Personalized Antiplatelet Therapy: State of the Art

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<table>
<thead>
<tr>
<th>Research Grants/Support</th>
<th>Honoraria/Consulting</th>
</tr>
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<tbody>
<tr>
<td>Nanosphere</td>
<td>Pozen</td>
</tr>
<tr>
<td>Haemonetics</td>
<td>Astra Zeneca</td>
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<tr>
<td>Daiichi Sankyo/Lilly</td>
<td>Daiichi Sankyo/Lilly</td>
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<tr>
<td>CSL Pharmaceuticals</td>
<td>Accumetrics</td>
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<td>HCRI</td>
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<td>NIH</td>
<td>Boehringer</td>
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<td>Merck</td>
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<td>Medtronic</td>
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<td>CSL</td>
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<tr>
<td></td>
<td>CSL t2 Biosystems</td>
</tr>
</tbody>
</table>

Dr. Gurbel has patents in the field of platelet function testing
The Core of Individualization:

“The Platelet Hypothesis”

If you don’t have reactive platelets, then you will be protected from post-PCI ischemic event occurrence.

Your risk for thrombosis will be less.

Why Should We Personalize Antiplatelet Therapy?

5 Key Facts
Fact 1:

Reactive platelets and P2Y$_{12}$ play important role in post-PCI ischemic event occurrence.

What is the Evidence for Central Role of Platelets and P2Y\textsubscript{12}?

From Basic Research:
- platelet response to all agonists that degranulate
- procoagulant properties
- inflammatory cell function

From Pathology:
- MI and stent thrombosis are platelet laden events

From Pre-Clinical Studies:
- Reduced platelet deposition and thrombus weight proportional to degree of P2Y\textsubscript{12} blockade

From Clinical Trials: CURE, CREDO, CLARITY, COMMIT
- Prevention of ischemic events (MI and stent thrombosis) with addition of P2Y\textsubscript{12} blocker

Inhibited by P2Y\textsubscript{12} Blockade

Why Should We Personalize Antiplatelet Therapy?

Fact 2:

P2Y$_{12}$ inhibitors are given for only 1 reason:

TO BLOCK PLATELET FUNCTION

- NO OTHER PROVEN BENEFICIAL EFFECTS

IF THERE IS NO MEASURABLE ANTIPLATELET EFFECT

THEN THE DRUG IS WORTHLESS

Aggregation in 42% of pts on C+A:

In same range as 50% of pts treated with A alone!
Why Should We Trust an *Ex Vivo* Antiplatelet Measurement?

**Fact 3:**

The development of **ALL** antiplatelet agents are based **first** and **foremost** on an *ex vivo* assessment of platelet inhibition.

Why then should we discard the clinical utility of **the same** testing to determine if the drug is working or not?

Use of agents with more potent ex vivo antiplatelet effects (prasugrel and ticagrelor) directly translated into less MI and stent thrombosis.

The most potent support for the platelet hypothesis

Fact 4:

Why Should We Personalize Antiplatelet Therapy?

Fact 5:

We now have data in tens of thousands of patients:

High Platelet Reactivity (HPR) and

LOF allele carriage

are major risk factors for post-PCI thrombotic event occurrence.

Personalization of Antiplatelet Therapy
Role of Genetics
Metabolism of Clopidogrel

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?
The Future is Now for Genotyping: Verigene System

Bench top instrumentation

Single-use disposable cartridges

- Results available in 3 hours
- 10 SNP’s can be determined in one test

<table>
<thead>
<tr>
<th>Blinded Methods Comparison Study</th>
<th>Bi-Directional DNA Sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verigene® Test</td>
<td></td>
</tr>
<tr>
<td>(*2-*10, *13, *17 alleles)</td>
<td></td>
</tr>
<tr>
<td>*1/*1</td>
<td>38</td>
</tr>
<tr>
<td>*2/*1</td>
<td>26</td>
</tr>
<tr>
<td>*2/*2</td>
<td>2</td>
</tr>
<tr>
<td>*8/*1</td>
<td>1</td>
</tr>
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<td>*9/*1</td>
<td></td>
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<tr>
<td>*10/*1</td>
<td>1</td>
</tr>
<tr>
<td>*17/*1</td>
<td></td>
</tr>
<tr>
<td>*17/*17</td>
<td>2</td>
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</tbody>
</table>

Verigene® CYP2C19 Test Performance

- 100% concordance
- 100% sensitivity
- 100% specificity

Gurbel PA et al., Presented at ACC 2011, New Orleans
The RAPID Program: Spartan RX CYP2C19 System

- Buccal Swab/Real Time PCR
- 60 minutes to identify:
  - CYP2C19*2 carrier status
  - Heterozygous vs. Homozygous

Patients undergoing PCI for non ST-ACS or stable CAD
N=200

Rapid Genotyping
N=102

- CYP2C19*2 Carriers
  N=23
  - Prasugrel 10 mg OD

- Non-Carriers
  N=74
  - Clopidogrel 75 mg OD

Standard Therapy
N=98

- Clopidogrel 75 mg OD

Platelet Function Testing at 1 week

Point-of-Care Genotyping

## RAPID GENE Trial: Results

<table>
<thead>
<tr>
<th></th>
<th>Rapid Genotyping (N=91)</th>
<th>Standard Therapy (N=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carriers of CYP2C19*2 allele no.(%)</td>
<td>23 (25.3)</td>
<td>23 (24.0)</td>
</tr>
<tr>
<td>Heterozygous CYP2C19*2 no.(%)</td>
<td>19 (20.9)</td>
<td>20 (20.8)</td>
</tr>
<tr>
<td>Homozygous CYP2C19*2 no.(%)</td>
<td>4 (4.4)</td>
<td>3 (3.1)</td>
</tr>
</tbody>
</table>

### Performance Characteristics of Rapid Testing vs. Direct DNA Sequencing

- **Sensitivity** – 100%
- **Specificity** – 99.4%

![Prevalence of HPR (PRU>208)](chart)

- **Rapid Genotyping**: 15 cases
- **Standard Therapy**: 31 cases

*p = 0.01*
Pharmacogenomics of Antiplatelet Intervention (PAPI)-2 Study

The First Large Prospective, Multicenter, Randomized Trial of Genotype-Directed versus Standard of Care Antiplatelet Therapy

NCT01452152

Personalization of Antiplatelet Therapy
Role of Platelet Function Testing
Rationale for New P2Y$_{12}$ Inhibitors and Personalized Antiplatelet Therapy:

Limitations of Clopidogrel
Relation of On-Treatment Platelet Reactivity to ADP to Post-PCI Ischemic Events: Early Evidence

VerifyNow P2Y12 Patient Based Meta-Analysis: 2 Year Outcomes

6 studies, n=3,059

2 Yr MACE by PRU Quartile

2 Yr Stent Thrombosis by PRU Quartile

*P-values adjusted for multiple comparisons

- ~3x risk between Q1 and Q4
- ~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

PIs: 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 is Independently Associated with Risk

Multivariable (Cox PHR) model:

50% of 30 d definite or probable stent thrombosis solely attributable to HPR
Common Arguments Against Platelet Function Testing:

1) “Low PPV”
   - PPV affected by prevalence
   - low event rate **ALWAYS** assoc. with low PPV (like ST)

- Diagnostic test statistics (i.e. PPV):
  - not optimal to describe prognostic test utility
  - may lead to discard useful tests (PFT’s)
  - expectations from prognostic tests different from diagnostic tests:
    eg. **diagnosis** of MI (troponin) vs. **prognosis** for ST (PFT)

- Prognostic markers (clinical, procedural, PFT):
  - better described by relative risk or hazard ratio **NOT** PPV
2) “I don’t see stent thrombosis anymore”
   - true, event rates have fallen but event is often catastrophic

Absolute reduction in 1 y events in CURE = 2%:
   led to approval of clopidogrel

Absolute reduction in 1 y events in TRITON = 2%:
   led to approval of prasugrel

Absolute reduction in 1 y events in PLATO = 2%:
   led to approval of ticagrelor

Absolute difference in ST related to HPR at 30 d in ADAPT-DES = 0.6%

Small Personalized Antiplatelet Studies

**VASP-P Assay**

(N=162)

Effects of Additional Boluses of Clopidogrel on the VASP Index in the VASP-Guided Group

- VASP 1 (n=78)
- VASP 2 (n=78)
- VASP 3 (n=40)
- VASP 4 (n=26)

Kaplan-Meier Analysis for 30-Day MACE

**VerifyNow Assay**

3T/2R Study

- n = 1277 screened
- n = 147 CLOP NR (<40% inhibition)
- n = 23 ASA NR (ARU>550)
- n = 93 ASA and CLOP NR

(N=263)

UFH or Bival 1:1

- Tirofiban*
- Placebo

**Peri-procedural MI**

- 20.4
- 35.1
- p<0.05


Small Personalized Antiplatelet Studies

Multiplate

MADONNA (Prospective, non-randomized, non-blinded study)

ADP-induced Aggregation (U)

Nonresponders (n=106)
- 60mg prasugrel (n=56)
- 600mg clopidogrel up to 4x (n=48)
- 60mg prasugrel (n=2)

HPR Cutoff

30 D Events (n, %)

<table>
<thead>
<tr>
<th>Event</th>
<th>Guided Group n=403</th>
<th>Non-Guided Group n=395</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis (definite and probable)</td>
<td>1 (0.2)</td>
<td>7 (1.9)</td>
<td>0.027</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>0 (0)</td>
<td>10 (2.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>8 (2)</td>
<td>5 (1.3)</td>
<td>0.422</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>4 (1)</td>
<td>1 (0.3)</td>
<td>0.186</td>
</tr>
</tbody>
</table>

Siller-Matula J. Presented at ESC 2012
GRAVITAS Study

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

*Peri-PCI clopidogrel per protocol-mandated criteria to ensure steady-state at 12-24 hrs
†placebo-controlled All patients received aspirin (81-162mg daily)

Price MJ et al. JAMA. 2011;305(10):1097-105
GRAVITAS- Primary Endpoint

2.3% vs. 2.3%
HR 1.01 (95% CI 0.58 - 1.76)
p=0.98

Cumulative Incidence of CV death, non-fatal MI, or ST (%)

Days

No. at Risk
High Dose Clopidogrel 1109 1056 1029 1017 1007 998 747 54
Standard Dose Clopidogrel 1105 1057 1028 1020 1015 1005 773 53

Price MJ et al. JAMA. 2011;3051097-105
TRIGGER-PCI

Successful PCI with DES without major complication and NO GPIIb/IIIa use

3,525 patients screened
3,492 VerifyNow testing
PRU >208

No
209 Invalid test result
33 No test result

Yes
625 patients with PRU >208

202 patients declined

423 patients randomized

212 prasugrel
210 received ≥1 dose prasugrel
211 clopidogrel
210 received ≥1 dose clopidogrel

74 study discontinuations
15 Subject decision
1 Consent revoked
58 Early termination of study

136 completed study

73 study discontinuations
9 Subject decision
4 Consent revoked
60 Early termination of study

137 completed study

<table>
<thead>
<tr>
<th>Event</th>
<th>Prasugrel N=212</th>
<th>Clopidogrel N=211</th>
<th>p</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days on study treatment(median)</td>
<td>174</td>
<td>174</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Primary composite efficacy EP:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death or MI</td>
<td>0</td>
<td>1 (0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Key secondary efficacy EPs:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>1 (0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehospitalization for cardiac ischemic event</td>
<td>2 (0.9%)</td>
<td>4 (1.9%)</td>
<td>0.992</td>
<td>0.99 (0.14-7.03)</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>2 (0.9%)</td>
<td>1 (0.5%)</td>
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<tr>
<td>Definite ST</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>1 (0.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All cause death</td>
<td>0</td>
<td>1 (0.5%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2) “No large scale randomized trial evidence yet that HPR is a modifiable risk factor”

- GRAVITAS - neutral
- TRIGGER - stopped
  - very low event rates-very low risk patients
  - double dose clopidogrel poor remedy for HPR (GRAVITAS)
  - HPR cutpoint too high? (GRAVITAS)

Will patients with HPR allow randomization to a pharmacodynamically inferior therapy given the overwhelming evidence that HPR is bad?

- In TRIGGER ~30% refused randomization
- Superiority trial may not be possible

Relation of Antiplatelet Drug Response to Recurrent Ischemic Events in Stable Cardiovascular Patients (ADIRE Study)

Study Design

Pre-selected patients (n=940)
- No inclusion (n=169): Exclusion criteria, Did not attend outpatient visit, No informed consent

Included (n=771)
- Aspirin +/- clopidogrel (n=659)
- Clopidogrel +/- aspirin (n=534)

Visit 1
Platelet function tests – clinical evaluation

Visit 2
Platelet function tests – clinical evaluation

Three-year follow-up
Contact with patients every 6 months

3-year MACE
MI, UA, hospitalization for revascularization, acute limb ischemia, ischemic stroke, TIA, or CV death

<table>
<thead>
<tr>
<th>Variable (n)</th>
<th>MACEs, n (%)</th>
<th>Log-Rank P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA 1 mmol/L, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20 (631)</td>
<td>98 (16)</td>
<td>0.91</td>
</tr>
<tr>
<td>20 (138)</td>
<td>22 (16)</td>
<td></td>
</tr>
<tr>
<td>ADP 5 μmol/L, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;42 (181)</td>
<td>22 (12)</td>
<td>0.14</td>
</tr>
<tr>
<td>42 (568)</td>
<td>98 (17)</td>
<td></td>
</tr>
<tr>
<td>ADP 20 μmol/L, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;55 (236)</td>
<td>32 (14)</td>
<td>0.16</td>
</tr>
<tr>
<td>55 (533)</td>
<td>88 (17)</td>
<td></td>
</tr>
<tr>
<td>Collagen 1 μg/mL, percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;90th (691)</td>
<td>111 (16)</td>
<td>0.28</td>
</tr>
<tr>
<td>90th (77)</td>
<td>9 (12)</td>
<td></td>
</tr>
<tr>
<td>PFA-100%, S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;190 (373)</td>
<td>64 (17)</td>
<td>0.37</td>
</tr>
<tr>
<td>190 (395)</td>
<td>56 (14)</td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td></td>
<td></td>
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<tr>
<td>≤72 (578)</td>
<td>78 (13)</td>
<td>0.009</td>
</tr>
<tr>
<td>&gt;72 (193)</td>
<td>42 (22)</td>
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<tr>
<td>LDL cholesterol, mmol/L</td>
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<tr>
<td>&lt;2.6 (478)</td>
<td>65 (14)</td>
<td>0.035</td>
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<tr>
<td>2.6 (274)</td>
<td>53 (19)</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>No (534)</td>
<td>38 (11)</td>
<td>0.003</td>
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<tr>
<td>Yes (437)</td>
<td>82 (19)</td>
<td></td>
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<tr>
<td>Smoking</td>
<td></td>
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<tr>
<td>No (189)</td>
<td>23 (12)</td>
<td>0.14</td>
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<tr>
<td>Yes (582)</td>
<td>97 (17)</td>
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Multivariate Survival Analysis

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<tr>
<th>HR</th>
<th>p value</th>
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<tbody>
<tr>
<td>1.74</td>
<td>0.008</td>
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<tr>
<td>1.39</td>
<td>0.07</td>
</tr>
<tr>
<td>1.78</td>
<td>0.005</td>
</tr>
<tr>
<td>1.93</td>
<td>0.005</td>
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</tbody>
</table>

C-index = 0.63

Relation of HPR During Aspirin to Recurrent Ischemic Events in Stable Cardiovascular Patients (ASCET)

**Therapy:** Aspirin 160mg/d or clopidogrel 75mg/d

**2 year MACE:** death, myocardial infarction, ischemic stroke, and unstable angina

**High RPR cutoff:** >196 seconds in PFA-100

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### Therapy Summary

- **Aspirin Users** (n=502)

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>No.</th>
<th>High RPR (n=128)</th>
<th>Low RPR (n=374)</th>
<th>Rate Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>54</td>
<td>17 (13.3)</td>
<td>37 (9.9)</td>
<td>1.34 (0.76, 2.38)</td>
<td>0.31</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>15</td>
<td>4 (3.1)</td>
<td>11 (1.9)</td>
<td>1.06 (0.34, 3.34)</td>
<td>0.92</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>18</td>
<td>8 (6.3)</td>
<td>10 (2.7)</td>
<td>2.34 (0.92, 5.92)</td>
<td>0.07</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>17</td>
<td>4 (3.1)</td>
<td>13 (3.5)</td>
<td>0.90 (0.29, 2.76)</td>
<td>0.85</td>
</tr>
<tr>
<td>Death</td>
<td>4</td>
<td>1 (0.8)</td>
<td>3 (0.8)</td>
<td>0.97 (0.10, 9.36)</td>
<td>0.98</td>
</tr>
<tr>
<td>Person-years</td>
<td>.</td>
<td>256</td>
<td>748</td>
<td>...</td>
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</tr>
</tbody>
</table>

### Patients With High On-Aspirin RPR (n=259)

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>No.</th>
<th>Aspirin (n=128)</th>
<th>Clopidogrel (n=131)</th>
<th>Rate Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite</td>
<td>27</td>
<td>17 (13.3)</td>
<td>10 (7.6)</td>
<td>1.74 (0.80–6.77)</td>
<td>0.16</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>8</td>
<td>4 (3.1)</td>
<td>4 (3.1)</td>
<td>1.02 (0.26–4.09)</td>
<td>0.97</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>12</td>
<td>8 (6.3)</td>
<td>4 (3.1)</td>
<td>2.05 (0.62–6.80)</td>
<td>0.23</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>6</td>
<td>4 (3.1)</td>
<td>2 (1.5)</td>
<td>2.05 (0.37–11.17)</td>
<td>0.39</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
<td>Undefined</td>
<td>0.31</td>
</tr>
<tr>
<td>Person-years</td>
<td>.</td>
<td>256</td>
<td>262</td>
<td>...</td>
<td>..</td>
</tr>
</tbody>
</table>

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Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy

Randomization before DES implantation

ARCTIC Study

Group 2: Conventional Arm
- No assessment of oral antiplatelet treatment effect
- Conventional therapy

Group 1: Monitoring Arm
- Assessment of aspirin and clopidogrel effect before DES and at day 7-14
- Adjustment of antiplatelet treatment in suboptimal responders

Primary Endpoints (6-18 m) All Cause Mortality, MI, Urgent Revasc., ST, Ischemic Stroke

Montalescot, Will be presented at AHA 2012

Platelet Function in Patients Treated with Prasugrel versus Clopidogrel For Acute Coronary Syndromes without Revascularization

TRILOGY-Platelet Function Substudy

TRILOGY ACS Study
9326 Patients Enrolled

Patients enrolled in Platelet Function Substudy
N = 2690 (28.8%)

Randomized Patients <75 Years Old
N = 2128 (79.1%)

Prasugrel N = 1089
Clopidogrel N = 1039

Prasugrel N = 1362
Clopidogrel N = 1328

Prasugrel N = 273
Clopidogrel N = 289

Randomized Patients ≥75 Years Old
N = 562 (20.9%)

Prasugrel N = 273
Clopidogrel N = 289

Gurbel PA et al. Will be presented at AHA 2012
Consensus/Guidelines/Alerts/FDA Statements Addressing Platelet Function Testing

**ACCF/AHA FOCUSED UPDATE**

2011 ACCF/AHA Focused Update of the Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction (Updating the 2007 Guideline)

European Heart Journal Advance Access published August 26, 2011

ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

**PRACTICE GUIDELINE**

2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention

**SPECIAL REPORT: STS WORKFORCE ON EVIDENCE BASED SURGERY**

2011 Update to The Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists Blood Conservation Clinical Practice Guidelines*

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**Ill-No Benefit: Routine Analysis**

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**ACCF/AHA Clopidogrel Clinical Alert:** Approaches to the FDA “Boxed Warning”

A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association

Endorsed by the Society of Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons

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Conclusions

- Platelet function testing:
  - a rock solid biological rationale
  - fundamental basis for drug development

- Platelet inhibition:
  - sole reason for P2Y\textsubscript{12} inhibitors
  - irrational to blindly give a drug with unpredictable PD effect.
  - consistent data link HPR to thrombosis in tens of thousands of pts.
  - 2% poor metabolizers in Caucasians

- HPR and LOF carriage are not guarantees that thrombosis will occur
  - just as other clinical risk factors such as diabetes, ACS are not

- Inappropriate to use diagnostic test statistics to judge prognostic markers
  (i.e. HPR and LoF)
  If we did we would not treat DM or hypercholesterolemia!
Conclusions

- Clopidogrel is pharmacodynamically effective in ~65%.

- Unselected use of new agents: more bleeding, more cost.

- Selective use of generic clopidogrel: more economical.

- No evidence that prasugrel or ticagrelor confer more benefit in clopidogrel responders.

“Thus, at this time we must rely on the guidelines and the existing observational data while keeping fully in mind the role that platelet physiology plays in catastrophic event occurrence in the PCI patient.”
Who is the Optimal Patient for Testing?

- Selective testing in **High risk** PCI patients on clopidogrel - can they safely stay on it? (PFT) Should they be started on it? (Gene)

- What is “high risk”?  

  **Variables mostly associated with increased risk of ST, MI, HPR:**
  
  - ACS (current or prior)
  - H/O stent thrombosis, TVR
  - Poor LV function
  - Multivessel stenting
  - Complex anatomy (e.g. bifurcation, long, small stents)
  - BMI, DM, PPI