Genotype and platelet function test guided anti-platelet therapy in acute coronary syndrome

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Background
Background

- High on-treatment platelet reactivity after clopidogrel administration is linked to the loss-of-function CYP 2C19 allele and accompanied by an increased risk of adverse events.
- Prasugrel is more effective in reducing platelet reactivity, in CYP 2C19*2 carriers

### Recommendations for oral antiplatelet agents

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Ref&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin should be given to all patients without contraindications at an initial loading dose of 150–300 mg and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.</td>
<td>I</td>
<td>A</td>
<td>107, 108</td>
</tr>
<tr>
<td>A P2Y₁₂ inhibitor should be added to aspirin as soon as possible and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.</td>
<td>I</td>
<td>A</td>
<td>110, 130, 132</td>
</tr>
<tr>
<td>A proton pump inhibitor (preferably not omeprazole) in combination with DAPT is recommended in patients with a history of gastrointestinal haemorrhage or peptic ulcer, and appropriate for patients with multiple other risk factors (H. pylori infection, age ≥65 years, concurrent use of anticoagulants or steroids).</td>
<td>I</td>
<td>A</td>
<td>125–127</td>
</tr>
<tr>
<td>Prolonged or permanent withdrawal of P2Y₁₂ inhibitors within 12 months after the index event is discouraged unless clinically indicated.</td>
<td>I</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td><strong>Ticagrelor</strong> (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>
<td>132</td>
</tr>
<tr>
<td><strong>Prasugrel</strong> (60-mg loading dose, 10-mg daily dose) is recommended for P2Y₁₂ 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>
<td>130</td>
</tr>
<tr>
<td><strong>Clopidogrel</strong> (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>
<td>110, 146, 147</td>
</tr>
<tr>
<td>A 600-mg loading dose of clopidogrel (or a supplementary 300-mg dose at PCI following an initial 300-mg loading dose) is recommended for patients scheduled for an invasive strategy when ticagrelor or prasugrel is not an option.</td>
<td>I</td>
<td>B</td>
<td>108, 114, 115</td>
</tr>
<tr>
<td>A higher maintenance dose of clopidogrel 150 mg daily should be considered for the first 7 days in patients managed with PCI and without increased risk of bleeding.</td>
<td>IIA</td>
<td>B</td>
<td>108</td>
</tr>
<tr>
<td>Increasing the maintenance dose of clopidogrel based on platelet function testing is not advised as routine, but may be considered in selected cases.</td>
<td>IIb</td>
<td>B</td>
<td>124</td>
</tr>
<tr>
<td><strong>Genotyping and/or platelet function testing may be considered in selected cases when clopidogrel is used.</strong></td>
<td>IIb</td>
<td>B</td>
<td>119, 121</td>
</tr>
<tr>
<td>In patients pre-treated with P2Y₁₂ inhibitors who need to undergo non-emergent major surgery (including CABG), postponing surgery at least for 5 days after cessation of ticagrelor or clopidogrel, and 7 days for prasugrel, if clinically feasible and unless the patient is at high risk of ischaemic events should be considered.</td>
<td>IIa</td>
<td>C</td>
<td>-</td>
</tr>
<tr>
<td>Ticagrelor or clopidogrel should be considered to be (re-) started after CABG surgery as soon as considered safe.</td>
<td>IIa</td>
<td>B</td>
<td>134</td>
</tr>
<tr>
<td>The combination of aspirin with an NSAID (selective COX-2 inhibitors and non-selective NSAID) is not recommended.</td>
<td>III</td>
<td>C</td>
<td>-</td>
</tr>
</tbody>
</table>

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<sup>a</sup>Class of recommendation

<sup>b</sup>Level of evidence

<sup>c</sup>Reference

<sup>4</sup>Prasugrel is not recommended if the patient is taking a drug that is a CYP3A4 inducer. This recommendation as the overall indication including clopidogrel-pre-treated patients and/or unknown coronary anatomy. The class I recommendation here refers to the specifically defined subgroup.


**Background**

- Phenotyping of platelet response to clopidogrel was better predictor of stent thrombosis than genotyping. – *J Thromb Haemost* 2012;10(4):529-42.

- Personalized anti-platelet treatment for anti-platelet resistance was found to be associated with less occurrence of death or stent thrombosis. – *Heart* 2013 Nov 5. [Epub ahead of print]
**Background**

- The clinical evidence regarding the influence of tailored anti-platelet strategy on adverse outcomes has been controversial.

  – *Heart* 2013 Nov 5. [Epub ahead of print]
• The present study was designed to assess the effect of genotype and platelet function test guided anti-platelet therapy in patients with acute coronary syndrome (ACS).
Methods
Method

- Forty-six ACS patients undergoing percutaneous coronary intervention (PCI) were screened with CYP 2C19 *2*3 loss-of-function (LOF) polymorphism and VerifyNow® P2Y12 assay, defining high on-treatment platelet reactivity (HTPR) as platelet reaction unit (PRU) > 230.

- Before randomization step, in all cases, clopidogrel was administered. (600mg loading and then 75mg/day)
Method

• Those with homozygous LOF allele and HTPR (PRU>230), we switched clopidogrel over to prasugrel (10mg/day) (Group 1).

• Those with normal genotyping (*1*1) and normal platelet function test (PRU<230), we maintained clopidogrel (75mg/day) (Group 4).

• Others (intermediate characteristics) were randomized to prasugrel (Group 2) or clopidogrel (Group 3).
Clinical endpoints

• Primary endpoint was 1 month HTPR.

• Secondary endpoints included
  
  12 month death or MI

  12 month TLR, 12 month binary ISR, CV admission

GUSTO bleeding

1) Severe : Intracranial hemorrhage,
   
   Bleeding that causes hemodynamic compromise and requires intervention

2) Moderate : Bleeding that requires blood transfusion but does not lead to
   
   hemodynamic instability.

3) Mild : Bleeding that does not meet criteria for severe or moderate bleeding.
Acute coronary syndrome (ACS)

Exclusion criteria
Age > 75 years, 
Body weight < 60 kg, 
Gp IIb-IIIa Rc blocker use within 2 weeks, 
Life expectancy < 12 months

PRACS study

Inclusion criteria
Age > 20 years, 
Written informed consent, 
Patients who were done PCI because of ACS

ASA 300mg + Clopidogrel 600mg loading + PCI (day 0)

ASA 100mg + Clopidogrel 75mg daily (day 1-3)

Genotyping 2c19 *2*3*17 (day 2-3), VerifyNow® (P2Y12) (day 2-3)

G1 LOF (*2*2, *3*3, *2*3) & HTPR (PRU > 230)

Intermediate

G2 group (ASA 100mg + Prasugrel 10mg)

G3 group (ASA 100mg + Clopidogrel 75mg)

G4 Normal or GOF (*1*1, *1*17, *17*17) & PRU < 230

Randomization

Secondary endpoints: Death, MI, TLR, ISR, GUSTO bleeding

1 month VerifyNow® (P2Y12), **Primary endpoint**: 1 month HTPR
Results
## Baseline Characteristics (n=46)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 Prasugrel (N=8)</th>
<th>Group 2 random Prasugrel (N=13)</th>
<th>Group 3 random Clopidogrel (N=15)</th>
<th>Group 4 Clopidogrel (N=10)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD)</td>
<td>57.0 ± 8.9</td>
<td>54.9 ± 12.0</td>
<td>61.0 ± 11.6</td>
<td>58.1± 8.9</td>
<td>0.522</td>
</tr>
<tr>
<td>Male sex (number)</td>
<td>7 (87.5%)</td>
<td>13 (100%)</td>
<td>14 (93.3%)</td>
<td>10 (100%)</td>
<td>0.472</td>
</tr>
<tr>
<td>Diagnosis (number)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.637</td>
</tr>
<tr>
<td>STEMI</td>
<td>3 (37.5%)</td>
<td>5 (38.5%)</td>
<td>5 (33.3%)</td>
<td>1 (10%)</td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>3 (37.5%)</td>
<td>5 (38.5%)</td>
<td>4 (26.7%)</td>
<td>6 (60%)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>2 (25%)</td>
<td>3 (23.1%)</td>
<td>6 (40.0%)</td>
<td>3 (30%)</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus (number)</td>
<td>2 (25%)</td>
<td>5 (38.5%)</td>
<td>2 (13.3%)</td>
<td>2 (20%)</td>
<td>0.471</td>
</tr>
<tr>
<td>Hypertension (number)</td>
<td>3 (37.5%)</td>
<td>5 (38.5%)</td>
<td>7 (46.7%)</td>
<td>6 (60%)</td>
<td>0.724</td>
</tr>
<tr>
<td>Current smoking (number)</td>
<td>7 (87.5%)</td>
<td>8 (61.5%)</td>
<td>5 (33.3%)</td>
<td>7 (70%)</td>
<td>0.063</td>
</tr>
<tr>
<td>Family History (number)</td>
<td>0</td>
<td>0</td>
<td>1 (6.7%)</td>
<td>0</td>
<td>0.549</td>
</tr>
<tr>
<td>Previous MI (number)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Previous CVA (number)</td>
<td>0</td>
<td>0</td>
<td>1 (6.7%)</td>
<td>0</td>
<td>0.549</td>
</tr>
<tr>
<td>Previous PCI (number)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (20%)</td>
<td>0.057</td>
</tr>
<tr>
<td>Previous CABG (number)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chronic renal failure (number)</td>
<td>1 (12.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.183</td>
</tr>
</tbody>
</table>
2C19 Polymorphism (N=46)

% (number)

- *1*1: 35% (16)
- *1*2: 26% (12)
- *1*3: 17% (8)
- *2*2: 9% (4)
- *2*3: 13% (6)
Allele frequency (N=46)

% (number/total)

- *1: 57% (52/92)
- *2: 28% (26/92)
- *3: 15% (14/92)
Changes of platelet inhibition

**Prasugrel group (N=21)**

- PRU Mean ± SD: 271±44
- **P<0.001**

**Clopidogrel group (N=25)**

- PRU Mean ± SD: 196±78, 163±75
- **P=0.019**

*P value by Wilcoxon’s signed-ranks test*
Prasugrel Versus Clopidogrel

* P value by independent t-test
** P value by Wilcoxon’s signed-ranks test
Changes of platelet activity (PRU)

PRU

<table>
<thead>
<tr>
<th>Group</th>
<th>PRU Value</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group1 (N=8)</td>
<td>274</td>
<td>P=0.012*</td>
</tr>
<tr>
<td>Group2 (N=13)</td>
<td>269</td>
<td>P=0.001*</td>
</tr>
<tr>
<td>Group3 (N=15)</td>
<td>237</td>
<td>P=0.008*</td>
</tr>
<tr>
<td>Group4 (N=10)</td>
<td>199</td>
<td>P=0.285</td>
</tr>
</tbody>
</table>

*P value by Wilcoxon’s signed-ranks test
Primary endpoint: 1 month HTPR

Whole population (N=46)

<table>
<thead>
<tr>
<th>Patients number</th>
<th>Normal (PRU&lt;230)</th>
<th>HTPR (PRU&gt;230)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel Baseline</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Prasugrel f/u (N=21)</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Clopidogrel Baseline</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Clopidogrel f/u (N=25)</td>
<td>20</td>
<td>5</td>
</tr>
</tbody>
</table>

P=0.03*  
* P value by Chi-square test
## Clinical outcomes (n=46)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group 1 Prasugrel (N=8)</th>
<th>Group 2 random Prasugrel (N=13)</th>
<th>Group 3 random Clopidogrel (N=15)</th>
<th>Group 4 Clopidogrel (N=10)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (number)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MI (number)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>TLR (number)</td>
<td>1 (12.5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.183</td>
</tr>
<tr>
<td><strong>ISR, binary</strong> (number)</td>
<td>2 (25%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td><strong>0.039</strong>*</td>
</tr>
<tr>
<td>CV admission (number)</td>
<td>1 (12.5%)</td>
<td>1 (7.7%)</td>
<td>0</td>
<td>2 (20%)</td>
<td>0.362</td>
</tr>
<tr>
<td>GUSTO Bleeding, moderate ~ severe</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (20%)</td>
<td>0.057</td>
</tr>
<tr>
<td>GUSTO Bleeding, mild</td>
<td>2 (25%)</td>
<td>5 (38.5%)</td>
<td>1 (6.7%)</td>
<td>0</td>
<td>0.054</td>
</tr>
<tr>
<td>Cross-over (number)</td>
<td>0</td>
<td>2 (15.4%)</td>
<td>0</td>
<td>0</td>
<td>0.151</td>
</tr>
</tbody>
</table>

* Mean follow up duration was 269 ± 93 (days)
Binary ISR free survival

P = 0.039*
Prasugrel was associated with a significantly lower platelet reactivity than clopidogrel (PRU 271±44 to 88±42 vs 196±78 to 163±75 ; p<0.001).

And, there was no HTPR patient in prasugrel group compared to clopidogrel after 1 month (19/21 to 0/21 vs 8/25 to 5/25; p=0.03).

We achieved similar anti-platelet effects of prasugrel in the HTPR and LOF carriers compared to clopidogrel in the normal group.
Summary II

• There was no death or MI events in whole study population.

• There were two binary restenosis cases in Group 1 (HTPR and homozygous LOF allele carrier) (p=0.019)

• Our tailored anti-platelet strategy did not increase GUSTO moderate to severe bleeding.
Conclusions

• Genotype and platelet function test guided anti-platelet therapy is effective and safe in controlling platelet reactivity in patients with ACS.

• And, prasugrel showed excellent anti-platelet effects in patients with 2C19 LOF allele or HTPR.
Thank you for your attention.
Interpatient Variability to Clopidogrel

24 hours after 300mg clopidogrel
n=96, elective PCI

\( \Delta \) platelet aggregation before and after clopidogrel (%)

"Resistance" = \( \leq 10\% \) \( \Delta \) platelet aggregation

Effient: No impact of reduced function CYP2C19 Alleles

Cumulative incidence curves for the primary efficacy outcome (composite of cardiovascular death, myocardial infarction, or stroke)

Effient: Less Variable Platelet Inhibition

IPA at 24 Hours (Clopidogrel vs. Prasugrel)

Healthy Volunteers, N=68 administered both clopidogrel and prasugrel in a crossover fashion

Data from Brandt JT et al. Am Heart J 2007;153:66.e9-66.e16
Changes of platelet inhibition

Random clopidogrel group

- Baseline: 263, Δ -22, 240
- Follow up: 244, Δ -41

P of Δ = 0.595

LOF & HPPR (N=2), P = 0.508

LOF or HPPR (N=9)
Changes of platelet inhibition

Random clopidogrel group

- PRU

Baseline: Δ -13, P=0.046
Follow up: Δ -64, P=0.189

Genotyping guided (N=4) P=0.046 PFT guided (N=5)
Changes of platelet inhibition

LOF & HPPR group

Baseline | follow up  | P of Δ=0.023

<table>
<thead>
<tr>
<th>PRU</th>
<th>Baseline</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prasugrel (N=11)</td>
<td>82</td>
<td>284</td>
</tr>
<tr>
<td>Clopidogrel (N=2)</td>
<td>241</td>
<td>263</td>
</tr>
</tbody>
</table>

P=0.102