presenter

Russell Higgins, MD, FCAP

Assistant Professor, University of Texas Health Sci Ctr San Antonio

Medical Director, UHS Hematology

Chair, CAP Coagulation Resource Committee
Objectives

- Compare point-of-care and bench top methods.
- Identify point-of-care testing limitations for coagulation.
- Apply point-of-care testing for PT/INR, ACT, and D-dimer to appropriate clinical settings.
- Develop strategies to improve utilization of point-of-care testing for coagulation.
Point-of-Care (POC) Testing in Coagulation

Laboratory Centered Tests
• Clinical Laboratory Scientists
• Laboratory Technologists

Decentralized Testing
• Physicians
• Physician Assistants
• Nurses
• Patients

INR/Clinic
ACT
D-dimer
PT
APTT
Thromboelastometry
INR/Home Testing
POC PT/INR

- Monitor warfarin (INR)
- Factor deficiency (eg, PT for perioperative coagulopathy)
Evolution of POC INR

1935
Tilt Tube/Quick's Prothrombin Time

1941
Warfarin Used Clinically

1960’s
Fibrometer

1980’s
INR

Today’s Automation

1990’s
POC INR

Self Monitoring INR

Unique Features of POC INR

- Fingerstick or venous whole blood
- Different end point detection
- Different reagents (e.g., Lack heparin neutralization)
- ISI is programmed on chip or test card

© 2013 College of American Pathologists. All rights reserved.
POC INR: Complaint from the “Warfarin Clinic”

- “…significant result (POC INR) differences compared to blood draws (central laboratory INR)”
  - Examples
    - 5.4 (POCT) versus 7.1 (Lab)
    - 5.0 (POCT) versus 6.8 (Lab)
POC INR: Relevant LAP Requirements

- POC.07568 Comparability of Instrument/Method
  - Waived tests are exempt
  - Non-waived tests
    - *POC site with separate CLIA# than central laboratory*
      - 6 mo. POC instrument to POC instrument comparison
    - *POC site (eg, hospital based) under same CLIA#*
      - 6 mo. comparison with central laboratory required
POC INR: Relevant LAP Requirements

• **POC.03800 Troubleshooting Responsibilities Phase II**
  o Backup testing (eg, central laboratory)
  o Trained individuals available for troubleshooting
POC INR: Method Comparison

- POC vs. Central Laboratory
  - Almost always linear
    - $High R^2$
  - Line of identity (or slope) demonstrates bias

![INR Correlation Graph]

$y = 1.2003x - 0.2362$

$R^2 = 0.9817$
POC INR: Method Comparison

- POC vs. Central Laboratory
  - Bias Plot for INR
    - Good correlation for lower INR values
    - Poor correlation for high INR values

© 2013 College of American Pathologists. All rights reserved.
INR Method Comparison
How well does INR harmonize central laboratory methods?

Variance at Increasing INR Levels
(CGL-C 2012)

© 2013 College of American Pathologists. All rights reserved.
POC INR: Strategies/Tools

- Assessing INR Agreement
  - Absolute Difference
    - ±0.4: 1.0 to 4.5
  - % Error
    - ±20% error
  - ISO 17593
    - * +/- 0.5 for INR <2 and...
    - * +/-30% for INR 2.0 - 4.5

*Very Broad; More stringent criteria have been proposed
POC INR: Strategies for Compliance

- Medical director defines the allowable error
  - Focus on **clinically relevant error** near therapeutic range
    - *Discuss with warfarin clinic staff/physicians*
  - Troubleshoot high INRs with central laboratory INR
    - *Refer INR > X to central laboratory*
POC INR: Case Presentation

- 45 year-old male with venous thromboembolism (VTE) seen at the warfarin clinic to bridge low molecular weight heparin (LMWH) to warfarin

- POC INR = 5.2
  - *Sample sent to central laboratory to verify “unusual result”
  - Central Laboratory INR = 2.7
POC INR: Interferences/LMWH

% Participants Reporting Prolonged PT in Plasma Spiked with Heparin

<table>
<thead>
<tr>
<th></th>
<th>No Heparin</th>
<th>Therapeutic</th>
<th>Supertherapeutic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unfractionated (UF) Heparin</strong></td>
<td>0.9 - 1.2%</td>
<td>1.8 - 6.4%</td>
<td>23.0 - 37.0%</td>
</tr>
<tr>
<td><strong>Low Molecular Weight Heparin</strong></td>
<td>0.9 - 1.2%</td>
<td>5.5 - 15.4%</td>
<td>17.4 - 50.2%</td>
</tr>
</tbody>
</table>

Data from CGS4 Survey 2009-2011

© 2013 College of American Pathologists. All rights reserved.
INR: Interferences/Heparin

- **Central Laboratory INR**
  - Heparin neutralized up to ~0.8 IU/ml
  - LMWH may not be neutralized as effectively
  - Used for bridging warfarin and heparin therapy

- **POC INR**
  - Variable claims about heparin interference
  - Bridging warfarin to heparin may not be safe
    - Very limited literature on effect of heparin + warfarin
INR: Interferences/Dabigatran

• Neither POC or central laboratory INR can be used to monitor dabigatran

Joanne van Ryn et al. The American Journal of Medicine 2012; 125(4): 418
INR: Interferences/Lupus Anticoagulant (LA)

• Both POC and Central Laboratory INR
  o Phospholipid dependent tests
  o Variable affect of LA
  o *Some POC INR exquisitely LA sensitive

INR: Common Interferences

- Lupus anticoagulants
- Parenteral anticoagulants
  - Hirudin, bivalrudin, argatroban, UF heparin, LMWH
- “New” oral anticoagulants
  - Dabigatran, rivaroxaban, apixaban
- Bilirubin
- Hemolysis
- Lipemia
- Low or elevated hematocrit
INR Interferences: Relevant LAP Requirements

- COM.04050 Unusual Laboratory Results Phase II
- POC.03700 Unusual Laboratory Results Phase II
  - Procedure must include common interferences (e.g., Heparin and LMWH)
INR Interferences: Strategies for Compliance

• Anticoagulants
  o Procedure addresses “other” anticoagulants
    - *Heparin/LMWH sent to central laboratory*
    - *Other (non-warfarin) anticoagulants can’t be monitored by INR*

• Lupus Anticoagulant
  o Procedure addresses LA positive patients
    - *Monitor with LA insensitive PT/INR central laboratory method or…*
    - *Chromogenic Xa assay*

• Other interferences
  o Review package insert and address interferences in procedure
Activated Partial Thromboplastin Time (APTT)

- Monitor Heparin
- Factor deficiencies (e.g., perioperative coagulopathy)
POC APTT

- If POC APTT is used to monitor heparin...
  - Then heparin therapeutic range must be established by comparing APTT and heparin concentration
Relevant LAP Requirements: APTT

- **HEM.23453 Heparin Therapeutic Range Phase I**
  - There is documentation that the aPTT-based heparin therapeutic range is established and subsequently validated using an appropriate technique, when appropriate.
APTT: POCT versus Central Laboratory

Reiss RA et al. Pharmacotherapy 2002;22(6):677
APTT: Strategies for Compliance

- Monitor unfractionated heparin with central laboratory method only or…

- Establish therapeutic range on POC instrument
  - *Use heparinized patients to establish range
  - May be hazardous if 2 separate ranges (central and POC) are used

Activated Clotting Time (ACT)

- Monitor high doses of heparin during cardiac bypass surgery (high dose heparin)
- Monitor “moderate” doses of heparin during other procedures [eg, percutaneous coronary intervention (PCI)]
- No corresponding central laboratory test
  - Nonwaived
  - Compare POC ACT to POC ACT
ACT: Example Scenario

• *An institution changed its ACT instrument…
  o New method led to less heparin utilized for cardiac bypass (~10,000 fewer units per surgery)
  o Less bleeding
  o Less need for blood products

• Same therapeutic target does not apply to all ACT methods

*Karen Lusky CAP Today 2003 September
ACT: Method Comparison

Raymond PD et al. Perfusion 2003;18: 269-276
ACT

• No harmonization between ACT methods

• ACT target varies with methodology
  - 1975 -- target ~300 – 600 sec (visual clot detection)
  - 1979 -- target ~480 sec (Hemochron)
  - 2012 – target method dependent (>9 methods)

• ACT target varies with procedure
  - eg, PCI target >> Mitral Valve Replacement
ACT: Relevant LAP Requirements

• POC.04500 Reference Intervals  Phase II
  o When applicable, all patient results are reported with accompanying reference (normal) intervals or interpretive ranges.
ACT: Strategies for Compliance

• Establishing method specific therapeutic ranges
  o Method specific literature
  o Compare with existing ACT
  o Correlate with plasma anti-Xa activity
  o In-vitro spiked heparin
  o Correlation with clinical findings (clots in circuit, microvascular bleeding)

• Establish ranges for alternative anticoagulants
Quantitative D-dimer

- Evaluate disseminated intravascular coagulation
- **Evaluate venous thromboembolism**
- Evaluate risk of recurrent thrombosis after warfarin therapy
- Detection and risk stratification of malignancy
POC Quantitative D-dimer

- No FDA approved POC D-dimer tests for exclusion of VTE
- No POC D-dimer tests have the performance characteristics recommended by CLSI
  - *NPV ≥ 98% (lower limit of CI >95%) and sensitivity ≥ 97%*

Quantitative D-dimer: Relevant LAP Requirements

- **HEM.37925 Method Validation - D-dimer/Phase II**
  - If a D-dimer method is used in the exclusion of venous thromboembolism, the method is validated for this purpose.

- **HEM.37935 Utilization of D-dimer Test/Phase I**
  - If a D-dimer test is not used for exclusion of deep vein thrombosis and/or pulmonary embolism, the laboratory informs clinicians that the test should … not be used to exclude deep vein thrombosis or pulmonary embolism.
Quantitative D-dimer: Units

- Magnitude and type of D-dimer units required
  - ng/ml DDU...or
  - ng/ml FEU...but
  - **NOT** ng/ml

- Molecular weight of an FEU is twice that of a DDU
  - Eg, 800 ng/ml FEU = 400 ng/ml DDU
Quantitative D-dimer: Relevant LAP Requirements

• HEM.37918  D-dimer Report  Phase I
  o The results in laboratory reports are specified as D-dimer Units (DDU) or Fibrinogen Equivalent Units (FEU).
D-dimer: Units of Measure

- CAP CGL Survey Participants
  - *~ 7% using wrong units or incorrect conversion!!!

- Correct Units Found in Package Insert

*Olson JD et al. Archives of Pathology and Laboratory Medicine: 2013: Accepted
D-dimer: Method Comparison

• No Harmonization of D-dimer Methods
D-dimer: Strategies for Compliance

- POC D-dimers lack sensitivity to exclude VTE
- Report magnitude and type of D-dimer units
- Report units from the package insert
- No harmonization between methods
Summary

• INR
  o Allowable error of POC defined by medical director
  o Interferences of POC devices need to be addressed

• ACT
  o Define target ranges for various uses in procedure

• D-dimer
  o POC not sufficient to excluded VTE
  o Use package insert units (magnitude & type)

© 2013 College of American Pathologists. All rights reserved.
Thank you!

Questions?