Pharmacodynamic Effects of Switching therapy in PCI patients with high on Treatment platelet reactivity and genotype variation: high Clopidogrel dose versus Prasugrel (RESET GENE Study). (ClinicalTrials.gov NCT01465828)

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I, GENNARO SARDELLA, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Background

Impact of Platelet Reactivity

High dose vs. standard dose Clopidogrel:
Primary Endpoint: CV death, MI, stent thrombosis

Lower reactivity is associated with better outcomes even in elective cases

MV analyses for CV death, MI and ST at 60 days in Gravitas
N=2796

<table>
<thead>
<tr>
<th>PRU &lt;208</th>
<th>HR [95% CI]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.23 [0.05, 0.98]</td>
<td>0.047</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACS</th>
<th>3.95 [1.83, 8.53]</th>
<th>&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>2.49 [1.10, 5.64]</td>
<td>0.028</td>
</tr>
<tr>
<td>Stent Length (per mm)</td>
<td>1.01 [1.01, 1.02]</td>
<td>0.003</td>
</tr>
<tr>
<td>Prior MI</td>
<td>2.16 [0.94, 4.93]</td>
<td>0.068</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>1.27 [0.42, 3.85]</td>
<td>0.668</td>
</tr>
<tr>
<td>CrCl &lt;60</td>
<td>1.48 [0.69, 3.18]</td>
<td>0.668</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>1.76 [0.74, 4.16]</td>
<td>0.201</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>1.92 [0.87, 4.23]</td>
<td>0.108</td>
</tr>
</tbody>
</table>

Price MJ et al Circulation 2011;124:1132-1137
Background

Impact of Genotype variation

Reduced-Function CYP2C19 Genotype and Risk of Adverse Clinical Outcomes Among Patients Treated With Clopidogrel Predominantly for PCI
A Meta-analysis

<table>
<thead>
<tr>
<th>Carriers of 1 CYP2C19 Reduced-Function Alleles vs Noncarriers</th>
<th>No. of Events/</th>
<th>Hazard Ratio (95% CI)</th>
<th>Increased Risk in Noncarriers</th>
<th>Increased Risk in Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>1.75 (0.96-3.17)</td>
<td>2.50 (1.01-6.21)</td>
<td>3.75 (1.04-13.03)</td>
</tr>
</tbody>
</table>

Holmes M et al JAMA. 2011;306(24):2704-2714

CYP2C19 Genotype, Clopidogrel Metabolism, Platelet Function, and Cardiovascular Events
A Systematic Review and Meta-analysis

<table>
<thead>
<tr>
<th>Cases, No./Total No.</th>
<th>RR (95% CI)</th>
<th>Lower Risk of CVD</th>
<th>Higher Risk of CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;2+</td>
<td>10</td>
<td>2.00 (1.00-4.00)</td>
<td>2.00 (1.00-4.00)</td>
</tr>
</tbody>
</table>


Systematic review

This meta-analysis suggests significant heterogeneity between studies, analyzing the relationship between CYP2C19 loss-of-function alleles and major cardiovascular outcomes. This heterogeneity was partially related to study sample size, smaller studies reported a significant association between the loss-of-function alleles and a higher risk of cardiovascular outcomes, whereas no significant effect was observed in the pooled analysis of studies with a sample size ≥500 patients with coronary artery disease treated with clopidogrel.

Holmes M et al JAMA. 2011;306(24):2704-2714

Mega J et al JAMA. 2010;304(16):1821-1830

Conclusion

Carriage of even 1 reduced-function CYP2C19 allele appears to be associated with a significantly increased risk of major adverse cardiovascular events, particularly thrombosis.
**Primary end-point:**
We sought to investigate the antiplatelet effect in terms of platelet reactivity level (PRL) (Area Under the Curve (AUC)) of standard dose of Prasugrel (10 mg/day) versus high dose of Clopidogrel (150 mg/day) at the end of two (pre-crossover and post-crossover) study periods in stable High on Treatment Platelet Reactivity (HTPR) patients (≥450 AUC/min) and its relationship to genotype variation (CYP2C19*2 polymorphism).

**Secondary end-points:**
MACCE and bleedings in overall population at 3-9-12 months follow-up
Successful PCI for SA with DES without major complication and NO GPIIb/IIIa use

Post-PCI Multiplate P2Y12 Assay (AUC/min)
Immediately (MD >7d of Clopidogrel 75 mg/300mg LD 24h) or at day 1 post-LD of Clopidogrel 600mg

Non-Responders

CYP2C19*2 Carriage Genotyping

Prasugrel arm
Prasugrel MD 10 mg/day

Clopidogrel arm
Clopidogrel150 mg/day

15±2 days Multiplate P2Y12 Assay (AUC)

CROSS-OVER

Prasugrel 10 mg/day

Clopidogrel 150 mg/day

15±2 days Multiplate P2Y12 Assay (AUC)

Responders

“Standard Therapy”
Clopidogrel MD 75 mg/daily

3 months Clinical Follow-up
**Key Inclusion and Exclusion Criteria**

### Inclusion Criteria
- Successful DES-PCI in patients with stable CAD and clinical indication for PCI
- Pts. on Clopidogrel 600-mg LD if naïve or < 7d on 75 mg.
- Pts. on Clopidogrel 75-mg MD if > 7d or on Clopidogrel 300mg 24h pre-PCI

### Exclusion Criteria
- ACS patients
- History of bleeding diathesis
- History of stroke
- Patients weighting <60 kg
- Age >75 years old
- Chronic oral anticoagulation treatment
- Contraindications to antiplatelet therapy
- Hemodynamic instability
- Platelet count <100,000/μl
- Hematocrit <30%
- Creatinine clearance <25 ml/min
Hypothesis

We assumed that, in HTPR patients, Prasugrel 10mg would result in a PRL absolute difference of 150 AUC (35% reduction) compared to Clopidogrel 150mg (with the assumption that the within patient standard deviation of the response variable is 12), based on previously published data\(^1\)-\(^2\)

Sample size

- On the basis of a two-sided test size of 5% and a power of 95%, it was calculated that a minimum of 16 patients would need to be recruited in each group (32 pts. total).
- 40 pts. (resulted by an increase of 25% to adjust for potential inclusion criteria unmet) would need to be assessed as non-responders


PCI stable patients recruited (Sept-Nov.2011) N= 180

PR Multiplate assessment for AUC value

RESPONDERS
119 pts. (77%) with AUC ≤450

NON-RESPONDERS
42 (23%) patients with AUC >450

16 pts Prasugrel (10 mg)

0 side effects
0 low compliance

16 pts Prasugrel (10 mg)

15±2 days Multiplate P2Y12 Assay (AUC)

CYP2C19*2 Carriage Genotyping

16 pts Clopidogrel (150 mg)

0 side effects
0 low compliance

16 pts Clopidogrel (150 mg)

15±2 days Multiplate P2Y12 Assay (AUC)

CROSS-OVER

3 months Clinical Follow-up (100%)

10 patients excluded:
- 7 Age > 75 years old
- 2 weight < 60 Kg
- Chronic renal failure
- 1 History of STROKE
- History of major Bleeding

119 pts. (77%) with AUC ≤450

119 pts (77%) with AUC ≤450
## RESULTS

### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Allocated to Prasugrel→Clopidogrel n=16</th>
<th>Allocated to Clopidogrel→Prasugrel n=16</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male,%</td>
<td>87,5 (14/16 pts)</td>
<td>83,3 (13/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>Age (yrs) ± SD</td>
<td>61,8±10,4</td>
<td>62,2±8,6</td>
<td>ns</td>
</tr>
<tr>
<td>BMI (Kg/m²) ± SD</td>
<td>27,8 ± 3,6</td>
<td>28,3 ± 2,7</td>
<td>ns</td>
</tr>
<tr>
<td>Creatinine mg/dL ± SD</td>
<td>0,98±0,61</td>
<td>0,86±0,3</td>
<td>ns</td>
</tr>
<tr>
<td>Hyperlipidemia,%</td>
<td>62,5 (10/16 pts)</td>
<td>50 (8/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>Hypertension,%</td>
<td>75 (12/16 pts)</td>
<td>68,7 (11/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>Diabetes mellitus,%</td>
<td>25 (4/16 pts)</td>
<td>31,2 (5/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>Smoking,%</td>
<td>50 (8/16 pts)</td>
<td>50 (8/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>Prior MI,%</td>
<td>37,5 (6/16 pts)</td>
<td>18,7 (3/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>Prior PCI,%</td>
<td>37,5 (6/16 pts)</td>
<td>18,7 (3/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>Prior CABG,%</td>
<td>6,25 (1/16 pts)</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Medical Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Statin,%</td>
<td>75 (12/16 pts)</td>
<td>87,5 (14/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>- PPIs,%</td>
<td>56,2 (9/16 pts)</td>
<td>62,5 (10/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>- B-blocker,%</td>
<td>62,5 (10/16 pts)</td>
<td>62,5 (10/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>- Nitrates,%</td>
<td>25 (4/16 pts)</td>
<td>37,5 (6/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>- Ace-Inhibitors,%</td>
<td>37,5 (6/16 pts)</td>
<td>25 (4/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>- Aspirin 325 mg,%</td>
<td>100 (16/16 pts)</td>
<td>100 (16/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>CYP2C19*2 Heterozygous % (37%)</td>
<td>50 (8/16 pts)</td>
<td>25 (4/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>CYP2C19*2 Homozigous %  (6%)</td>
<td>0</td>
<td>12,5 (2/16 pts)</td>
<td></td>
</tr>
<tr>
<td>Chronic clopidogrel use, &gt;7days</td>
<td>50 (8/16 pts)</td>
<td>37,5 (6/16 pts)</td>
<td>ns</td>
</tr>
<tr>
<td>PR day O (AUC) ± SD</td>
<td>576 ± 97.20</td>
<td>573,33 ± 87.10</td>
<td>ns</td>
</tr>
</tbody>
</table>
# RESULTS

## PRIMARY END-POINT

<table>
<thead>
<tr>
<th></th>
<th>PRASUGREL</th>
<th>CLOPIDOGREL HD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC mean, +SD</td>
<td>576 ± 97.20</td>
<td>573.33 ± 87.10</td>
<td>0.957</td>
</tr>
<tr>
<td><strong>15 days therapy/each AUC mean, +SD</strong></td>
<td>325.82 ± 104.70</td>
<td>478.52 ± 208.54</td>
<td>0.028</td>
</tr>
<tr>
<td><strong>Difference in AUC from baseline to day 15</strong></td>
<td>251.18±102.10</td>
<td>94.48±150.62</td>
<td>0.0017</td>
</tr>
<tr>
<td><em><em>IPA</em> mean%, +SD</em>*</td>
<td>49.69 ± 42.88</td>
<td>9.31 ± 5.19</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*Inhibition Platelet Aggregation: (baseline aggregation response - post-dose aggregation response) 
(IPA) = baseline aggregation response × 100
RESULTS

Individual response according to treatment

AUC by treatment sequence
Data for pre- and post-crossover

AUC by treatment sequence

Individual response according to treatment

Base Line  Prasugrel  Clopidogrel

AUC

0 d  15 d  30 d

Prasugrel
Clopidogrel

Data for pre- and post-crossover

$AUC_p = 0.038$

$P = 0.038$
RESULTS

Mean individual response according to treatment

Poor responders rate
RESULTS

**AUC by treatment sequence**
Data for pre- and post-crossover

**CARRIERS** (n=14) of CYP2C19*2Allele

**NON CARRIERS** (n=18) of CYP2C19*2Allele

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![Graph showing AUC by treatment sequence for CARRIERS and NON CARRIERS of CYP2C19*2Allele.](attachment:image.png)

- **CARRIERS** (n=14)
  - Clopidogrel
  - Prasugrel

- **NON CARRIERS** (n=18)
  - Clopidogrel
  - Prasugrel

**p=0.045** (for CARRIERS)

**p=0.575** (for NON CARRIERS)
RESULTS

HTPR rate (AUC>450)

- Clopidogrel and Prasugrel treatment analyzed for Genotype variation
- Non carriers and carriers, separately for each treatment arm

![Bar graph showing HTPR rate for carriers and non-carriers with p-values](image)

- Carriers: 43.7% HTPR (p=0.003)
- Non-carriers: 12.5% HTPR (p=0.274)

![Bar graph showing HTPR rate for Clopidogrel and Prasugrel](image)

- Clopidogrel: 43.7% HTPR
- Prasugrel: 12.5% HTPR (p=0.248)
### 3 months Clinical Follow-up

#### MACCE and MINOR Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Allocated to Prasugrel→Clopidogrel n=16</th>
<th>Allocated to Clopidogrel→Prasugrel n=16</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial Infarction</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>STROKE</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Major Bleeding (BARC Classification)</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Number of patients with at least one event</td>
<td>7</td>
<td>3</td>
<td>ns</td>
</tr>
<tr>
<td>Number of events</td>
<td>7</td>
<td>3</td>
<td>ns</td>
</tr>
<tr>
<td>Haematocrit or Haemoglobin Decreased*</td>
<td>1</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>4</td>
<td>2</td>
<td>ns</td>
</tr>
<tr>
<td>Vessel puncture site haemorrhage</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>1</td>
<td>1</td>
<td>ns</td>
</tr>
<tr>
<td>Oral bleeding</td>
<td>2</td>
<td>0</td>
<td>ns</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Investigator defined.
RESULTS

3 months Clinical follow-up

Individual response according to time of onset

At Cross-over time

- All Causes of death
- Cardiac Death
- Non-fatal MI
- ST
- TVR
- STROKE
- Chest Pain *
- Major Bleeding
- Minor Bleeding

* No ECG changes
RESULTS

ROC Curve

AUC > 600

SENSIBILITY 75%
SPECIFICITY 72%

Cut-off for Genetic variation of CYP2C19*2 Allele
Conclusions

- Up to one third of the population studied on MD or LD clopidogrel treatment may exhibit High on clopidogrel Platelet Reactivity (HTPR).

- Compared with high-dose Clopidogrel 150 mg MD, Prasugrel 10 mg significantly decreased platelet reactivity in patients with HTPR.

- No patients remaining non-responsive after Prasugrel.

- Up to half of the population studied showed a genotype variation in terms of presence of the allelic variant of CYP2C19*2.

- High Clopidogrel dose, in contrast to Prasugrel, is frequently ineffective in the presence of the CYP2C19*2 allele, while in non-carriers CYP2C19*2 allele both drugs have similar effects.

- This study achieved with an optimal sensitivity and specificity an AUC cut-off for Genetic variation of CYP2C19*2 Allele.
Major study limitations

- The **small population** analyzed in spite of the study was powered for the sample size calculated.

- The overall population PR analyzed at baseline, **but not at 1 month**, could mislead his over time variation assessment*.

- The lack of the **drug wash-out** between treatments, due to the coronary stent implantation could affect the platelet response in the second phase of administration after cross-over.

- The **gain-of-function CYP2C19**\(^{**17}\) allele was not tested*.

- The present study was not powered to detect **clinical safety** differences between the 2 treatment groups.

* Campo G. et al JACC 2011;57:2474-2483
** Zabalza M. et al Heart 2012;98:100-108
Thank You !
Methods

Platelet Reactivity Assessment

- Maximum Platelet Aggregation
  - $\leq 450$ AUC
  - $> 450$ AUC

Genotype Assessment for CYP2C19*2 Genotyping variability

- COLLECTED BLOOD in K3 EDTA tube 4 ml

CYP2C19*2 (OMIM # 124020) allelic variant (rs1799990) was determined by a 200-bp PCR amplification on the basis of the PRNP Ensembl (Ensembl accession number ENST00000371321).