Response variability to clopidogrel: is tailored treatment, based on laboratory testing, the right solution?

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Unità di Medicina III, Ospedale San Paolo
Dipartimento di Scienze della Salute
Università degli Studi di Milano
Milan, ITALY
Distribution of Platelet Reactivity Units (PRU), measure with VerifyNow P2Y12 in Clopidogrel-treated Patients, by Study and Quartile
Distribution of Platelet Reactivity Units (PRU), measure with VerifyNow P2Y12 in Clopidogrel-treated Patients, by Study and Quartile

~35% with high on-treatment platelet reactivity (non/poor responders)
Incidence of MACE for Normal and High On-Treatment Platelet Reactivity: Meta-analysis of Studies of ACS Patients on Treatment with Clopidogrel.
Response variability to Clopidogrel

The solution?

“Tailored treatment”: increase the dose of Clopidogrel in poor responders (based on the results of platelet function tests)
Two questions about «tailored» clopidogrel treatment, based on platelet function monitoring

1. Is it a desirable solution to the problem of the wide inter-individual variability of response?
Is tailored treatment with clopidogrel, based on platelet function testing, a desirable solution to the problem of the wide inter-individual variability of response to the drug?

• Although it is often considered a desirable evolution of modern medicine, which ideally should be personalized based on individual needs, tailored treatment based on laboratory tests is actually an old remedy (of yet unproven efficacy, in the case of antiplatelet therapy) to the problem of response variability to antithrombotic drugs with unpredictable bioavailability (e.g., unfractionated heparin; vitamin K antagonists).
Laboratory monitoring of antithrombotic therapy - CONS

- Costs
- Workload
- Inaccuracy
- Patients’ discomfort
Is tailored treatment with clopidogrel, based on platelet function testing, a desirable solution to the problem of the wide inter-individual variability of response to the drug?

- Although it is often considered a desirable evolution of modern medicine, which ideally should be personalized based on individual needs, tailored treatment based on laboratory tests is actually an old remedy (of yet unproven efficacy, in the case of antiplatelet therapy) to the problem of response variability to antithrombotic drugs with unpredictable bioavailability (e.g., unfractionated heparin; vitamin K antagonists).

- When possible, the use of alternative drugs with more uniform and predictable bioavailability, and favourable risk/benefit and cost-benefit ratios should be preferred.
Evolution of antithrombotic therapy

**ANTICOAGULANT**

**Need** for laboratory monitoring

**No Need** for laboratory monitoring
Evolution of antithrombotic therapy

**ANTICOAGULANT**

*Need* for laboratory monitoring

*No Need* for laboratory monitoring

**ANTIPLATELET**

*Need* for laboratory monitoring

*No Need* for laboratory monitoring
Two questions about «tailored» clopidogrel treatment, based on platelet function monitoring

1. Is it a desirable solution to the problem of the wide inter-individual variability of response?

2. Supposing that it is the only solution to the problem of inter-individual variability of response to clopidogrel, are we ready for it? (should we implement it in the clinical practice, today?)
1. Identification of the most accurate laboratory test [??]

Validation of laboratory monitoring of clopidogrel treatment
Which one is right?

Figure 2: Correlation and agreement of results obtained by multiple electrode aggregometry (MEA) and VerifyNow P2Y12 Assay in 801 CAD patients. Horizontal arrowed line represents cut-off value for RPR by VerifyNow P2Y12 Assay (>240 PRU). Vertical arrowed line represents cut-off value for RPR by MEA (≥37 AUC).
Validation of laboratory monitoring of clopidogrel treatment

1. Identification of the most accurate laboratory test [??]
2. Standardization of pre-analytical and analytical variables [??]
Prevalence of clopidogrel nonresponsiveness (impedance aggregometry) as a function of the time of blood sampling

<table>
<thead>
<tr>
<th>Time</th>
<th>n</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
<th>n</th>
<th>(%)</th>
<th>P</th>
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<tr>
<td>6.00 AM</td>
<td>5</td>
<td>8.5%</td>
<td>12</td>
<td>20.3%</td>
<td>6</td>
<td>10.2%</td>
<td>6</td>
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<td>&lt;0.02</td>
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<tr>
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<td>12</td>
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<td>2.00 PM</td>
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<td>7.00 PM</td>
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<td></td>
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<td>6</td>
<td>10.2%</td>
<td></td>
</tr>
</tbody>
</table>

Kozinski et al, Platelets 2011
Validation of laboratory monitoring of clopidogrel treatment

1. Identification of the most accurate laboratory test [??]
2. Standardization of pre-analytical and analytical variables [??]
3. Identification of universal cut-off values [??]
Validation of laboratory monitoring of clopidogrel treatment

1. Identification of the most accurate laboratory test

2. Standardization of pre-analytical and analytical variables

3. Identification of universal cut-off values

4. Clinical validation
**GRAVITAS Study Design**

**Standard-Dose Clopidogrel**
- Clopidogrel 75 mg/day

**High-Dose Clopidogrel†**

**Normal On-treatment Reactivity**

**Random Selection**
- N=586

**VerifyNow® P2Y12 Test 12-24 h Post-PCI**
- PRU ≥230

**Randomised**
- High-Dose Clopidogrel†
- Standard-Dose Clopidogrel†

*Peri-PCI clopidogrel per protocol—mandated criteria to ensure steady state at 12-24 hrs. †Placebo-controlled; all patients received aspirin (81-162 mg daily).*
Cumulative Kaplan-Meier Estimates of the Time to the First Adjudicated Occurrence of the Primary Efficacy End Point

Patients with high on-treatment platelet reactivity receiving high- or standard-dose clopidogrel

Cumulative Incidence of Primary End Point, %

Hazard ratio, 1.01; 95% CI, 0.58-1.76; $P = .97$

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel dose</th>
<th>High</th>
<th>Standard</th>
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</thead>
<tbody>
<tr>
<td>High-dose clopidogrel</td>
<td>1109</td>
<td>1056</td>
<td>1029</td>
</tr>
<tr>
<td>Standard-dose clopidogrel</td>
<td>1105</td>
<td>1057</td>
<td>1028</td>
</tr>
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</table>
High Residual Platelet Reactivity After Clopidogrel Loading and Long-term Cardiovascular Events Among Patients With Acute Coronary Syndromes Undergoing PCI

Guido Parodi, MD
Rossella Marcucci, MD
Renato Valenti, MD
Anna Maria Gori, BS
Angela Migliorini, MD
Betti Giusti, BS
Piergiorgio Buonamici, MD
Gian Franco Censini, MD
Rosanna Abbate, MD
David Antoniucci, MD

**RECLOSE 2-ACS Study:**
prospective, observational, single centre cohort study of 1798 consecutive patients with ACS undergoing PCI

*JAMA. 2011;306(11):1215-1223*
RECLOSE 2-ACS Study

design

• Identification of patients with «high residual platelet reactivity» (HRPR) 12-18 h after 600 mg clopidogrel (≥70% [10 µM]ADP-induced platelet aggregation)

• Treat patients with HRPR with high-dose clopidogrel (up to 300 mg qd) or ticlopidine (250-500 mg bid)

• End point: cardiac death, myocardial infarction, any urgent coronary revascularization, and stroke at 2-year followup
RECLOSE2-ACS
Incidence of Primary End Point Events at 2y F.U. in ACS patients on DAPT undergoing PCI, according to their platelet reactivity at baseline and F.U.

<table>
<thead>
<tr>
<th>HRPR</th>
<th>LRPR</th>
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<td>14.6%</td>
<td>8.7%</td>
<td>0.003</td>
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therapy adjustment

HRPR at F.U. LRPR at F.U.

Parodi et al, JAMA 2011;306:1215-23
RECLOSE 2-ACS
Incidence of Primary End Point Events at 2y F.U. in ACS patients on DAPT undergoing PCI, according to their platelet reactivity at baseline and F.U.

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<td>0.003</td>
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<td>therapy adjustment</td>
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14.9% 14.4% 0.91

Parodi et al, JAMA 2011;306:1215-23
Studies of «tailored treatment» (based on platelet function testing) with clopidogrel

• Randomized Clinical Trials
  – GRAVITAS (2011): NEGATIVE RESULTS
  – TRIGGER PCI (2012): NEGATIVE RESULTS

• Large observational study
  – RECLOSE 2-ACS (2011): NEGATIVE RESULTS
Response variability to clopidogrel: is tailored treatment, based on laboratory testing, the right solution?

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Dipartimento di Medicina, Chirurgia e Odontoiatria, Università degli Studi di Milano, Unità di Medicina 3, Ospedale San Paolo, Milan, Italy

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The criticisms that have been raised about the GRAVITAS trial, the amendments that have subsequently been proposed by its authors and the therapeutic failure of RECLOSE 2-ACS further emphasize our uncertainties and, as a consequence, the prematurity and incorrectness of tailoring clopidogrel treatment based on laboratory tests in clinical practise. Other trials of tailored clopidogrel treatment based on laboratory monitoring are ongoing and their results are expected in the near future [3].
Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting

Jean-Philippe Collet, M.D., Ph.D., Thomas Cuisset, M.D., Ph.D.,
Grégoire Rangé, M.D., Guillaume Cayla, M.D., Ph.D., Simon Elhadad, M.D.,
Christophe Pouillot, M.D., Patrick Henry, M.D., Ph.D., Pascal Motreff, M.D., Ph.D.,
Didier Carrié, M.D., Ziad Boueri, M.D., Ph.D., Loic Belle, M.D.,
Eric Van Belle, M.D., Ph.D., Hélène Rousseau, Ph.D., Pierre Aubry, M.D.,
Jacques Monséguy, M.D., Pierre Sabouret, M.D., Stephen A. O'Connor, M.B., B.Ch.,
Jérémie Abtan, M.D., Mathieu Kerneis, M.D., Christophe Saint-Etienne, M.D.,
Olivier Barthélémy, M.D., Farzin Beygui, M.D., Ph.D., Johanne Silvain, M.D., Ph.D.,
Eric Vicaut M.D., Ph.D., and Gilles Montalescot, M.D., Ph.D.,
for the ARCTIC Investigators*
Proportion of patients with Primary Outcome Events

A Primary End Point

Hazard ratio, 1.13 (95% CI, 0.98–1.29)
P=0.10

No. at Risk
Conventional treatment 1227 835 801 767
Monitoring 1213 790 762 730

Collet et al, NEJM november 2012
• “... maybe if we combine these tests along with genetic tests we can identify a group of patients who will benefit from intensification of therapy” *(Why? Moreover: Let’s make it simple!)*

• “... there are six or seven different receptors on platelets, and we have just measured one” *(?!?!?!)*

• “... I don't think this means that monitoring is not a viable strategy in selected patients, but we may need to do much more work to understand what affects platelet reactivity that is driven by common clinical characteristics” *(????)*
The most common criticism: GRAVITAS and ARCTIC enrolled mostly patients with stable disease.
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1. We do not care if these patients suffer an AMI or die of CV causes
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1. We do not care if these patients suffer an AMI or die of CV causes: NO!!
2. It is irrelevant if these patients respond to clopidogrel
The most common criticism: GRAVITAS and ARCTIC enrolled mostly patients with stable disease

1. We do not care if these patients suffer an AMI or die of CV causes: NO!!
2. It is irrelevant if these patients respond to clopidogrel: then why do we treat them?
The most common criticism:
GRAVITAS and ARCTIC enrolled mostly patients with stable disease

1. We do not care if these patients suffer an AMI or die of CV causes: NO!!
2. It is irrelevant if these patients respond to clopidogrel: then why do we treat them?
3. The CV risk of these patients is very low
The most common criticism:
GRAVITAS and ARCTIC enrolled mostly patients with stable disease

1. We do not care if these patients suffer an AMI or die of CV causes: NO!!
2. It is irrelevant if these patients respond to clopidogrel: then why do we treat them?
3. The CV risk of these patients is very low (studies are underpowered to detect a statistically significant effect of monitoring) (?)
### Incidence of the primary end point* in the GRAVITAS and ARCTIC studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Monitoring + high dose clopidogrel (or other drugs)</th>
<th>No monitoring + standard dose clopidogrel</th>
<th>Hazard ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GRAVITAS</td>
<td>2.3%</td>
<td>2.3%</td>
<td>1.01 (0.58-1.76)</td>
</tr>
<tr>
<td>ARCTIC</td>
<td>34.6%</td>
<td>31.1%</td>
<td>1.14 (0.98-1.29)</td>
</tr>
</tbody>
</table>

*6-month incidence of death from cardiovascular causes, nonfatal myocardial infarction, or stent thrombosis (GRAVITAS)

*composite of death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization 1 year after stent implantation (ARCTIC)
Comment by **Sanjay Kaul** (Cedars Sinai Medical Center, Los Angeles, CA):
Comment by Sanjay Kaul (Cedars Sinai Medical Center, Los Angeles, CA):

... as Einstein said best, the definition of insanity is “doing the same thing over and over again and expecting different results”
Response variability to Clopidogrel

Another solution?

Change the drug!
**Presenter Disclosure Information**

**Speaker: Marco Cattaneo, M.D.**

<table>
<thead>
<tr>
<th>Company Name</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eli Lilly/Daiichi Sankyo</td>
<td>Honoraria, Research grant</td>
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<tr>
<td>AstraZeneca</td>
<td>Honoraria, Research grant</td>
</tr>
</tbody>
</table>
In addition, my research lab is specialized in platelet function testing: therefore it would be rewarding for my profession if laboratory monitoring of antiplatelet therapy would be necessary.