Εξελίξεις στην Αντιαιμοπεταλιακή αγωγή
New developments in Antiplatelet treatment

D. Alexopoulos
ICE 2012
15.12.2012
I, Dimitrios Alexopoulos, have received honoraria for lecturing and research grants from:

Astra Zeneca
PharmaServe Lilly
Efficacy Outcomes: PCI Patients

CV Death, MI, Stroke

- Clopidogrel Standard
- Clopidogrel Double

HR 0.85
95% CI 0.74-0.99
P=0.036

Definite Stent Thrombosis

- Clopidogrel Standard
- Clopidogrel Double

HR 0.58
95% CI 0.42-0.79
P=0.001
TRITON Study Design

ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

Double-blind

N = 13,600

CLOPIDOGREL
300 mg LD/ 75 mg MD

PRASUGREL
60 mg LD/ 10 mg MD

Median duration of therapy - 12 months

1° endpoint: CV death, MI, Stroke

2° endpoints: CV death, MI, Stroke, Rehosp-Rec Isch

CV death, MI, UTVR

Stent Thrombosis (ARC definite/prob.)

Safety endpoints: TIMI major bleeds, Life-threatening bleeding

Key Substudies: Pharmacokinetic, Genomic
Triton TIMI 38 - Prasugrel vs. Clopidogrel


Primary Endpoint: CV Death, MI, Stroke

Clopidogrel

Prasugrel

HR 0.77
P=0.0001

HR 0.80
P=0.0003

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

ITT= 13,608
LTFU = 14 (0.1%)
Triton TIMI 38 - Prasugrel vs. Clopidogrel


Stent Thrombosis (ARC Definite + Probable)

- **Any Stent at Index PCI**
  - N = 12,844

- **Clopidogrel**
  - HR 0.48
  - P < 0.0001
  - NNT = 77
  - 2.4 (142)

- **Prasugrel**
  - 1.1 (68)

Days

Endpoint (%)

0 30 60 90 180 270 360 450
STEMI cohort 30 days

Montalescot G et al. Lancet 2009
PLATO Study Design

- NSTE-ACS (moderate-to-high risk) and STEMI (if primary PCI)
  - Clopidogrel-treated or -naive;
  - Randomized within 24 hours of index event (N=18,624)

- Clopidogrel (n=9291)
  - If pre-treated, no additional loading dose;
  - If naive, standard 300 mg loading dose, then 75 mg qd maintenance;
  - (additional 300 mg allowed pre PCI)

- Ticagrelor (n=9333)
  - 180 mg loading dose, then 90 mg bid maintenance;
  - (additional 90 mg pre-PCI)

6–12-month exposure

- Primary endpoint: CV death + MI + Stroke
- Primary safety endpoint: Total major bleeding
PLATO: primary endpoint:
K-M estimate of time to major CV event
(composite of CV death, MI or stroke)

<table>
<thead>
<tr>
<th>Months after randomization</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11.7</td>
<td>9.8</td>
</tr>
<tr>
<td>12</td>
<td>11.7</td>
<td>9.8</td>
</tr>
</tbody>
</table>

Cumulative incidence (%)

(HR, 0.84; 95% CI, 0.77-0.92; P<0.001)

No. at risk

<table>
<thead>
<tr>
<th>Drug</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor</td>
<td>9333</td>
<td>8628</td>
<td>8460</td>
<td>8219</td>
<td>6743</td>
<td>5161</td>
<td>4147</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>9291</td>
<td>8521</td>
<td>8362</td>
<td>8124</td>
<td>6650</td>
<td>5096</td>
<td>4047</td>
</tr>
</tbody>
</table>

Secondary efficacy endpoints over time

**Myocardial infarction**
- Clopidogrel: 6.9%
- Ticagrelor: 5.8%
- HR 0.84 (95% CI 0.75–0.95), p=0.005

**Cardiovascular death**
- Clopidogrel: 5.1%
- Ticagrelor: 4.0%
- HR 0.79 (95% CI 0.69–0.91), p=0.001

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Ticagrelor versus Clopidogrel in ACS Stent Thrombosis

<table>
<thead>
<tr>
<th>Category</th>
<th>Ticagrelor HR</th>
<th>Clopidogrel HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definite</td>
<td>0.67</td>
<td>0.75</td>
</tr>
<tr>
<td>Probable or Definite</td>
<td>0.77</td>
<td></td>
</tr>
<tr>
<td>Definite, Probable or Possible</td>
<td></td>
<td>0.77</td>
</tr>
</tbody>
</table>

HR = Hazard Ratio

P-values:
- Definite: P=0.009
- Probable or Definite: P=0.02
- Definite, Probable or Possible: P=0.01

KM estimated rate (% per year):
- Definite: 1.3%
- Probable or Definite: 2.2%
- Definite, Probable or Possible: 3.8%
TRITON: bleeding events
Safety Cohort (N=13,457)

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI Major Bleeds</td>
<td>1.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Threatening ARD</td>
<td>0.9%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Nonfatal ARD</td>
<td>0.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Fatal ARD</td>
<td>0.1%</td>
<td>0.4%</td>
</tr>
<tr>
<td>ICH in Pts w Prior Stroke/TIA</td>
<td>0.3%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

ARD: Absolute Risk Difference
HR: Hazard Ratio
NNH: Number Needed to Harm

Patras University Hospital
TRITON-TIMI 38: Net Clinical Benefit
Bleeding Risk Subgroups
Post-hoc analysis

<table>
<thead>
<tr>
<th>Prior Stroke / TIA</th>
<th>Risk (%)</th>
<th>$P_{int}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>+37</td>
<td>.006</td>
</tr>
<tr>
<td>No</td>
<td>-16</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>$P_{int}$</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 75</td>
<td>.006</td>
<td>-1</td>
</tr>
<tr>
<td>&lt; 75</td>
<td>.18</td>
<td>-16</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Wgt</th>
<th>$P_{int}$</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60 kg</td>
<td>.36</td>
<td>+3</td>
</tr>
<tr>
<td>≥ 60 kg</td>
<td>.18</td>
<td>-14</td>
</tr>
</tbody>
</table>

OVERALL           |   | -13|

Time to major bleeding – primary safety event

HR 1.04 (95% CI 0.95–1.13), p=0.434

No. at risk
Ticagrelor 9,235 7,246 6,826 6,545 5,129 3,783 3,433
Clopidogrel 9,186 7,305 6,930 6,670 5,209 3,841 3,479

*PLATO: CABG and NonCABG Major Bleeding*

- **NonCABG Major Bleeding**
  - Ticagrelor/clopidogrel: 4.5% (P=0.03)
  - Ticagrelor/clopidogrel: 3.8% (P=NS)

- **CABG Major Bleeding**
  - Ticagrelor/clopidogrel: 2.8% (P=NS)
  - Ticagrelor/clopidogrel: 2.2% (P=0.03)

- **Procedural Major Bleeding**
  - Ticagrelor/clopidogrel: 9.0% (P=NS)
  - Ticagrelor/clopidogrel: 9.3% (P=NS)

*Both groups included aspirin; Patients may be counted in more than 1 bleeding event category. The graded areas in the middle of the columns represent patients with both a CABG bleed and a non-CABG bleed, or both a procedural bleed and a nonprocedural bleed; NS, not significant; CABG, coronary artery bypass graft; K-M, Kaplan Meier*
Primary endpoint (creatinine clearance <60 mL/min),

N=3237

- Clopidogrel CKD: 22.0%
- Ticagrelor CKD: 17.3%
- Clopidogrel normal: 8.9%
- Ticagrelor normal: 7.9%

Days after randomization
PLATO intent for non-invasive management: Primary composite endpoint

Initially intended for non-invasive management

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n=2601)</th>
<th>Clopidogrel (n=2615)</th>
<th>HR (95% CI)</th>
<th>p for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.85 (0.73–1.00)</td>
<td>0.045</td>
</tr>
</tbody>
</table>

Initially intended for invasive management

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n=6732)</th>
<th>Clopidogrel (n=6676)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.84 (0.75–0.94)</td>
</tr>
</tbody>
</table>

Primary endpoint benefit with ticagrelor was consistent with the overall PLATO trial results

PLATO elderly patient subgroup analysis: Primary composite endpoint according to age

Primary endpoint benefit with ticagrelor was consistent with the overall PLATO trial results

No interaction between age and treatment was observed [Husted 2011:1]

ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation

Table 12  Periprocedural antithrombotic medication in primary percutaneous coronary intervention

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiplatelet therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin oral or i.v. (if unable to swallow) is recommended</td>
<td>I</td>
<td>B</td>
<td>133,134</td>
</tr>
<tr>
<td>An ADP-receptor blocker is recommended in addition to aspirin. Options are:</td>
<td>I</td>
<td>A</td>
<td>135,136</td>
</tr>
<tr>
<td>• Prasugrel in clopidogrel-naive patients, if no history of prior stroke/TIA, age &lt;75 years.</td>
<td>I</td>
<td>B</td>
<td>109</td>
</tr>
<tr>
<td>• Ticagrelor.</td>
<td>I</td>
<td>B</td>
<td>110</td>
</tr>
<tr>
<td>• Clopidogrel, preferably when prasugrel or ticagrelor are either not available or contraindicated.</td>
<td>I</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>
ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P2Y&lt;sub&gt;12&lt;/sub&gt;-inhibitor-naive patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.</td>
<td>I</td>
<td>A</td>
</tr>
</tbody>
</table>
Table 2. Recommendations for Antiplatelet Therapy

<table>
<thead>
<tr>
<th>Class I</th>
<th>2012 Focused Update Recommendations</th>
<th>2012 Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Aspirin should be administered to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it (59–66). <em>(Level of Evidence: A)</em></td>
<td>2011 recommendation remains current.</td>
<td></td>
</tr>
<tr>
<td>2. A loading dose followed by daily maintenance dose of either clopidogrel (13,67,68) <em>(Level of Evidence: B)</em>, prasugrel* (in PCI-treated patients) (7) <em>(Level of Evidence: C)</em>, or ticagrelor† (9) <em>(Level of Evidence: C)</em> should be administered to UA/NSTEMI patients who are unable to take aspirin because of hypersensitivity or major GI intolerance.</td>
<td>2011 recommendation modified (included prasugrel and ticagrelor).</td>
<td></td>
</tr>
<tr>
<td>3. Patients with definite UA/NSTEMI at medium or high risk and in whom an initial invasive strategy is selected (Appendix 6) should receive dual antiplatelet therapy on presentation (13,16,45,69). <em>(Level of Evidence: A)</em> Aspirin should be initiated on presentation (59,61–66). <em>(Level of Evidence: A)</em> The choice of a second antiplatelet therapy to be added to aspirin on presentation includes 1 of the following (note that there are no data for therapy with 2 concurrent P2Y12 receptor inhibitors, and this is not recommended in the case of aspirin allergy):</td>
<td>2011 recommendation modified (included ticagrelor).</td>
<td></td>
</tr>
<tr>
<td><strong>Before PCI:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Clopidogrel (13,16) <em>(Level of Evidence: B)</em>; or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ticagrelor† (9) <em>(Level of Evidence: B)</em>; or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- An IV GP IIb/IIIa inhibitor (45,50,51,70,71). <em>(Level of Evidence: A)</em> eptifibatide and tirofiban are the preferred GP IIb/IIIa inhibitors (50,51). <em>(Level of Evidence: B)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>At the time of PCI:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Clopidogrel if not started before PCI (13,16) <em>(Level of Evidence: A)</em>; or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Prasugrel* (7) <em>(Level of Evidence: B)</em>; or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ticagrelor† (9) <em>(Level of Evidence: B)</em>; or</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- An IV GP IIb/IIIa inhibitor (46,50,51). <em>(Level of Evidence: A)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. For UA/NSTEMI patients in whom an initial conservative (i.e., noninvasive) strategy is selected, clopidogrel or ticagrelor† (loading dose followed by daily maintenance dose) should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for up to 12 months (9,10,13). <em>(Level of Evidence: B)</em></td>
<td>2011 recommendation modified (included ticagrelor and changed duration of therapy to “up to 12 months”).</td>
<td></td>
</tr>
</tbody>
</table>
Clopidogrel: Response Variability

Light transmission aggregometry

Multiplate (whole blood aggregometry)

Large response variability to standard clopidogrel treatment

Gurbel et al., Circulation 2003
Sibbing et al., Thromb Haemost 2010
Genome Wide Association Study ~ 500,000 SNP’s

13 SNP’s cluster (1.5 mb on 10q24)

- Healthy Amish subjects (n=429) with extensive family relationships treated with 75mg x 7d clopidogrel
- Contribution of genetic component to clopidogrel response variability ~70%
- Contribution of CYP2C19 locus to clopidogrel response variability is only ~12%
- Majority of clopidogrel response variability remains unexplained
    (rare/other genetic variants that escaped detection with GWAS)

Clopidogrel ‘black box’ warning

WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

See full prescribing information for complete boxed warning.

- Effectiveness of Plavix depends on activation to an active metabolite by the cytochrome P450 (CYP) system, principally CYP2C19. (5.1)
- Poor metabolizers treated with Plavix at recommended doses exhibit higher cardiovascular event rates following acute coronary syndrome (ACS) or percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function. (12.5)
- Tests are available to identify a patient's CYP2C19 genotype and can be used as an aid in determining therapeutic strategy. (12.5)
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers. (2.3, 5.1)
Influence of Genetics on Clopidogrel vs. Prasugrel/Ticagrelor

TRITON TIMI-38
- Clopidogrel: 12.1%
- Prasugrel: 8.5%
- P int = ?
- LOF Carriers: 30%
- LOF Non-carriers: 8.0%

PLATO
- Clopidogrel: 11.2%
- Ticagrelor: 8.6%
- P int = 0.46
- LOF Carriers: 30%
- LOF Non-carriers: 10.0%
Ticagrelor Effectively Eliminates HPR
Pooled RESPOND and ONSET-OFFSET Studies (n=212)
VerifyNow P2Y12 Assay

% of Patients with PRU > 235

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predose</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>0.5 hr</td>
<td>94</td>
<td>42</td>
</tr>
<tr>
<td>1 hr</td>
<td>81</td>
<td>3</td>
</tr>
<tr>
<td>2 hr</td>
<td>56</td>
<td>36</td>
</tr>
<tr>
<td>8 hr</td>
<td>49</td>
<td>36</td>
</tr>
<tr>
<td>24 hr</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>≥2 wks</td>
<td>35</td>
<td>0</td>
</tr>
</tbody>
</table>

p<0.0001 for all post-dose comparisons

Same true for LTA and VASP Assays

Gurbel PA et al. ACC 2010
Prasugrel Overcomes High On-Clopidogrel Platelet Reactivity Post-Stenting More Effectively Than High-Dose (150-mg) Clopidogrel

The Importance of CYP2C19*2 Genotyping

Dimitrios Alexopoulos, MD,* Gerasimos Dimitropoulos, MD,* Periklis Davlouros, MD,* Ioanna Xanthopoulou, MD,* George Kassimis, MD,* Eleana F. Stavrou, PhD,† George Hahalis, MD,* Aglaia Athanassiadou, PhD†

Patras, Greece

![Graph showing PRU levels over time for prasugrel and clopidogrel. PRUs decrease over time with prasugrel showing a faster decline than clopidogrel.](image-url)
Letters to the Editor

Variability and treatment of high on-prasugrel platelet reactivity in patients with initial high on-clopidogrel platelet reactivity

Dimitrios Alexopoulos *, Theodora-Eleni Plakomyti, Ioanna Xanthopoulou

Department of Cardiology, Patras University Hospital, Rio, Patras, Greece

Fig. 1. Individual platelet reactivity values at first and second measurement and following 20 mg of prasugrel. PRU: platelet reactivity units. HTPR: high on treatment platelet.
Pharmacodynamic effect of prasugrel 5 mg vs clopidogrel 150 mg in elderly patients with high on-clopidogrel platelet reactivity


Platelet reactivity by treatment sequence. Data for the pre- and post-crossover periods are depicted. Error bars represent 95% CIs. Comparisons between treatments groups (solid lines) and within therapies (dotted lines) are shown (analysis of covariance models with baseline PR as a covariate).
Letter to the Editor
Reloading patients chronically treated with P2Y12 inhibitors and presenting with ACS/PCI: Facing a crossroad?

Dimitrios Alexopoulos,*

Patient requiring PCI

Stable CAD, on chronic

P2Y12 inhibitor

No role for reloading

Reload with clopidogrel
PDV: +
CLV: ±

ACS, on chronic

Clopidogrel

Switch to prasugrel or ticagrelor +/- reloading
PDV: +++
CLV: ?

Prasugrel

Reload with prasugrel
PDV: +
CLV: ?

Ticagrelor

No need for reloading
PDV: ?
CLV: ?
Review

P2Y12 inhibitors **adjunctive to primary PCI therapy in STEMI**: Fighting against the activated platelets

**Dimitrios Alexopoulos**

*Department of Cardiology, Patras University Hospital, Kion 26500, Patras, Greece*

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**Table 2**
Comparative outcome results between TRITON\(^a\) and PLATO\(^b\) studies in STEMI/PPCI patients.

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death/MI/stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRITON</td>
<td>11.6%</td>
<td>10.2% (p = 0.27)</td>
<td>N/A</td>
</tr>
<tr>
<td>PLATO</td>
<td>10.8%</td>
<td>N/A</td>
<td>9.4% (p = 0.07)</td>
</tr>
<tr>
<td><strong>Stent thrombosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRITON</td>
<td>2.7%</td>
<td>1.5% (p = 0.0476)</td>
<td>N/A</td>
</tr>
<tr>
<td>PLATO</td>
<td>2.4%</td>
<td>N/A</td>
<td>1.6% (p = 0.03)</td>
</tr>
<tr>
<td><strong>Bleeding (TIMI major unrelated to CABG)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRITON</td>
<td>1.9%</td>
<td>3.1% (p = 0.11)</td>
<td>N/A</td>
</tr>
<tr>
<td>PLATO</td>
<td>2.2%</td>
<td>N/A</td>
<td>2.5% (p = 0.6)</td>
</tr>
</tbody>
</table>

\(^a\) Data from 2438 PPCI treated patients [Ref. 44].

\(^b\) Data from 7544 patients with ST elevation or left-bundle branch block of whom 5439 (72.1%) were treated with PPCI [Ref. 48].
Prasugrel Versus High Dose Clopidogrel to Overcome Early High on Clopidogrel Platelet Reactivity in Patients with ST Elevation Myocardial Infarction

D. Alexopoulos · K. C. Theodoropoulos · E. F. Stavrou · I. Xanthopoulou · G. Kassimis · G. Tsigkas · A. Damelou · P. Davlouros · G. Hahalis · A. Athanassiadou

Consecutive patients with STEMI
N=168

Eligible patients for platelet reactivity assessment, 2 hours post clopidogrel loading
N=93

PRU ≥235 and all randomized, Hour 0
N=60 (64.5%)

Allocated to clopidogrel N=29
Platelet reactivity assessed at Hour 2, Hour 24 and Day 5
Patients with complete Day 5 data N=29

Allocated to prasugrel N=31
Platelet reactivity assessed at Hour 2, Hour 24 and Day 5
1 patient died at Day 5
Patients with complete Day 5 data N=30

Exclusion criterion fulfillment
IIb/IIIa administration N=31
Cardiogenic shock N=6
Prior stroke N=8
Anatomy not suitable for primary PCI N=8
Hemodialysis N=2
Loading with other antiplatelets N=8
Death N=2
Anemia/Thrombocytopenia N=5
Weight<60 Kg, or age≥75 years N=5
Fig. 2 Individual values of platelet reactivity (PRU) at 2, 24 h and 5 days post randomization. A dotted line represents the high on-treatment platelet reactivity threshold. High on-treatment platelet reactivity rates are shown at the top of each column. *p<0.001, †p=0.001 and ‡p=0.02 versus clopidogrel.

Fig. 3 Platelet reactivity (PRU) at 0, 2, 24 h and 5 days post randomization, separately for non-carriers and carriers of CYP2C19*2 loss of function allele. Values represent least squares estimates and error bars 95% confidence intervals. A dotted line represents the high on-treatment platelet reactivity threshold, *p<0.001, †p=0.001 and ‡p=0.008 versus clopidogrel.
Ticagrelor Versus Prasugrel in Acute Coronary Syndrome Patients With High On-Clopidogrel Platelet Reactivity Following Percutaneous Coronary Intervention

A Pharmacodynamic Study

Dimitrios Alexopoulos, MD, Anastasia Galati, MD, Ioanna Xanthopoulou, MD, Eleni Mavronasiou, MD, George Kassimis, MD, Konstantinos C. Theodoropoulos, MD, George Makris, MD, Anastasia Damelou, MD, Grigorios Tsigkas, MD, George Hahalis, MD, Periklis Davlouros, MD

Patras, Greece

Objectives

The study aimed to compare the antiplatelet action of ticagrelor with prasugrel in acute coronary syndrome (ACS) patients with high on-treatment platelet reactivity (HTPR) while on clopidogrel after percutaneous coronary intervention (PCI).

Background

Newer P2Y12 inhibitors like prasugrel and ticagrelor provide stronger platelet inhibition compared with clopidogrel. Both agents are efficacious in patients with HTPR while on clopidogrel, but direct comparison between them has not yet been reported.

Methods

In a prospective, single-center, single-blind study, 44 (of 139 screened, 31.7%) ACS patients with HTPR while on clopidogrel 24 h post-PCI were randomized to either ticagrelor 90 mg twice daily or prasugrel 10 mg once daily for 15 days with a crossover directly to the alternate treatment for another 15 days. HTPR was defined as platelet reactivity units (PRU) ≥235 as assessed by the VerifyNow P2Y12 function assay.

Results

The primary endpoint of platelet reactivity at the end of the 2 treatment periods was lower for ticagrelor (32.9 PRU, 95% confidence interval [CI]: 18.7 to 47.2) compared with prasugrel (101.3 PRU, 95% CI: 86.8 to 115.7) with a least squares mean difference of −68.3 PRU (95% CI: −88.6 to −48.1; p < 0.001). The secondary endpoint of HTPR rate was 0% for ticagrelor and 2.4% for prasugrel (1 of 42, p = 0.5). No patient exhibited a major bleeding event at either treatment group.

Conclusions

In patients with ACS exhibiting HTPR while on clopidogrel 24 h post-PCI, ticagrelor produces a significantly higher platelet inhibition compared with prasugrel. (Ticagrelor Versus Prasugrel In Acute Coronary Syndromes After Percutaneous Coronary Intervention; NCT01360437) (J Am Coll Cardiol 2012;60:193–9) © 2012 by the American College of Cardiology Foundation
Randomized Assessment of Ticagrelor vs. Prasugrel: Antiplatelet Effects in Patients with STEMI

Single-center study of 55 patients randomized to ticagrelor or prasugrel for 5 days and assessed for platelet reactivity.

<table>
<thead>
<tr>
<th>P2Y12 Reaction Units</th>
<th>Ticagrelor</th>
<th>Prasugrel</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hour</td>
<td>257.3</td>
<td>231.3</td>
<td>0.2</td>
</tr>
<tr>
<td>2 Hours</td>
<td>196.1</td>
<td>153.6</td>
<td>0.2</td>
</tr>
<tr>
<td>5 Days</td>
<td>25.6</td>
<td>50.3</td>
<td>0.01</td>
</tr>
</tbody>
</table>

**Conclusion:** Both ticagrelor and prasugrel show evidence of delay in the onset of antiplatelet action in patients with STEMI.

Pre-treatment platelet reactivity contribution to residual, post-treatment platelet reactivity in prasugrel and ticagrelor treated patients

Antiplatelet effects of prasugrel vs. double clopidogrel in patients on hemodialysis and with high on-treatment platelet reactivity

D. ALEXOPOULOS,* A. PANAGIOTOU,* I. XANTHOPOULOU,* D. KOMNINAKIS,† G. KASSIMIS,* P. DAVLOUROS,* C. FOURTOUNAS† and D. GOUMENOS†
Departments of *Cardiology; and †Nephrology, Patras University Hospital, Patras, Greece

Fig. 3. Individual platelet reactivity responses according to treatment. Lines represent means, and error bars represent 95% confidence intervals. PRU, P2Y12 reaction units; HTPR, high on-treatment platelet reactivity.
RESEARCH LETTER
Prevalence of Inadequate Platelet Inhibition by Clopidogrel in Patients Receiving Hemodialysis

To the Editor:
A variable antiplatelet response to clopidogrel is a well-recognized phenomenon studied mostly in patients with percutaneous coronary intervention (PCI), for whom high on-treatment platelet reactivity is associated with an elevated risk of adverse events, including stent thrombosis. Patients undergoing maintenance hemodialysis (HD) therapy present enhanced platelet reactivity, and clopidogrel often is prescribed to prevent atherothrombotic or, specifically, vascular access thrombotic complications.\(^1,2\) However, few and contradictory data for clopidogrel’s platelet inhibitory effect in HD patients are available.\(^3,4\) In a randomized comparison of prasugrel versus high clopidogrel in HD patients,\(^5\) we identified 21 of 25 (84%) with high on-treatment platelet reactivity. In the present prospective multicenter study, we extend this observation by defining the prevalence of high on-treatment platelet reactivity in a larger number of HD patients.

In one tertiary center and 2 regional hospitals, all maintenance HD patients receiving ongoing (≥2 months) treatment with clopidogrel, 75 mg/d, were approached for platelet reactivity assessment. Exclusion criteria included long-term oral anticoagulation treatment, acute coronary syndrome, hemodynamic instability, PCI or coronary artery bypass grafting within 3 months, platelet count <100 × 10^3/μL, and hematocrit <28%. Peripheral venous blood samples were drawn with a loose tourniquet through a short venous catheter inserted into a forearm vein immediately before HD. Platelet-function testing was performed with the VerifyNow (Accumetrics Inc, www.accumetrics.com) point-of-care P2Y12 assay. Results are reported as P2Y12 reaction units (PRU), with ≥235 PRU considered high on-treatment platelet reactivity. We used Fisher exact test and 2-sample t test to analyze categorical and normally distributed continuous data and Mann-Whitney U test for data with skewed distribution (presented as medians). Because several log-binomial models did not converge, we used univariate Poisson regression models with a robust estimator (which approximates the log-binomial maximum likelihood estimators) to assess the crude relative risks of clopidogrel hyporesponsiveness for various patient characteristics. A final multiple Poisson regression model (enter method) was fitted including all factors found to be related to clopidogrel hyporesponsiveness status at the \(P < 0.2\) level in univariate analyses. All tests were 2-tailed, and statistical

Table 1. Patient Demographic Characteristics

<table>
<thead>
<tr>
<th>Table 1. Patient Demographic Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n = 85)</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Men</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Time on HD therapy (mo)</td>
</tr>
<tr>
<td>Time on clopidogrel therapy (mo)</td>
</tr>
<tr>
<td>Time since last clopidogrel dose (h)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Prior MI</td>
</tr>
<tr>
<td>Prior CABG</td>
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<tr>
<td>Prior PCI</td>
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</tbody>
</table>

\(P\)
Ticagrelor in Clopidogrel-Resistant Patients Undergoing Maintenance Hemodialysis

To the Editor:

Patients with chronic kidney disease (CKD) and particularly those receiving hemodialysis (HD) frequently are poor responders to clopidogrel (ie, have high on-treatment platelet reactivity).\textsuperscript{1-3} Ticagrelor is a cyclooctyl-triazolo-pyrimidine that acts directly on the P2Y\textsubscript{12} receptor, reversibly antagonizing it. In 3,237 patients with non-dialysis-dependent CKD, ticagrelor reduced ischemic end points and mortality compared with clopidogrel, with no difference in bleeding.\textsuperscript{4} To the best of our knowledge, there is no previous report of ticagrelor administration in maintenance HD patients who are clopidogrel poor responders.

This was a prospective 2-center study in which consecutive patients receiving regular maintenance (\geq 6 months) HD and ongoing (\geq 2 months) treatment with clopidogrel, 75 mg/d, were approached for platelet reactivity assessment. Exclusion criteria and blood sampling details are provided in Item S1. Platelet function was tested with the VerifyNow (Accumetrics Inc, www.accumetrics.com) point-of-care P2Y\textsubscript{12} assay (results reported as P2Y\textsubscript{12} reaction units [PRU], with \geq 235 PRU considered high on-treatment platelet reactivity) and the Multiplate Analyzer (Dynabyte Informationssysteme, www.multiplate.net; results given in arbitrary aggregation units [AU] per minute).\textsuperscript{5,6} Patients with high on-treatment platelet reactivity were prescribed ticagrelor, 90 mg, twice daily for 15 days, when platelet reactivity was assessed. Drug identity was masked from physicians and those assaying platelet function; an independent physician monitored

Alexopoulos D, et al. AJKD 2012
TRILOGY ACS Study Design

Medically Managed UA/NSTEMI Patients

Randomization Stratified by:
Age, Country, Prior Clopidogrel Treatment
(Primary analysis cohort — Age < 75 years)

Medical Management Decision ≤72 hrs
(No prior clopidogrel given) — 4% of total

- **Clopidogrel**
  - 300 mg LD
  - 75 mg MD

Medical Management Decision ≤10 days
(Clopidogrel started ≤72 hrs in-hospital OR on chronic clopidogrel) — 96% of total

- **Prasugrel**
  - 30 mg LD
  - 5 or 10 mg MD

- **Clopidogrel**
  - 75 mg MD

- **Prasugrel**
  - 5 or 10 mg MD

Minimum Rx Duration: 6 months; Maximum Rx Duration: 30 months

Primary Efficacy Endpoint: CV Death, MI, Stroke

1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients <60 kg or ≥75 years, 5 mg MD of prasugrel was given. Adapted from Chin CT et al. Am Heart J 2010;160:16-22.e1.
Primary Efficacy Endpoint to 30 Months (Age < 75 years)

HR (95% CI) ≤ 1 Year: 0.99 (0.84, 1.16)
HR (95% CI) > 1 Year: 0.72 (0.54, 0.97)

HR (95% CI): 0.91 (0.79, 1.05)
P = 0.21

Interaction P = 0.07

No. at risk:
Prasugrel: 3620, 3248, 2359, 1611, 953, 389
Clopidogrel: 3623, 3244, 2390, 1596, 946, 399
First Large Scale Platelet Function Evaluation in a Major Clinical Trial: The TRILOGY ACS — Platelet Function Substudy


Duke Clinical Research Institute

SINAI
Center for Thrombosis Research

www.clinicaltrials.gov Identifier: NCT00699998
Continuous Frequency Distribution:
30-day PRU in Patients With vs. Without Events

TRILOGY Primary Outcome:
- Event (N = 214)
- No Event (N = 1794)

P = 0.07

Duke Clinical Research Institute
ARCTIC trial design

Coronary angiogram

VerifyNow P2Y12 + ASA

Drug (ASA, clopidogrel, prasugrel, GP2b3a I.) and Dose adjustments if high platelet reactivity

Stent-PCI

Drug (ASA, clopidogrel, prasugrel) and Dose adjustments at day 14

Rd

Standard of care

Stent-PCI

Standard of care

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

Statistical considerations:
- Assuming an annual risk of 9% and a 33% relative risk reduction (α risk at 5% and error β at 80%, bilateral test), 2,466 patients were necessary to demonstrate the superiority of the strategy of monitoring and adjustment

12-month FU
Primary Endpoint to 1 year

Death, MI, stroke, stent thrombosis, urgent revascularization

**Event Probability (primary end point)**

- Monitoring
- Conventional

**Follow-up (Days)**

- HR = 1.13 [0.98-1.29]
- p = 0.096

**Follow-up (Days)**

- 0
- 100
- 200
- 300

**Event Probability (primary end point)**

- Monitoring: 34.6%
- Conventional: 31.1%

**N at risk**

<table>
<thead>
<tr>
<th></th>
<th>Monitoring</th>
<th>Conventional</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1213</td>
<td>1227</td>
</tr>
<tr>
<td>Days 0</td>
<td>790</td>
<td>883</td>
</tr>
<tr>
<td>Days 100</td>
<td>762</td>
<td>801</td>
</tr>
<tr>
<td>Days 200</td>
<td>730</td>
<td>767</td>
</tr>
<tr>
<td>Days 300</td>
<td>730</td>
<td></td>
</tr>
</tbody>
</table>
ADAPT-DES
Assessment of Dual AntiPlatelet Therapy with Drug-Eluting Stents

Up to 11,000 pts prospectively enrolled
No clinical or anatomic exclusion criteria
11 sites in US and Germany

PCI with ≥1 non-investigational DES
Successful and uncomplicated
(IVUS/VH substudy; Up to 3000 pts enrolled)

Assess platelet function after adequate DAPT loading and GPI washout: Accumetrics VerifyNow Aspirin, VerifyNow P2Y12, and VerifyNow IIb/IIIa assays (results blinded)

Clinical FU at 30 days, 1 year and 2 years
Angio core lab assessment all STs w/1:2 matching controls

TCT2011
clinicaltrials.gov NCT00638794
ADAPT-DES: Stent thrombosis (definite or probable) according to post-PCI PRU

HR [95%CI] = 2.54 [1.55, 4.16], P=0.0001

Number at risk:
- PRU > 208: 3610
- PRU ≤ 208: 4839
ADAPT-DES: MI and major bleeding according to post-PCI PRU

**Myocardial infarction**

HR [95%CI] = 1.47 [1.15, 1.87]  
P=0.002

- PRU >208 (n=3610)  
  - 3.9%
- PRU ≤208 (n=4839)  
  - 2.7%

**Major bleeding**

HR [95%CI] = 0.83 [0.69, 0.99]  
P=0.04

- PRU >208 (n=3610)  
  - 6.7%
- PRU ≤208 (n=4839)  
  - 5.6%
ADAPT-DES: Multivariable propensity score adjusted risk of VerifyNow PRU >208 for subsequent 1-year adverse events (n=8,583)

<table>
<thead>
<tr>
<th>Event</th>
<th>Adj HR [95%CI]</th>
<th>P value</th>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>

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)
Prevalence of contraindications and conditions for precaution for prasugrel administration in a real world acute coronary syndrome population. (N=646/1016)

Alexopoulos et al, J Thromb Thrombolysis 2011
REGISTRY 8 GREEK HOSPITALS

ΠΠΓΝ ΠΑΤΡΩΝ
ΠΕΠΑΓΝ ΗΡΑΚΛΕΙΟΥ
ΠΠΓΝ ΑΛΕΞΑΝΔΡΟΥΠΟΛΗΣ
ΠΠΓΝ ΛΑΡΙΣΑΣ
ΠΠΓΝ ΙΩΑΝΝΙΩΝ
Α ΠΑΝ/ΚΗ ΚΛΙΝΙΚΗ ΙΠΠΟΚΡΑΤΕΙΟΥ
ΓΝ ΚΡΑΤΙΚΟ ΑΘΗΝΩΝ
ΓΝ ΑΛΕΞΑΝΔΡΑ

ΣΤΟΧΟΣ 1000 ΑΣΘ F-UP 1 ΕΤΟΣ

At least one absolute contraindication or special condition requiring precaution for administering

- clopidogrel 16.7%
- prasugrel 42.7%
- ticagrelor 35.5%
TREATMENT AT DISCHARGE FROM PCI HOSPITAL

Clopidogrel N=313 (36.5%)

Prasugrel N=225 (26.3%)

Ticagrelor N=318 (37.1%)
Prevalence of at least one contraindication/special condition/overlapping

- **Клопидогрель**
  - 16 (1.8%)

- **Πρασουγκρέλη**
  - 116 (13.3%)

- **Τικαγκρελόρη**
  - 147 (16.8%)

- 43 (4.9%)

- 9 (1.0%)

- 102 (11.7%)
At least one contraindication/special condition for clopidogrel/prasugrel/ticagrelor simultaneously

N=117 (13.3%)

NO LABEL CATEGORY???

Treatment at discharge

- Clopidogrel: 70 (59.8%)
- Prasugrel: 16 (13.7%)
- Ticagrelor: 31 (26.5%)
Risk factors for in-hospital bleeding events

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt; 20</td>
<td>3.79 (0.89-16.21)</td>
<td>0.07</td>
</tr>
<tr>
<td>Υπέρταση</td>
<td>2.41 (1.19-4.88)</td>
<td>0.02</td>
</tr>
<tr>
<td>ΙΙΒ/ΙΙΑ αναστολέας</td>
<td>2.41 (1.01-5.72)</td>
<td>0.047</td>
</tr>
<tr>
<td>Ηλικία ≥ 75 ετών</td>
<td>4.35 (2.07-9.17)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Τικαγκρελή</td>
<td>3.02 (1.39-6.55)</td>
<td>0.005</td>
</tr>
<tr>
<td>Πρασογκρέλη</td>
<td>3.56 (1.32-9.55)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
• In 21 (6.3%) cases there was switch from strong agent to clopidogrel (downgrade)
• 5 received clopidogrel during triple antithrombotic treatment
• 4 had bleeding event in-hospital
Risk factors for bleeding events during 30 days

Multivariate analysis (logistic regression-enter method)
Figure 2 Detailed incremental cost with ticagrelor over time.

Figure 3 Results of the probabilistic analysis on the cost-effectiveness plane (all ACS). Incremental costs and effects are calculated as ticagrelor minus generic clopidogrel.