Anti-Platelet Therapy Post Stent: When and How to Monitor Platelet Inhibition

Contemporary Multi-Disciplinary Cardiovascular Medicine
October 7, 2011

Improving People's Lives
through innovations in personalized health care
The Primacy of the Platelet in Acute Coronary Syndromes and Stent Thrombosis

- Aspirin is a relatively weak platelet inhibitor
- Aspirin alone reduces mortality 23% in AMI
- As effective as Streptokinase in reducing death in AMI (ISIS-2)
Numerous agonists activate platelets via specific receptors.

All platelet activators ultimately work by stimulating IIb/IIIa receptors.
The Primacy of the Platelet in Acute Coronary Syndromes and Stent Thrombosis

Inferior STEMI
100% native RCA

Acute thrombosis of LAD stent
Stent Thrombosis: Then and Now

- Early stent experience. Stent thrombosis common, even on:
  - IV Heparin
  - IV Dextran
  - Coumadin
  - ASA
  - Dipyridamole
Stent Thrombosis: Then and Now

- Early Experience

- Stent thrombosis was common because stent underdeployment was common.
Stent Thrombosis: Then and Now

- IVUS-guided stent deployment led to well apposed stents, and stent thrombosis rates dropped dramatically . . .

. . . But are still not zero!
Stent Thrombosis: Then and Now

With IVUS guidance and high pressure inflation of stents, antithrombotic therapy could be simplified

- IV Heparin
- IV Dextran
- Coumadin
- ASA + Ticlopidine
- Dipyridamole

To dual antiplatelet therapy
Peri Stent Antiplatelet Therapy

- Platelet IIb/IIIa receptor antagonists
  - Intravenous, for the immediate peri-stent period
  - Reduce peri-stent events (MACE)
    - Eptifibatide (ESPRIT Trial)
    - Abciximab (EpiSTENT)
    - Tirofiban (PRISM-PLUS)
Figure 2 Sites of action of platelet inhibitors

Raju NC et al. (2008) Platelet ADP-receptor antagonists for cardiovascular disease: past, present and future
Nat Clin Pract Cardiovasc Med  doi:10.1038/ncpcardio1372
Table 1 Properties of P2Y$_{12}$ receptor antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Route of administration</th>
<th>Frequency of administration</th>
<th>Activation via CYP450 metabolism</th>
<th>Time to peak platelet inhibition</th>
<th>Reversibility (half-life)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>Oral</td>
<td>Once daily</td>
<td>Yes$^a$</td>
<td>2–6 h$^b$</td>
<td>No</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Oral</td>
<td>Once daily</td>
<td>Yes$^a$</td>
<td>2 h</td>
<td>No</td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Intravenous</td>
<td>Continuous</td>
<td>No</td>
<td>30 min</td>
<td>Yes (3–5 min)</td>
</tr>
<tr>
<td>AZD6140</td>
<td>Oral</td>
<td>Twice daily</td>
<td>No</td>
<td>2 h</td>
<td>Yes (12 h)</td>
</tr>
</tbody>
</table>

$^a$These agents are prodrugs. $^b$After 600 mg clopidogrel loading dose. Abbreviation: CYP, cytochrome P.

Raju NC et al. (2008) Platelet ADP-receptor antagonists for cardiovascular disease: past, present and future

*Nat Clin Pract Cardiovasc Med* doi:10.1038/ncpcardio1372
Stent Thrombosis Rates Are Not Zero

- Causes of Stent Thrombosis:
  - Stent Factors
  - Lesion Factors
  - Procedural Factors
  - Patient Factors
    - Hyporesponsiveness to antiplatelet therapy
Hyporesponsiveness to antiplatelet therapy

- **Aspirin Resistance**
  - Increased risk of MI, CVA, death
  - Clinical Definition: CV Events on ASA
  - Lab Definition: Inability of ASA to inhibit TXA2 production by platelets *in vitro*
  - Clinical definition ≠ lab definition

- **Clopidogrel Resistance**
  - Increased MACE, stent thrombosis
  - Clinical Definition: CV Events on Clopidogrel
  - Lab Definition: Inability of Clopidogrel to inhibit ADP-induced platelet activation *in vitro*
  - Clinical definition ≠ lab definition
Figure 3 Causes of variation in responsiveness to clopidogrel

Raju NC et al. (2008) Platelet ADP-receptor antagonists for cardiovascular disease: past, present and future
Nat Clin Pract Cardiovasc Med doi:10.1038/ncpcardio1372
Clopidogrel “Black Box” Warning, 3/12/2010

- Warning about reduced effectiveness of Clopidogrel in patients who are poor metabolizers

- Informed healthcare professionals that tests are available to identify genetic differences in CYP2C19 function.

- Advised healthcare professionals to consider use of other antiplatelet medications or alternative dosing strategies for Plavix in patients identified as poor metabolizers.
CYP 2C19: What is it?

- Liver enzyme necessary for conversion of Clopidogrel to its active metabolite

- At least 3 variants (genetic polymorphisms) exist: CYP 2C19*1, CYP 2C19*2, and CYP 2C19*3

- CYP 2C19*1 is normally functioning, while 2 and 3 are “loss of function” alleles that have decreased function
  
  - Normal metabolizers: homozygous for CYP 2C19*1
  - Intermediate metabolizers: heterozygous
  - Poor metabolizers: homozygous for CYP 2C19*2
ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning"

- “There are several different platelet function tests that can be used to assess the platelet response to clopidogrel, and the clinician should use the method with the greatest reliability and reproducibility at his or her specific facility.”

- “However, because platelet inhibition still may not be optimal with these regimens (Prasugrel or high dose Clopidogrel), follow-up platelet function testing might be considered to ensure adequate platelet inhibition.”

J Am Coll Cardiol, 2010; 56:321-341
The Concept of Clinical Clopidogrel Resistance

- Has been studied extensively

- Consensus definition of high “On-Treatment” Platelet Reactivity in the setting of PCI (JACC White Paper Vol. 56, No. 12, 2010):
  
  1) PRI>50% by VASP-P analysis
  
  2) >235 P2Y12 reaction units (PRUs) by VerifyNow assay
  
  3) >46 micromolar ADP-induced platelet aggregation
  
  4) >468 arbitrary aggregation units/min in response to ADP by Multiplate analyzer
VerifyNow P2Y12 Assay

- Whole blood of pts on Clopidogrel sampled ex vivo
- ADP added to whole blood sample
- Turbidimetric assay based on platelet aggregation to fibrinogen coated beads
- Results reported in “P2Y12 Reaction Units” (PRU)
  - >235-240 PRU deemed to be Clopidogrel resistance
### Studies Documenting Relationship Between High “On-Treatment” Platelet Reactivity and Adverse PCI Outcomes

<table>
<thead>
<tr>
<th>Citation</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barragan 2003</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td>Gurbel 2005</td>
<td>Peri PCI enzyme rise</td>
</tr>
<tr>
<td>Matetzky 2004</td>
<td>6 month MACE</td>
</tr>
<tr>
<td>Bliden 2007</td>
<td>1 year MACE</td>
</tr>
<tr>
<td>Price 2008</td>
<td>6 month MACE/ST</td>
</tr>
<tr>
<td>Gurbel 2008</td>
<td>Stent thrombosis</td>
</tr>
<tr>
<td>Buonamici 2007</td>
<td>Stent thrombosis</td>
</tr>
</tbody>
</table>

At least 30 studies document a relationship between HPR and adverse post PCI outcomes.
Clopidogrel effectiveness is variable

This variability can lead to adverse clinical outcomes

Reduced Clopidogrel effectiveness can be detected by point of care testing

Reduced Clopidogrel effectiveness can be overcome by increasing the dose or using other agents (Prasugrel)

Can clinical outcomes be improved by tailoring antiplatelet therapy based on platelet function?
Standard- vs High-Dose Clopidogrel Based on Platelet Function Testing After Percutaneous Coronary Intervention
The GRAVITAS Randomized Trial  JAMA. 2011;305(11):1097-1105

- Randomized, double blind, active control trial

- 2214 pts with high on-treatment platelet reactivity 12-24 hrs after DES placement

- High dose Clopidogrel (600 mg load, 150 BID) vs. 600 mg load, 75 mg/day

- Primary outcome: 6 month cardiovascular death, MI, stent thrombosis (composite)
Figure 1. Trial Profile

5429 Patients assessed by VerifyNow P2Y12 test

2214 Randomized

2214 Had high on-treatment reactivity (PRU ≥230)

1109 Randomized to receive high-dose clopidogrel
1095 Received intervention as randomized
14 Did not receive intervention
11 Patient decision
1 Had protocol deviation
1 Unknown reason

1105 Randomized to receive standard-dose clopidogrel
1092 Received intervention as randomized
13 Did not receive intervention
5 Did not meet inclusion criteria
8 Patient decision

0 Lost to follow-up
157 Discontinued intervention
12 Had a cardiovascular event
16 Had bleeding
31 Had an adverse event
98 Had other reasons

108 Had other reasons
1109 Included in primary analysis

3215 Did not have high on-treatment reactivity (PRU <230)

586 Randomly selected for observational cohort

2629 Excluded per study protocol

586 Received standard-dose clopidogrel as assigned
584 Received intervention as randomized
2 Did not meet inclusion criteria

2 Lost to follow-up
78 Discontinued intervention
2 Had a cardiovascular event
14 Had bleeding
22 Had an adverse event
40 Had other reasons

1105 Included in primary analysis

586 Included in primary analysis

Price, M. J. et al. JAMA 2011;305:1097-1105
Figure 3. Pharmacodynamic Effect of High- and Standard-Dose Clopidogrel in Randomized Patients With High On-Treatment Platelet Reactivity

Price, M. J. et al. JAMA 2011;305:1097-1105
Table 2. Major Efficacy and Safety End Points at 6 Months in Randomized Patients With High On-Treatment Platelet Reactivitya.

<table>
<thead>
<tr>
<th>End Point</th>
<th>No. (%) of Patients Taking Clopidogrel</th>
<th>HR for High-Dose Clopidogrel (95% CI)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis (primary end point)</td>
<td>25 (2.3)</td>
<td>1.01 (0.58-1.76)</td>
<td>.97</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>3 (0.3)</td>
<td>0.38 (0.10-1.43)</td>
<td>.14</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>20 (1.8)</td>
<td>1.12 (0.59-2.12)</td>
<td>.72</td>
</tr>
<tr>
<td>Stent thrombosisc</td>
<td>5 (0.5)</td>
<td>0.63 (0.21-1.93)</td>
<td>.42</td>
</tr>
<tr>
<td>Death from cardiovascular causes or nonfatal myocardial infarction</td>
<td>23 (2.1)</td>
<td>0.93 (0.53-1.64)</td>
<td>.80</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>7 (0.6)</td>
<td>0.70 (0.27-1.85)</td>
<td>.48</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, hazard ratio.
aPercentages are event rates from observed data.
bHazard ratios and P values were calculated with the log-rank test stratified by acute coronary syndromes status.
cStent thrombosis was defined as definite or probable thrombosis, according to the Academic Research Consortium.

Price, M. J. et al. JAMA 2011;305:1097-1105
First Study of “Personalized” Antiplatelet Therapy

- When High “On-Treatment” platelet reactivity is detected by platelet function testing, increased doses of Clopidogrel do not alter clinical outcomes.

- Maybe not a total strike out:
  - Perhaps such patients would benefit from a different drug (Prasugrel, Ticagrelor)
Summary

- The platelet is centrally important in the pathophysiology of ACS and stent thrombosis

- The most widely used platelet ADP receptor antagonist (Clopidogrel) has significant variability in its effectiveness

- Genetics seem to play a part in this variability of response
Summary

- Platelet function testing to tailor or “personalize” antiplatelet therapy is an intriguing notion.

- The initial experiment testing the concept of tailored antiplatelet therapy failed.

- Although platelet function testing is available and “should be considered” according to ACC/AHA guidelines, evidence that treatment decisions based on such testing is lacking.

- More studies are underway.