POCT in the Management of Antiplatelet Therapy – Patient Response, Treatment Optimization and Personalized Medicine

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Goals and Objectives

• After reviewing the material you should gain an understanding of the variability in patient response to antiplatelet therapy
• Studies will be presented that will help you understand the importance of platelet reactivity testing on patient outcomes
• A discussion of methods of analysis will enable you to be aware of methods to measure platelet reactivity in response to antiplatelet medications
• Review emerging data showing the clinical utility of assessing response and practical impact on therapy
Hemostasis is achieved thru both platelet aggregation and coagulation.

Platelets

Platelet Aggregation

Clotting

Fibrin

RBCs

Thrombin

Hemostatic Clot

Measured by PT, aPTT, fibrinogen, D-dimer

Measured by Platelet Function Assays

COAGULATION

AGGREGATION
Atherosclerotic Plaque Rupture
Percutaneous Coronary Intervention (PCI) Stent Placement
Platelet Cascade: Adhesion
Platelet Cascade: Activation
Platelet Cascade: Release of Activators

- ADP
- Thromboxane A$_2$
Studies have shown substantial interpatient variability of platelet inhibition when using GP IIb/IIIa inhibitors during PCI

Abciximab platelet inhibition during and following standard bolus and infusion

GOLD study was the first direct correlation of platelet function to clinical outcome

500 patients undergoing PCI with a IIb/IIIa antagonist

MACE = Death, Q-wave MI, Urgent TVR, Non-Q-wave MI (CKMB >3x ULN)

**ATC: Efficacy of Aspirin at Various Doses in Reducing Vascular Events* in High-Risk Patients**

<table>
<thead>
<tr>
<th>Aspirin (mg daily)</th>
<th>No. of Trials</th>
<th>% Odds Reduction</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-1500</td>
<td>34</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>160-325</td>
<td>19</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>75-150</td>
<td>12</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Any aspirin</td>
<td>65</td>
<td>23</td>
<td></td>
</tr>
</tbody>
</table>

*Vascular events included nonfatal MI, nonfatal stroke, and death from vascular causes.


Treatment effect $P<.0001$
Krasopoulous, BMJ, 2008

- 20 studies, 2930 patients with CV disease. Compliance confirmed in 14 studies.
- 28% (810) ASA resistant
- ASA regime on most 75 – 325 mg/day, 6 included adjunct antiplatelet therapy
- Higher in women (p<0.001) and patients with previous renal impairment (p<0.03)
Meta Analysis Results

<table>
<thead>
<tr>
<th>CV Outcome</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All CV events*</td>
<td>3.85</td>
<td>3.08 – 4.80</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death</td>
<td>5.99</td>
<td>2.28 – 15.72</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>ACS</td>
<td>4.06</td>
<td>2.96 – 5.56</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Graft Failure</td>
<td>4.35</td>
<td>2.26 – 8.37</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New Cerebral Event</td>
<td>3.78</td>
<td>1.25 – 11.41</td>
<td>&lt;0.02</td>
</tr>
</tbody>
</table>

* Death, Stroke, MI, ACS

Krasopoulous et al, *BMJ* published online 17 Jan 2008
Aspirin non-responsiveness decreases with increasing dose

CAPRIE: Superior Efficacy of Clopidogrel versus ASA

Patients with recent ischemic stroke, recent MI or symptomatic PAD

CURE Study:
Primary End Point: MI/Stroke/CV Death

N=12,562

20% Relative Risk Reduction

Clopidogrel + Aspirin (n=6259)

Placebo + Aspirin (n=6303)

Cumulative Hazard Rate

Months of Follow-up

0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00

0
3
6
9
12

0.12
0.14
0.10
0.06
0.08
0.00

Variability in Plavix® Response

Change in ADP-Induced Platelet Aggregation 75 mg chronic dosing

Maximal aggregation 5 µmol/L ADP (%) following 600 mg loading dose

Serebruany. J Am Coll Cardiol. 2005

N=544

Hochholzer W et al., Circulation 2005

N=1001
The Reclose Study: 6 Month Outcomes After DES Implantation Stratified By Post-Plavix ADP-mediated Platelet Reactivity to 600 mg loading dose clopidogrel

Buonamici et al, JACC, June 2007
Distribution of Post-Treatment Reactivity (n=380)

Mean PRU=184.85
Upper Tertile: PRU > 231

“High post-treatment reactivity”

Price et al, Eur Heart J, 2008
Out-of-hospital 6 Month Outcomes Stratified By Reactivity In Patients On Consistent Clopidogrel Therapy At 6 months*

- **n=321**

<table>
<thead>
<tr>
<th></th>
<th>Low Post-Treatment Reactivity</th>
<th>High Post-Treatment Reactivity</th>
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<tbody>
<tr>
<td>CV Death</td>
<td>2.6%</td>
<td>5.3%</td>
</tr>
<tr>
<td>non-fatal MI</td>
<td>1.0%</td>
<td>4.4%</td>
</tr>
<tr>
<td>ST</td>
<td>1.8%</td>
<td>0%</td>
</tr>
<tr>
<td>CV Death/MI/ST</td>
<td>0%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

*p=0.04  p=0.6  p=0.005  p=0.025*

*on clopidogrel at 30 day & 6 month FU, or reached an endpoint on clopidogrel by 6 month FU
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

Patti et al
N=160

Price et al
N=380

Marcucci et al
N=683
ISAR-CHOICE 2

Doubling the Daily Dose of Clopidogrel After PCI Improves Inhibition At 30 Days

\[ P=0.006 \]

von Beckerath, Eur Heart J 2007
• Each additional bolus of 600 mg of clopidogrel decreased the number of patients with low response from 35 to 49%.

• Despite 2400 mg of clopidogrel 11 (14%) patients remained low-responders.

Bonello L. et al, Eur Heart J 2008
WHY?
Thienopyridines: Formation of Active Metabolite

**Clopidogrel**

85% Inactive Metabolites

CYPs:
- 1A2
- 2C19
- 2B6

Oxidation (Cytochrome P450)

Active Metabolite

CYPs:
- 3A
- 2B6
- 2C9
- 2C19
- 2B6

**Prasugrel**

Hydrolysis (Esterases)

CYPs:
- 3A
- 2B6
- 2C9
- 2C19

Oxidation (Cytochrome P450)

Active Metabolite
What is the probability that an individual has this genetic variant?

The Plavix package insert was recently updated to include the information regarding the frequency of the genetic variants that may contribute to decreased response as 26% in the white population, 33% in the black population, and 64% in the Asian population.
Omeprazole reduces antiplatelet effect of clopidogrel

Gilard M, Arnaud B, Cornily J-C, et al

Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: the randomized, double-blind OCLA (Omeprazole CLopidogrel Aspirin) study.

J Am Coll Cardiol 2008;51:256–60.
Conclusion

There is more than a fourfold greater chance of being a clopidogrel "bad responder" when patients were treated with omeprazole.
Inadequate Response to Antiplatelet Medications: Many Factors Can Contribute

- Genetics e.g. CYP2C19 (2-14% poor metabolizers)¹
- Concomitant Medications e.g. PPIs
- Pre-Existing Health Conditions e.g. Diabetes
- Non-Compliance (~22%)²

Functional test measures combined effect of all factors

Up to 1 in 3 patients may not respond adequately to aspirin or Plavix³

Patients who do not respond adequately may be at 5-10 times greater risk for heart attack or death⁴-⁷

References
Healthy Volunteer Crossover Study

N=66

- Clopidogrel Responder
- Clopidogrel Non-responder

IPA at 24 hours (%)

Response to Clopidogrel 300 mg

Response to Prasugrel 60 mg

From Brandt JT AHJ 153: 66e9, 2007
Balance of Efficacy and Safety

CV Death / MI / Stroke

Prasugrel

Clopidogrel

TIMI Major NonCABG Bleeds

Prasugrel

Clopidogrel

138 events
HR 0.81
(0.73-0.90)
P=0.0004
NNT = 46

35 events
HR 1.32
(1.03-1.68)
P=0.03
NNH = 167
P2Y12 Treatment Regimes

• Clopidogrel 75 mg daily or 300 mg bolus with maintenance dose of 75 mg daily. (CAPRIE, CURE) Note: This is the FDA approved dosing for clopidogrel. Discussion of other regimes is off-label.
• Clopidogrel 600 mg bolus with maintenance dose of 75 mg daily (Most common current practice)
• Clopidogrel 600 mg bolus followed by 150 mg for 7 days then 75 mg daily (OASIS-7 presented at ESC 2009, TCT 2009)
• Prasugrel, 60 mg loading dose followed by 10 mg daily. Note Black Box Warning. (Triton TIMI-38 and 44)
• Prasugrel, 60 mg loading dose followed by 5 mg daily (patient <60 kg). Per package insert, the effectiveness and safety of the 5 mg dose have not been prospectively studied.
• Ticlopidine (STARS) (used if clopidogrel option required)
• Refer to Surgeon
• Combination
Discontinuation of Antiplatelet Medications

Safety and Bleeding Management
Patients on Plavix® have increased risk of bleeding

- During CABG surgery, patients on Plavix® received 3.5X more blood products\(^1\)
- Blood loss in first 24 hours after surgery was almost 2X when comparing patients off Plavix <4 days vs. patients off Plavix ≥5 days\(^2\)
- Associated with higher postoperative bleeding and morbidity and mortality\(^3\)
- 10X greater rate of re-operation\(^4\)

\(^1\)Chen et al. *J Thorac Cardiovasc Surg* 2004;128:425-31
\(^2\)Chu et al. *Ann Thorac Surg* 2004;78:1536-41
\(^4\)Hongo et al. *J Am Coll Cardiol* 2002;40:231-7
As % platelet inhibition increases, so does the need for transfusions

<table>
<thead>
<tr>
<th>ADP aggregometry % inhibition</th>
<th># pts</th>
<th>Last Plavix dose days (range)</th>
<th>Platelet transfusion Incidence (%)</th>
<th># units</th>
<th>RBC transfusion (# units)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;60%</td>
<td>12</td>
<td>2.0 0.4 (1-5)</td>
<td>92*</td>
<td>16.6</td>
<td>2.8*</td>
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<tr>
<td>40-60</td>
<td>17</td>
<td>2.5 0.5 (1-6)</td>
<td>35</td>
<td>3.4</td>
<td>1.2</td>
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<tr>
<td>&lt;40%</td>
<td>14</td>
<td>2.3 0.4 (&lt;1-5)</td>
<td>21</td>
<td>1.7</td>
<td>1.0</td>
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*p<0.05 compared with 40-60% and <40%

Frequency Distribution of Platelet Inhibition After Cessation of Daily Clopidogrel Therapy
A Multimodal Approach for the Reduction of Allogeneic Blood Products Following Coronary Artery Bypass Grafting Utilizing Transcollation™ Technology

Shankha Biswas, MD; Bradford Ray, NRABT
Riverside Community Hospital, Riverside, CA

Cardiac Surgery Center Experience
46% Reduction of Exposure to allogenic blood products
47% Reduction of prevalence of allogenic blood transfusions
  66% Reduction in RBC exposure
  88% Reduction in platelet exposure
  86% Reduction in Fresh Frozen Plasma
76% Reduction in Average Number of Units Transfused
Case Study: Female in ER with Hip Fracture would have been admitted for 7 days post-plavix prior to surgery. Able to perform surgery on third day post Plavix.
What Assay Should I Choose and Why?
Laboratory Measurements of Antiplatelet Effect

• Fibrin Formation Based Assay
  – Bleeding Time (POC)
  – TEG (POC or Lab)

• Aggregation Based Assays
  – Light transmission aggregometry (Lab)
  – Accumetrics VerifyNow (POC or Lab)
  – Plateletworks (POC or Lab)

• Shear-Based Platelet Function Assay (Dade)
  (Rarely POC – mainly Lab)

• Urine thromboxane metabolite (Aspirinworks) (POC)
Bleeding Time

- First described in 1901
- Involves touching a piece of filter paper to the edge of a controlled, superficial wound.
- Previously used extensively for pre-operative evaluation of bleeding risk, but subsequent found to have no correlation with bleeding events.
- It is influenced by aspirin therapy.
Light Transmittance Aggregometry
Baseline Light Transmission – the unaggregated platelets in plasma creates a turbid solution that absorbs light.

Light transmission increases as platelets aggregate and fall to the bottom of the tube.

Aggregating Reagent
- Arachidonate
- ADP
- TRAP
- Collagen
- Epinephrine
Aggregometry Tracing
Aggregation-Based Rapid Platelet Function Assay

Light Source

Mixing Chamber

Rate and extent of change in light transmittance measured.

Platelets in whole blood + Fibrinogen-coated beads → Agglutinated beads fall out of solution
Patient % aggregation or inhibition is easily determined based on actual platelet baseline and agonist counts.
Shear-Based Platelet Function Assay - PFA-100®

900 µl Citrated Whole Blood

150 µm Aperture

Collagen + (epinephrine or ADP) Membrane

200 µm Capillary

Platelet Aggregate
Thromboelastograph (TEG)
Urinary Thromboxane – AspirinWorks

• 11-dehydroxy thromboxane B₂ is the most stable and abundant urinary metabolite of thromboxane A₂, which is synthesized by activated platelets and inhibited by ASA

• Requires only a random urine sample

• Ship to a core reference lab for ELISA testing

• May be other interferences, e.g. medication, obesity – studies pending
Goals of Antiplatelet Therapy

- Right Drug
- Right Dose
- Right Time
- Right Duration
- Right Strategy