Clopidogrel Response Variability and Platelet Function Testing: Should Routine Practice Be Changed in Interventional Cardiology?

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Is Routine POC Testing of Platelet Function Reasonable?

Requirements Of A Screening Tool

- The test must be practical in the clinical setting.
- The test must accurately characterize low- and high-risk patients.
- Identification of at-risk individuals should lead to a treatment that improves outcome.
- The process should be cost-effective.

Adapted from Miller et al, J Am Coll Cardiol 2006;48:761-4
Bedside and Near-Bedside Platelet Function Tests
Moving from Bench-top to Clinic

- VerifyNow (Accumetrics)
- Multiplate Analyzer (Dynabyte)
- TEG Platelet Function Mapping (Haemoscope)

- Whole Blood (no processing)
- Minimal or no pipetting
- Can be implemented in clinical laboratory (for some devices, in office/ICU/cath lab.)
Platelet Function Testing Can Identify Patients At-Risk For Ischemic Events after PCI

**Clinically-Derived Cut-Offs from Prospective Studies:**

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Device</th>
<th>Primary Endpt</th>
<th>Cutoff</th>
<th>Method</th>
<th>Sens</th>
<th>Spec</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Price et al</td>
<td>380</td>
<td>VerifyNow P2Y12</td>
<td>6M CV death, MI, ST</td>
<td>PRU &gt; 235</td>
<td>ROC curve</td>
<td>78%</td>
<td>70%</td>
<td>99%</td>
</tr>
<tr>
<td>Patti et al</td>
<td>160</td>
<td>VerifyNow P2Y12</td>
<td>30-day CV death, MI, TVR</td>
<td>PRU &gt; 240</td>
<td>ROC curve</td>
<td>81%</td>
<td>53%</td>
<td>nr</td>
</tr>
<tr>
<td>Marcucci et al</td>
<td>683</td>
<td>VerifyNow P2Y12</td>
<td>1 yr CV death, MI</td>
<td>PRU &gt; 240</td>
<td>ROC curve</td>
<td>61%</td>
<td>70%</td>
<td>96%</td>
</tr>
<tr>
<td>Sibbing et al</td>
<td>1608</td>
<td>Multiplate Analyzer</td>
<td>30-day Stent thrombosis</td>
<td>468 AU·min</td>
<td>ROC curve</td>
<td>70%</td>
<td>84%</td>
<td>nr</td>
</tr>
<tr>
<td>Bliden et al</td>
<td>100</td>
<td>TEG Platelet Mapping</td>
<td>1 year CV death/MI/TVR/CVA/Non-TV/R/Re-hosp Ischemia</td>
<td>nr</td>
<td>ROC curve</td>
<td>nr</td>
<td>nr</td>
<td>nr</td>
</tr>
</tbody>
</table>

Sibbing et al, J Am Coll Cardiol 2009;53:849-856
Patti, G. et al. J Am Coll Cardiol 2008;52:1128-1133
Bliden et al, JACC 2007;49(6):657-66

nr = not reported
Potential Management Strategies for Patients With High Platelet Reactivity on Standard Clopidogrel Therapy

*Increase the clopidogrel maintenance dose*

Re-loading followed by 150-mg/day overcomes “non-responsiveness”

Matetzky et al, Am J Cardiol 2008; 102(5) :524-9
Potential Management Strategies for Patients With High Platelet Reactivity on Standard Clopidogrel Therapy

Add Cilostazol

Clopidogrel 150-mg day (High MD) vs. Clopidogrel + Cilostazol (Triple Group) in non-responders to standard dosing

NR defined as > 50% Agg (max) with 5μmol of ADP at least 12hrs after clop 300-mg

Jeong YH et al, J Am Coll Cardiol, 2009; 53:1101-110
Potential Management Strategies for Patients With High Platelet Reactivity on Standard Clopidogrel Therapy

Switch to prasugrel

Responder = \geq 25\% IPA at 4 and 24 hours

Increasing Risk With Greater Residual Reactivity
Event Rates In Prospective PCI Studies Stratified By PRU Quartile

Patti, G. et al. J Am Coll Cardiol 2008;52:1128-1133
Marcucci et al, Circulation 2009
The Balance Between Ischemic and Bleeding Risk

Decreasing Returns With Even Lower Reactivity?

Absolute baseline risk of ischemia or bleeding may differ between patients based on different clinical/procedural characteristics.

Clopidogrel (conventional dose)

Ischemic/Thrombotic Events

Bleeding

Risk

Post-treatment reactivity
**Standard Therapy**
placebo loading dose, then
clopidogrel 75mg +placebo/day

**Tailored Therapy**
clopidogrel 600mg*, then
clopidogrel 150-mg/day

**Successful PCI with DES without major complication or GPIIb/IIIa use**

VerifyNow P2Y12 Assay 12-24 hours post-PCI

**PRU ≥ 230?**

- **Yes**
  - **Non-Responder**
  - **Responder**

- **No**
  - Random Selection

**Clinical Follow-up And Platelet Function Assessment at 30 days, 6M**

**Primary Endpoint:** 6 month CV Death, Non-Fatal MI, ARC definite/prob ST

**Safety Endpoint:** GUSTO Moderate or Severe Bleeding

Price MJ et al, Am Heart J 2009
Assessment with a double Randomization of 1) a monitoring-adjusted antiplatelet treatment versus a Common antiplatelet regimen for DES implantation, and 2) Interruption versus Continuation of double antiplatelet therapy, one year after stenting: The ARCTIC study

Randomization before DES implantation

Group 2 : Conventional Arm
1- No assessment of the biological response to oral antiplatelet treatment
2- Oral Antiplatelet Strategy is left at the physician discretion according to local practice

Group 1 : Monitoring Arm
1- Systematic Assessment of the biological response to both aspirin and clopidogrel before drug eluting stent placement and at day 7-14
2- Adjustment of the dose regimen of oral antiplatelet treatment in suboptimal responders

Assessment of the primary endpoint every 6 month (6 up to 18 months)
1. All Cause Mortality
2. Myocardial Infarction
3. All Urgent Revascularization
4. Stent Thrombosis requiring revascularisation or not
5. Ischemic Stroke requiring a new hospitalisation
**DANTE trial**

**AMI FLORENCE 2 Registry**

*Dual ANtiplatelet Tailored therapy based on the Extent of platelet inhibition supported by Tuscany Region Health Service and University of Florence*

**Platelet function - driven antiplatelet therapy in patients with acute coronary syndromes undergoing PCI: rationale and design**

Randomized, parallel-groups, prospective clinical trial.

Approximately 450 ACS patients with RPR by ADP -VerifyNow- will be randomized to: clopidogrel 150 mg daily or clopidogrel 75 mg daily for the duration of the dual antiplatelet therapy according to the current guidelines.

**Inclusion criteria:** UA/NSTEMI patients undergoing PCI on dual antiplatelet therapy enrolled in the AMI-Florence 2 registry

**Exclusion criteria:** bleeding diathesis; history of TIA/stroke; platelet count <100000/mm3; PT-INR >1.5; Hb <10 g/dl at the time of screening; body weight <60 Kg; creatinine ≥4 mg/dl; recent (within 3 weeks) major trauma/surgery, OAT, pregnancy, severe hepatic disease, active peptic ulcer.
Does POC testing of Platelet Function Fulfill the Criteria For a Screening Tool?

- The test must be practical in the clinical setting. ✓
- The test must accurately characterize low- and high-risk patients. ✓
- Identification of at-risk individuals should lead to a treatment that improves outcome …GRAVITAS and others
- Stay tuned for data that may support a change in routine practice!