Oral Antiplatelet Agents in PCI:
Stronger Agents for All, Tailored Therapy, or Both?

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## Disclosures

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<th>Research Grants/Support</th>
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Dr. Gurbel has patents in the field of platelet function testing.
What Are the Main Fears We Have As Interventionalists?

**Biggest Fear:** Stent Thrombosis

**Second Biggest Fear:** Bleeding
Should We Even Worry About Stent Thrombosis? When Does It Occur?

Definite/Probable Stent Thrombosis

Elective PCI Very Low Risk
SPIRIT IV Trial (non-complex disease, no recent MI, EF>30%)

Primary PCI
Meta-analysis of 11 trials (n=6,298)

The randomized trials are probably the best ST rates we can hope for

ADAPT-DES (~50% Stable) : Time to First Stent Thrombosis

N=8,583

Definite or probable 0.84% (70)
- Definite 0.63% (53)
- Probable 0.20% (17)

40 (57.1%) of ST events occurred within 30 days

Platelets Are Major Culprits in Post-PCI Ischemic Events and Stent Thrombosis


Colorized scanning electron micrograph of a portion of a human coronary artery thrombus.
Tailored Antiplatelet Therapy

3 Major Goals:

- Reduce ischemic event occurrence (ST)
- Avoid serious bleeding
- Save money
How Do We Prevent Post-PCI Thrombosis with Oral Antiplatelet Therapy in 2013?

Clopidogrel is a highly unpredictable and overall weak antiplatelet agent.

Aggregation in 42% of pts on C+A is in the same range as 50% of pts treated with A alone!

How can we rationalize giving this drug blindly to patients with high risk CVD?
Clopidogrel vs. Prasugrel


Clopidogrel vs. Ticagrelor

Do All P2Y$_{12}$ Inhibitors Have the Same Basic Effect?

- Molecular structure of clop and pras are ~same
- Equipotent AM
- No known significant off target effects
- At same level of platelet reactivity: Thrombotic risk should be same

Ticagrelor binds reversibly and independently from ADP - inhibits conformational change

- Ticagrelor is in different class (CPTP)
- ? Important off target effects:
  - At same level of platelet reactivity: thrombotic risk ? less due to off target effect
- Off-target effect can’t be measured by PFT

What Are the Requirements for Implementation of Tailored Therapy?

1) Evidence that:

*ex vivo* platelet reactivity is associated with ischemic events

2) Evidence for a threshold or therapeutic target:

- Upper end: Ischemia
- Lower end: Bleeding
Do We Have the Evidence?

**Yes:** For Ischemic Threshold (n > 10,000)

Consensus and Future Directions on the Definition of High On-Treatment Platelet Reactivity to Adenosine Diphosphate

Laurent Bonello, MD,* Udaya S. Tantry, PhD, §§ Rossella Marcucci, MD, PhD, || Ruediger Blindt, MD, # Dominick J. Angiolillo, MD, PhD, ||| Richard Becker, MD, ¶¶
Deepak L. Bhatt, MD, MPH, ## Marco Cattaneo, MD, † Jean Philippe Collet, MD, PhD, ‡
Thomas Cuisset, MD, † Christian Gachet, MD, PhD, § Gilles Montalescot, MD, PhD, ‡
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Dietmar Trenk, PhD, †† Jochem W. Van Werkum, MD, PhD, ## Franck Paganelli, MD,*
Matthew J. Price, MD, ‡‡‡ Ron Waksman, MD, §§§ Paul A. Gurbel, MD, §§ for the Working Group on High On-Treatment Platelet Reactivity

- Primarily Elective Patients Treated with Clopidogrel
- Platelet Function Measured at Discharge

**Maybe:** For Bleeding Threshold
Relation of Platelet Aggregation to Stent Thrombosis (n=123)

Relation of Platelet Aggregation to Peri-Procedural MI (n=281)

Relation of Platelet Aggregation to 2 Year Ischemic Events (n=297)


(Gurbel PA et al. *J Am Coll Cardiol*. 2008;51:B86 (abstract))
First Major Analysis of VerifyNow P2Y12 Assay Utility: Outcomes In Patients Receiving DES in the SCRIPPS Registry

<table>
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<th>Event</th>
<th>With HPR</th>
<th>No HPR</th>
<th>P value</th>
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<tbody>
<tr>
<td>CV death, non-fatal MI, or ST</td>
<td>6.5%</td>
<td>1.4%</td>
<td>0.035</td>
</tr>
<tr>
<td>CV death</td>
<td>2.8%</td>
<td>0%</td>
<td>0.04</td>
</tr>
<tr>
<td>Any ST</td>
<td>4.6%</td>
<td>0%</td>
<td>0.004</td>
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VerifyNow P2Y12 Patient Based Meta-Analysis: 2 Year Outcomes

6 studies, n=3,059

2 Yr MACE by PRU Quartile

~3x risk between Q1 and Q4

2 Yr Stent Thrombosis by PRU Quartile

~8x risk between Q1 and Q4

Very low ST rate ~ immunity

ADAPT DES TRIAL

10,000 consecutive pts receiving DES at up to 12 sites

Aspirin and Clopidogrel responsiveness evaluated (Accumetrics VerifyNow system)

Clinical FU for 2-5 years

Angiographic core lab assessment of all stent thromboses and 1:3 matching controls

Pls: Gregg W. Stone and Chuck Simonton
Sponsors: CRF and the Dickinson Inst.
Principal study group: STENT Registry investigators

Supported by grants from Boston Scientific (lead contributor), Accumetrics, Abbott Vascular, Cordis, and Medtronic
High Platelet Reactivity to ADP is Independently Associated with 
High Thrombosis Risk in the PCI Patient.

Multivariable (Cox PHR) model:

50% of 30 d definite or probable stent thrombosis solely attributable to HPR!
ADAPT-DES: Multivariable propensity score adjusted risk of VerifyNow PRU >208

1-year adverse events

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<tr>
<th>Event</th>
<th>Adj HR [95%CI]</th>
<th>P value</th>
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<tbody>
<tr>
<td>ST, def/prob</td>
<td>2.49 [1.43, 4.31]</td>
<td>0.001</td>
</tr>
<tr>
<td>- Definite</td>
<td>3.05 [1.62, 5.75]</td>
<td>0.0006</td>
</tr>
<tr>
<td>MI</td>
<td>1.42 [1.09, 1.86]</td>
<td>0.01</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.73 [0.61, 0.89]</td>
<td>0.002</td>
</tr>
<tr>
<td>Death, all-cause</td>
<td>1.20 [0.85, 1.70]</td>
<td>0.30</td>
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Variables in model: age, gender, diabetes, hypertension, hyperlipidemia, current smoking, prior MI, CKD, stable vs NSTEMI vs STEMI, hemoglobin, WBC, platelet count, creatinine clearance, MVD, premature DAPT discontinuation within 6 months, PRU >208 (forced in), ARU >550 (forced in)

Role of POC Testing: Bleeding Risk in Clopidogrel-Treated Patients

VerifyNow Assay


Multiplatele Analyzer

188 AU x min
TIMI Major Bleeding


Thrombelastography

All Major Bleeding Events ~within 1st Quartile: ROC for Bleeding=31 MA_{ADP}

Gurbel PA et al. Am Heart J. 2010;160:346-54
Evidence for Ischemic Threshold During Prasugrel Therapy

ACS-PCI (n=301)

1 Year Event Rate (%)

The Platelet Function Therapeutic Window and the Concept of “Thrombosis Immunity”

Figure 3

Post-PCI Ischemic/Thrombotic Clinical Events

The sigmoid cumulative frequency curve in patients with post-percutaneous coronary intervention ischemic/thrombotic clinical events relative to platelet reactivity to adenosine diphosphate. These data support the concept of a therapeutic window for P2Y12 blockade. Adapted, with permission, from Gurbel et al. (7). Abbreviation as in Figure 1.

“Immunity” Thresholds

- ~170 PRU
- ~50% VASP-PRI
- ~35% 5 µM ADP
- ~46% 20 µM ADP
- ~416 AU* MULTIPLATE
- ~65 mm MA_KH-TEG

Bleeding Threshold

- <85 PRU
- <188 AU*
- <31mm MA_KH
Genetic Testing
A genetic locus unequivocally associated with clopidogrel response variability

Genome Wide Association Study ~ 500,000 SNP’s

- Healthy Amish subjects (n=429)
- Contribution of genetic component to clopidogrel response variability ~70%
- Contribution of CYP2C19 locus to clopidogrel response variability ~12%
- Majority of clopidogrel response variability remains unexplained (rare/other genetic variants that escaped detection with GWAS)
Relation of CYP2C19*2 Allele to PD Response and Clinical Outcome

Sinai Hospital of Baltimore Study

Preclopidogrel

- Platelet Aggregation, %
- No. of CYP2C19*2 Alleles
- P = 0.92
- No. of participants: 102, 37, 4

Postclopidogrel

- Platelet Aggregation, %
- No. of CYP2C19*2 Alleles
- P = 0.02
- No. of participants: 131, 54, 3


No. of CYP2C19*2 alleles

HR = 2.42; 95% CI, 1.18-4.99; P = 0.02

% Experiencing Event

Days

0 90 180 270 360
CYP2C19 LoF = ~30% Caucasians & ~2% are homozygotes

Platelet reactivity in the clopidogrel-treated homzygotes is very high - a subject of FDA "boxed warning"

Is it rational take this 2% chance when we have the capability of easily detecting 2C19 LoF?
Why Aren't We Tailoring?

3 Major Prospective Trials of Personalized Antiplatelet Therapy Using Platelet Function Testing In the PCI Patient Have Failed to Show Benefit of Tailoring.
1) GRAVITAS (n=2214)

Elective or Urgent PCI with DES*

VerifyNow P2Y12 Test 12-24 hours post-PCI

PRU ≥ 230

- High-Dose Clopidogrel†
  - clopidogrel 600-mg, then
clopidogrel 150-mg daily X 6 months

- Standard-Dose Clopidogrel
  - clopidogrel 75-mg daily X 6 months

Primary Efficacy Endpoint: CV Death, Non-Fatal MI, Stent Thrombosis at 6 mo
(5% Predicted Event Rate)

Key Safety Endpoint: GUSTO Moderate or Severe Bleeding at 6 mo

Pharmacodynamics: Repeat VerifyNow P2Y12 at 1 and 6 months

†placebo-controlled   All patients received aspirin (81-162mg daily)

Price MJ et al. JAMA. 2011;305:1097-105
- Low risk patients: Low event occurrence
- Underpowered
- High HPR cutoff value
- Remedy to overcome HPR (high dose clopidogrel) is suboptimal:
  
  40% of HPR group still had HPR at 30d
Study Aborted Due to Futility:
Low Risk Patients: Too Few Endpoints
3) ARCTIC (n=2440)

- patients scheduled for DES
- oral antiplatelet therapy Pre Rd left to physician’s discretion
- P2Y_{12} inhibitor LD ≥6 h pre-stent recomm.

Primary endpoint at 12 months:
Death, MI*, stent thrombosis, stroke, urgent revascularization

* non-uniform detection of MI
** incomplete protocol adherence
- 87% with HPR got GPI
- 77% with HPR got P2Y_{12} LD

- 80% of primary endpoint is peri-MI- KM curves then flat
- Post-D/C event rate very similar to GRAVITAS
- Low risk patients: Low post-D/C event occurrence
- Underpowered for stent thrombosis, post-D/C MI
- Remedy for HPR (high dose clopidogrel) suboptimal (< 15% use of prasugrel for HPR)
- “GRAVITAS revisited?”
What Happens When We Nonselectively Give More Potent Agents For All?

We Only Know in the ACS Patient
What Happens When We Non-Selectively Give More Potent Agents For All?
Ischemic Outcomes

**TRITON TIMI-38**
- **n=13,608**
- **Cumulative Incidence (%)**
- **Days after randomization**
- **Clopidogrel**
- **Prasugrel**
- **HR = 0.81 (95% CI 0.73-0.90, p<0.001)**

**PLATO**
- **n=18,624**
- **Cumulative incidence (%)**
- **Days after randomisation**
- **Clopidogrel**
- **Ticagrelor**
- **HR 0.84 (95% CI 0.77–0.92), p=0.0003**

**Early Separation**
- Parallel Curves Post-30D

**No early Separation**
- Diverging Curves Post-30d

- In Non-Clopidogrel Pretreated Patient:
  ? Use Prasugrel Early then Switch to Clopidogrel

- Load with Clopidogrel and treat for ~ 30 d then Switch to Ticagrelor?
- Use Ticagrelor from the Start?


Is the mortality reduction the trump card for ticagrelor in ACS?
What Happens When We Non-Selectively Give More Potent Agents For All?

Bleeding

Non-CABG Major Bleeding

Prasugrel

Clopidogrel

Kaplan-Meier Estimated Rate (%)

Non-Procedural Major Bleeding

Ticagrelor (235 / 9235)

Clopidogrel (180 / 9186)

Kaplan-Meier Estimated Rate (%)

Non-CABG Major Bleeding

Non-Procedural Major Bleeding

? More Cost


Conclusions

Stronger Agents for All?
- Ticagrelor for all ACS PCI: Mortality benefit grows over time
- Not for all elective PCI: Bleeding, unknown efficacy, cost

Tailored Therapy?
- Current studies underpowered to refute utility
- Data not supportive in low risk PCI

- For High Risk non-ACS PCI:
  1) Test from beginning: Genotype before starting therapy or Platelet function post-clopidogrel
  2) Test later:
     - Stronger agents for all with low bleed risk first 60 d (highest ST rate)
     - Then save big guns for clop non-responders

Both?
- Ticagrelor for all ACS pts and then tailor:
- ? lowering dose to reduce bleeding - option for future investigations