Coagulation Testing at the Point of Care
Applications, Controversies and the Evidence Base

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Chicago Pathology Society, AACC Chicago Section
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Disclosures

• Conflict of interest: none

• Off label uses: none
Point of Care Testing

• The Good
  • Rapid turnaround time
  • Easy to use in general
  • Accessible

• The Not So Good
  • Comparability to laboratory methods
  • Cost
  • Oversight issues

Point of Care Testing

• True clinical utility depends on:
  • Facilitation of clinical workflow
  • Facilitation of clinical decision-making
  • Improved patient outcomes
Oral Anticoagulation

Major Indications for Warfarin Therapy

• Primary & secondary prevention of venous thromboembolism
• Prevention of systemic embolism in patients with prosthetic heart valves or atrial fibrillation
Why in Ongoing Monitoring Important?

- Narrow therapeutic window
- Variability in patient response
  - Genetics
  - Co-morbidities
- Drug and diet interactions

Warfarin Therapy

- Times of increased risk with sub- or supra-therapeutic levels
  - Initiation of therapy
  - Changes in medications and/or diet
  - Illness, hospitalization
  - Change of testing laboratory
  - Transitions of care
    - Hospital discharge
    - Provider change
Variability in Patient Response

- Artifact of testing variability
  - Thromboplastins vary in responsiveness to coagulation factor deficiency
  - Different instrument reagent combinations can give different results
  - Standardization to the INR, but it’s not perfect

Anticoagulant Therapy, Target INR Range 2.0 to 3.0

Ortho RecombiPlasTin (ISI 1.05) at 0 h
Dade Thromboplastin C-Plus (ISI 1.85) at 0 h
Dade Innovin (ISI 0.85) at 0 h

What is Important to Know About POC INR Performance When Considering Clinical Use?

• Technical performance
  • Equivalency to your laboratory method – bias
  • Reproducibility with intended sample type
    • Intra & inter device
  • Cutoff for requiring confirmatory lab result
  • Performance at key decision point(s)

POC INR Monitors

• Varying thromboplastins and endpoint detection methods
• Designed to use capillary whole blood
• Designed primarily for patient use
• Data management capabilities to enhance professional use just starting to be available
POC INR vs Lab

Method Comparison

CoaguChek  ProTime  INRatio  CoaguChek S

Mayo data
Method Comparison


Agreement Between Duplicates

Mayo data
POC INR Monitoring  
Warfarin ± LMWH

<table>
<thead>
<tr>
<th></th>
<th>Warfarin Only (n=59)</th>
<th>Warfarin + LMWH (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>INR ± SD</td>
<td>P</td>
</tr>
<tr>
<td>POCT</td>
<td>3.02 ± 1.47</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Laboratory</td>
<td>2.77 ± 1.25</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Difference</td>
<td>0.24 ± 0.63</td>
<td>0.04</td>
</tr>
<tr>
<td>Confidence interval</td>
<td>0.08 – 0.40</td>
<td></td>
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</table>

POC INR Monitoring  
Warfarin ± LMWH

<table>
<thead>
<tr>
<th></th>
<th>No. (%) patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Warfarin only (n=59)</td>
</tr>
<tr>
<td>Concordant pairs</td>
<td></td>
</tr>
<tr>
<td>No dosage change indicated by POC &amp; Lab</td>
<td>25 (42)</td>
</tr>
<tr>
<td>Dosage change indicated by POC &amp; Lab</td>
<td>29 (49)</td>
</tr>
<tr>
<td>Discordant pairs</td>
<td></td>
</tr>
<tr>
<td>Dosage change indicated by POC but not Lab</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Dosage change indicated by Lab but not POC</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
What is Important to Know About POC INR Performance When Considering Clinical Use?

- Technical performance
  - Equivalency to your laboratory method – bias
  - Reproducibility with intended sample type
    - Intra & inter device
  - Cutoff for requiring confirmatory lab result
  - Performance at key decision point(s)

- Health care setting
  - Professional or home use
  - Patient populations (hospice, nursing home, oncology clinic, pediatric clinic, etc)
  - Frequency of concurrent heparin use

- The evidence base to support the intended clinical application

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**Therapeutic Control with Warfarin in the First 6 Months of Outpatient Therapy**

<table>
<thead>
<tr>
<th></th>
<th>0-1 month n=261</th>
<th>1-3 months n=230</th>
<th>3-6 months n=165</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention group (%)</td>
<td>Usual care group (%)</td>
<td>Intervention group (%)</td>
</tr>
<tr>
<td>Subtherapeutic</td>
<td>32.2</td>
<td>33.9</td>
<td>29.9</td>
</tr>
<tr>
<td>Therapeutic</td>
<td>48.6*</td>
<td>31.4</td>
<td>58.9*</td>
</tr>
<tr>
<td>Supratherapeutic</td>
<td>19.2</td>
<td>34.7*</td>
<td>11.3</td>
</tr>
</tbody>
</table>

*P<0.001

Ann Intern Med 133:687, 2000
Cumulative Incidence of Major Bleeding at 6 Months According to Intention-to-Treat Analysis

Patients with major bleeding (%)

0 2 4 6 8 10 12 14

0 1 2 3 4 5 6

Months

Usual care
n=162
(97)
(74)

Study intervention
n=163
(142)
(107)
(75)

P=0.05

Ann Intern Med 133:687, 2000

Self-monitoring of oral anticoagulation: a systematic review and meta-analysis

C Monaghan, P Alonso-Coello, J M García-Almendo, F Pérez, E Mata, P Glazov

- 14 randomized trials with a total of 3049 participants comparing self-monitoring with routine anticoagulation
  - Primary care as control group: 8
  - Anticoagulation clinic as control group: 6

Lancet 367:404, 2006
### Patient Self-Testing

<table>
<thead>
<tr>
<th></th>
<th>Thromboembolic Events</th>
<th>Major Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td>Self-adjust</td>
<td>0.27</td>
<td>0.12 – 0.59</td>
</tr>
<tr>
<td>Non-adjust</td>
<td>0.57</td>
<td>0.35 – 0.93</td>
</tr>
<tr>
<td>Total</td>
<td>0.45</td>
<td>0.30 – 0.68</td>
</tr>
</tbody>
</table>

**Lancet 367:404, 2006**

### Effect of Patient Self-Testing and Self-Management on Major Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Thromboembolic events</th>
<th>Major bleeding events</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total studies/</td>
<td>14 / 7759</td>
<td>16 / 7867</td>
<td>13 / 6370</td>
</tr>
<tr>
<td>participants</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk for bias</td>
<td>RCTs (fair)</td>
<td>RCTs (fair)</td>
<td>RCTs (fair)</td>
</tr>
<tr>
<td>design (quality)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consistency</td>
<td>Consistent</td>
<td>Consistent</td>
<td>Inconsistent</td>
</tr>
<tr>
<td>Directness</td>
<td>Direct</td>
<td>Direct</td>
<td>Direct</td>
</tr>
<tr>
<td>Precision</td>
<td>Precise</td>
<td>Precise</td>
<td>Precise</td>
</tr>
<tr>
<td>Peto odds ratio</td>
<td>0.58</td>
<td>0.87</td>
<td>0.74</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.45-0.75)</td>
<td>(0.75-1.05)</td>
<td>(0.63-0.87)</td>
</tr>
<tr>
<td>Strength of Evidence</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Low</td>
</tr>
</tbody>
</table>

**Ann Intern Med 154:472, 2011**
Home INR Study (THINRS)

- 2922 patients requiring warfarin therapy for mechanical heart valves or atrial fibrillation – randomized to
  - Weekly self-testing
  - Monthly high quality testing in clinic
    - Designated, trained staff
    - Standard local procedure for anticoagulation management
    - Regular INR testing about once a month
- 8730 patient years of follow-up
- Primary endpoint: time to first event (stroke, major bleeding, death)


<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Hazard Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first event</td>
<td>0.88</td>
<td>0.75-1.04</td>
<td>0.14</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.95</td>
<td>0.58-1.56</td>
<td>0.83</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.98</td>
<td>0.78-1.23</td>
<td>0.83</td>
</tr>
<tr>
<td>Death</td>
<td>0.91</td>
<td>0.73-1.12</td>
<td>0.41</td>
</tr>
</tbody>
</table>

Supervised Patient Self-Testing Using an Internet-Based Expert System

<table>
<thead>
<tr>
<th></th>
<th>Anticoagulation Management Service</th>
<th>Patient Self-Testing with Expert System</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time in Therapeutic Range, median (%)</td>
<td>58.6%</td>
<td>74%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean number of tests per patient</td>
<td>10.7 ± 5.2</td>
<td>41.7 ± 6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean frequency of testing (days)</td>
<td>19.6 ± 6.6</td>
<td>4.6 ± 0.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% of extreme INRs</td>
<td>6</td>
<td>1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adverse events</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

J Thromb Haemost 7:1284, 2009

Should POC Monitors Be Used for Pre-Procedural INR Checking?

- Dental clinic at large academic medical center
- POC INR performed by staff prior to dental procedure if:
  - Patient on warfarin and no INR performed within the past 48 hours
  - Patient with a history of liver disease

JADA 139:697, 2008
Should POC Monitors Be Used for Pre-Procedural INR Checking?

- INR considered out of range and treatment deferral possible if
  - >3.5 in patients on warfarin therapy
  - >1.4 in patients with liver disease
- Bleeding complications assessed by electronic record review to determine if patients returned to clinic or ED within 2 weeks post-procedure

JADA 139:697, 2008

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Should POC Monitors Be Used for Pre-Procedural INR Checking?

- 66 patients on warfarin
  - 11 (17%) with INR >3.5
    - 8 had treatment deferred
    - 3 were treated without bleeding complications
  - 25 (38%) with INR 2.0-3.5
  - 30 (45%) with INR <2.0
    - 4 had deliberately stopped taking warfarin prior to procedure
- 34 patients with history of liver disease
  - 7 (21%) with INR >1.4
    - 1 had treatment deferred
    - 6 were treated with 1 bleeding complication (also on enoxaparin)

JADA 139:697, 2008
Should POC Monitors Be Used for Pre-Procedural INR Checking?

• Issues
  • Given variability of results with some devices, how much can a one time result be trusted?
  • Depends on the instrument precision and comparability to the usual method
  • Comparability to the hospital lab method may not be relevant for referral patients who are routinely monitored elsewhere
  • INR calculation does not eliminate all differences

Should POC Monitors Be Used for Pre-Procedural INR Checking?

• Issues
  • This study doesn’t necessarily provide high level of certainty regarding safety – weak method for determining bleeding complications
  • Who is responsible for follow-up of patient
    • Subtherapeutic or supratherapeutic

JADA 139:697, 2008
Should Point of Care INR Testing Be Used in the Hospital Setting?

• No evidence base available for this application

What is the Role of Pharmacogenetic Testing?

• Principles for individualized care
  • Standardized way of identifying patients with altered metabolism
  • These patient have poorer outcomes
  • Change in dosing can mitigate risk
  • Altered treatment leads to better patient outcomes
Warfarin Genotyping Reduces Hospitalization Rates

- National prospective comparative effectiveness study
- 6 month incidence of hospitalization in patients receiving genotyping (n=896) compared to matched historical controls (n=2688)
- Secondary analysis compared to external control groups from the same two time periods to monitor for temporal changes in outcomes related to warfarin therapy
- Outpatient population

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Warfarin Dosage Changes Following Genotyping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin Sensitivity</td>
<td>Patients (n (%))</td>
</tr>
<tr>
<td>Very high</td>
<td>10 (2.4%)</td>
</tr>
<tr>
<td>High</td>
<td>17 (4.0%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>106 (25.0%)</td>
</tr>
<tr>
<td>Mild</td>
<td>49 (11.6%)</td>
</tr>
<tr>
<td>Normal</td>
<td>119 (28.1%)</td>
</tr>
<tr>
<td>Less than normal</td>
<td>123 (29.0%)</td>
</tr>
<tr>
<td>Total</td>
<td>424</td>
</tr>
</tbody>
</table>

JACC 55: 2804, 2010
Avoidance of INR values >5

- Process improvement interventions
  - Computerized physician order entry
  - Standardized order set with pharmacy management and clinical decision support
- Algorithms for risk assessment & dosing advice based on clinical information
Sensitivity risk factor model and dosing algorithm for initiation of therapy

- Very high
  - Baseline INR $\geq 1.7$
- Moderate
  - Age 70-79
  - Acute hyperthyroidism
  - Serum albumin 2.6-3.0
  - Heart failure diagnosis (stable/compensated)
  - Concomitant medication

- High
  - Hepatic disease or malignancy
  - Hepatic congestion
  - Acute heart failure
  - Age $\geq 80$
  - Concomitant medication
  - Serum albumin $< 2.5$
  - Baseline INR 1.4-1.6
  - Actual body weight $< 50$ kg
  - Poor nutrition state
  - Malabsorptive state

Hospital-Based Care Delivery

Appropriate follow-up after discharge

- Best practices identified & implemented
  - Date of follow-up INR within 4 calendar days of dismissal date
  - Prescriber identified/designated to receive the INR result and manage dosing
  - Scheduling & prescriber designation assigned to a specific role
  - First post-discharge INR $\leq 5.0$
Warfarin Anticoagulation

• Success and safety contingent on
  • Patient knowledge & compliance
  • Provider knowledge, experience & diligence
  • Systems of care delivery
  • Recognition & mitigation of risks
  • Good communication & understanding

• It’s all about designing the right care delivery system to meet the need

Parenteral Anticoagulation
Monitoring of Heparin Anticoagulation

- Necessary for unfractionated heparin due to
  - Non-linear response
  - Patient variability

Heparin Monitoring
Patient Variability

ACT (sec) vs Heparin dose (units/kg)

Therapeutic Targets

• Evidence base is poor for all targets due to lack of randomized controlled trials

• What is really the gold standard/truth for adequacy of anticoagulation?
  • No pathologic clot forms
  • Inhibition of active thrombin – to what degree?
  • How do we account for patient variability?

High Dose Heparin Therapy: Cardiopulmonary Bypass

• Typical protocol for heparin
  • High dose therapy (2-6 units/mL)
  • Baseline activated clotting time (ACT) at start of surgery
  • Bolus dose of heparin administered in preparation for CPB
  • ACT after bolus and periodically during CPB
  • ACT should be >480 seconds; if not, additional heparin administered
  • Protamine given at the conclusion of CPB to reverse heparin effect
Activated Clotting Time (ACT)

- Celite, kaolin, or mixtures used as activators
  - Very strong in order to detect change when heparin concentrations are >1 unit/mL
- Clot detection is most common method
  - One method detects thrombin generation and converts it to an ACT-like result
- Lack of standardization
- Hematocrit and temperature affects some methods

Anticoagulation in CPB Surgery
ACT-Instrument Differences

Andrew M et al: Thrombos Haemostas 70:937, 1993
Heparin Concentration by Protamine Titration Method

- Determining patient specific response to heparin (in vitro)
  - Patient specific target heparin concentration
- Determining adequacy of anticoagulation
  - Semi-quantitative heparin concentration
Anticoagulation During Pediatric CPB

<table>
<thead>
<tr>
<th>Time on CPB</th>
<th>ACT of group C</th>
<th>ACT of group HC</th>
<th>Heparin concentration of group HC</th>
<th>Heparin concentration of group C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre CPB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5' on CPB</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30' on CPB</td>
<td><strong>P=0.02</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60' on CPB</td>
<td><strong>P=0.02</strong></td>
<td><strong>P&lt;0.001</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90' on CPB</td>
<td><strong>P=0.02</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>120' on CPB</td>
<td><strong>P=0.02</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>150' on CPB</td>
<td><strong>P=0.02</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>180' on CPB</td>
<td><strong>P=0.02</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Group C = standard heparin dose
Group HC = heparin dose response

Volume (mls/kg) for 24 hr blood loss, RBC, and FFP:

- Group C: 24 mls/kg
- Group HC: 24 mls/kg

24 hr blood loss: P=0.05
RBC: P=0.04
FFP: P=0.01

Group C = standard heparin dose
Group HC = heparin dose response

Heparin Monitoring During CPB
Adults

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instrumentation</td>
<td>Hemochron</td>
<td>Hepcon HMS</td>
</tr>
<tr>
<td>Initial heparin dose</td>
<td>Fixed</td>
<td>Based on HDR</td>
</tr>
<tr>
<td>Additional doses</td>
<td>ACT &lt;480 s</td>
<td>Heparin conc.</td>
</tr>
<tr>
<td>Initial protamine dose</td>
<td>Total heparin</td>
<td>Heparin conc.</td>
</tr>
<tr>
<td>Neutralization effect</td>
<td>ACT</td>
<td>Heparinase ACT</td>
</tr>
</tbody>
</table>


Heparin Monitoring During CPB
Adults

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraop PT (s)</td>
<td>18.9 ± 2.9</td>
<td>17.2 ± 3.0</td>
<td>0.007</td>
</tr>
<tr>
<td>Intraop APTT (s)</td>
<td>59.4 ± 25.6</td>
<td>48.3 ± 13.0</td>
<td>0.01</td>
</tr>
<tr>
<td>Heparin (U/kg)</td>
<td>462 ± 114</td>
<td>612 ± 147</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Protamine (mg/kg)</td>
<td>4.3 ± 1.2</td>
<td>4.2 ± 3.6</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Heparin Monitoring During CPB
Adults

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Intervention</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet trx (U)</td>
<td>3.7 ± 6.7</td>
<td>1.7 ± 3.6</td>
<td>0.003</td>
</tr>
<tr>
<td>FFP trx (U)</td>
<td>1.4 ± 2.5</td>
<td>0.4 ± 1.3</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cryotrx (U)</td>
<td>0.2 ± 1.2</td>
<td>0.0 ± 0.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Closure time (min)</td>
<td>102 ± 34</td>
<td>92 ± 32</td>
<td>0.02</td>
</tr>
<tr>
<td>Chest tube out (mL)</td>
<td>924 ± 520</td>
<td>839 ± 377</td>
<td>0.14</td>
</tr>
</tbody>
</table>


Monitoring of Heparin Anticoagulation

- Moderate dose heparin therapy (cardiac catheterization, vascular surgery)
  - Unfractionated heparin
  - ACT with target of 250-300 sec depending on methodology
  - Procedures with ablation therapy often utilize a higher target of 300-400 sec
Monitoring of Heparin Anticoagulation

• Lower dose heparin therapy: venous thromboembolism
  • Weight based unfractionated heparin most common
  • Target & dosing algorithm specific to current laboratory method for APTT
  • May need to use anti-Xa method if patient appears to be heparin resistant
  • Point of care testing doesn’t seem to have much of a role here

Anti-Platelet Therapy
Anti-Platelet Therapy

• Agents

  • Aspirin (inactivates platelet cyclooxygenase-1)
  • Thienopyridines (bind to P2Y12 receptor thereby inhibiting ADP-induced platelet activation)
    • Ticlopidine
    • Clopidogrel
  • Glycoprotein IIb/IIIa antagonists (block fibrinogen receptors thereby inhibiting platelet aggregation)
    • Abciximab
    • Eptifibatide
    • Tirofiban

Anti-Platelet Therapy

• Current standard practice to prevent thrombotic events for patients with cardiovascular disease
  • Primary prevention: aspirin
  • Patients with acute coronary syndromes: aspirin and clopidogrel
  • Patients undergoing percutaneous coronary intervention and stent placement
    • Aspirin & clopidogrel
      • Bare metal stents – up to 1 yr
      • Drug eluting stents – at least 1 yr
    • Glycoprotein IIb/IIIa antagonist for high risk patients

Cardiovasc Drugs Ther 24:61-70.
Anti-Platelet Therapy

- Substantial inter-patient variability in response to therapy as measured by laboratory tests
  - Disease burden – increased platelet activation in acute events, diabetics
  - Genetic polymorphisms of cytochrome p450 (clopidogrel)
  - Co-administration of other medications that affect p450 activity

Platelet Function Tests for Anti-Platelet Therapy

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Drawbacks</th>
<th>ASA</th>
<th>Thienopyridines</th>
<th>GP 2b/3a inhib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet aggregometry</td>
<td>Historical gold standard</td>
<td>Imprecision, expensive, large sample volume,</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>- turbidometric</td>
<td></td>
<td>sample prep, time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet aggregometry</td>
<td>Whole blood</td>
<td>Expensive, large sample volume, sample prep,</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>- impedance</td>
<td></td>
<td>time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VerifyNow</td>
<td>Simple, rapid, POC, small</td>
<td>No instrument adjustment</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>sample volume, no sample prep,</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>whole blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plateletworks</td>
<td>Little sample prep, whole</td>
<td>Not well studied</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>blood</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cardiovasc Drugs Ther 24:61-70.
### Platelet Function Tests for Anti-Platelet Therapy

<table>
<thead>
<tr>
<th>Test</th>
<th>Advantages</th>
<th>Drawbacks</th>
<th>ASA</th>
<th>Thiienopyridines</th>
<th>GP 2b/3a Inhib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thromboelastogram – Platelet Mapping System</td>
<td>POC, whole blood, platelet clot formation &amp; clot lysis data</td>
<td>Limited studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td>Cessation of Blood Flow by Platelet Plug</td>
<td>Simple, rapid, POC, small sample volume, no simple prep, whole blood</td>
<td>No instrument adjustment, depends on vWF, Hct</td>
<td>Y</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = not recommended

Clin Cardiol (Suppl 1) 31(3): I-10, 2008

### Comparison of 6 Platelet Function Tests to Determine Prevalence of Aspirin Resistance in Patients with Stable Coronary Artery Disease

201 patients on daily ASA

European Heart J 28:1702, 2007
Comparison of 4 Tests to Assess Inhibition of Platelet Function by Clopidogrel in Stable Coronary Artery Disease Patients

P2Y12

European Heart J 29:2877, 2008

116 patients in clopidogrel dosing trial
> 50% resistance found by all assays except WBA (47%)
Poor correlation between tests

Comparison of LTA, VerifyNow and TEG

- Madsen et al., Clin Chem 2010;56:839-47
  - 33 patients post cath, followed for one year
  - TEG, VerifyNow, LTA repeated 5 times over year
  - Both ASA and clopidogrel effects measured
    - VerifyNow and TEG showed highest intra-individual variability (20-40%)
    - Non-response uncommon by all methods (0-6/33)
    - By LTA only 2 patients demonstrated clopidogrel non-response at all visits (3-5 at any one visit)
    - By VerifyNow and TEG no patients demonstrated clopidogrel non-response at all visits (TEG 2-6 at any one visit)
    - No patients demonstrated ASA non-response at > 1 visit by any method
    - Poor correlation between tests
Anti-Platelet Therapy – Key Concepts Necessary for Individualized Therapy

- Standardized definition of resistance
- Resistance leads to poorer patient outcomes
- Change in dosing can overcome resistance
- Altered treatment leads to better patient outcomes

CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events

- 32 studies, 42016 patients, 3545 cardiovascular events, 579 stent thrombosis events
  - 6 randomized trials, 26 treatment only design
- Treatment only: alleles indicating lower enzyme activity: decreased active clopidogrel metabolites: decreased platelet inhibition: increased risk of cardiovascular events
  - RR 1.18 (1.09-1.28)
  - Studies with >200 events: RR 0.97 (0.86-1.09)
- Randomized trials: alleles not associated with modification of clopidogrel effect on cardiovascular events

JAMA 306: 2704, 2011
Phenotyping vs Genotyping for Prediction of Clopidogrel Efficacy and Safety (PEGASUS-PCI)

Dosing Clopidogrel Based on CYP2C19 Genotype – Stable Cardiovascular Disease

<table>
<thead>
<tr>
<th>VerifyNow assay &lt;230 PRU</th>
<th>Non-carriers</th>
<th>CYP2C19*2 heterozygotes</th>
<th>CYP2C19*2 homozygotes</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 mg dose</td>
<td>163.6 (154.4-173.9)</td>
<td>225.6 (207.7-243.4)</td>
<td>328.8 (247.9-409.7)</td>
</tr>
<tr>
<td>150 mg dose</td>
<td>126.7 (117.7-137.5)</td>
<td>188.1 (170.8-205.4)</td>
<td>310.2 (247.5-372.9)</td>
</tr>
<tr>
<td>225 mg dose</td>
<td>152.9 (135.2-170.6)</td>
<td>286.0 (177.9-394.1)</td>
<td></td>
</tr>
<tr>
<td>300 mg dose</td>
<td>127.5 (109.9-145.2)</td>
<td>287.0 (170.2-403.8)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.32</td>
</tr>
</tbody>
</table>
Standard vs High Dose Clopidogrel Based on Platelet Function Testing After PCI (GRAVITAS)

- Randomized, double-blind, active-control trial
- VerifyNow assay
- 2214 patients with high on-treatment reactivity 12-24 hours after PCI with drug-eluting stents at 83 centers
- High dose: 600 mg initial, 150 mg daily
- Standard dose: 75 mg daily
- Outcomes at 6 months

### Outcomes at 6 Months

<table>
<thead>
<tr>
<th></th>
<th>Death from cardiovascular causes</th>
<th>Non-fatal myocardial infarction</th>
<th>Stent thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose clopidogrel (1109 patients)</td>
<td>3 (0.3%)</td>
<td>20 (1.8%)</td>
<td>5 (0.5%)</td>
</tr>
<tr>
<td>Standard dose clopidogrel (1105 patients)</td>
<td>8 (0.7%)</td>
<td>18 (1.6%)</td>
<td>8 (0.7%)</td>
</tr>
<tr>
<td>Hazard ratio for high dose clopidogrel</td>
<td>0.38 (0.1 – 1.43)</td>
<td>1.12 (0.59-2.12)</td>
<td>0.63 (0.21-1.93)</td>
</tr>
<tr>
<td>P value</td>
<td>0.14</td>
<td>0.72</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Anti-Platelet Therapy – Key Concepts Necessary for Individualized Therapy

- Standardized definition of resistance
  - Definition depends on platelet function tests that are used
  - Results among methods don’t correlate
- Resistance leads to poorer patient outcomes
  - Maybe, maybe not
- Change in dosing can overcome resistance
  - Yes, in patients with stable CV disease
- Altered treatment leads to better patient outcomes
  - Not according to GRAVITAS

Conclusions

- Oral anticoagulation
  - The evidence base supports the use of POC INR testing (clinic or home) for monitoring warfarin anticoagulation
  - POC INR testing not typically used in the hospital setting
  - POC INR testing prior to procedures commonly done but the evidence base is lacking
  - Key to avoiding adverse events is the right delivery system
Conclusions

- Parenteral anticoagulation
  - POC activated clotting times are the established means of monitoring high/medium dose unfractionated heparin therapy
  - POC testing for heparin concentration is available for high dose scenarios – literature is mixed in its support
  - POC testing not available or clear in its application to other anticoagulants

Conclusions

- Anti-platelet therapy
  - Multiple POC tests are available to measure platelet function
  - Tests can detect aspirin and clopidogrel effect
  - Use in monitoring or modifying treatment is not supported based on current evidence