P2Y12 Inhibitor Switching in Response to Routine Notification of CYP2C19 Clopidogrel Metabolizer Status Following Acute Coronary Syndromes

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Background

• Patients with reduced function alleles of CYP2C19 have higher platelet reactivity and appear to have an increased risk of ischemic events when treated with clopidogrel, particularly following PCI procedures

• Boxed warning added to label for clopidogrel in 2010 recommended pharmacogenomic testing for clopidogrel-treated patients with suggestion of switching to alternative anti-platelet therapies for the reduced/poor metabolizer (RM) phenotype

• The GEMINI-ACS trial randomized post-ACS patients to rivaroxaban vs. aspirin on top of either clopidogrel or ticagrelor chosen by treating physician

• For this trial regulatory guidance in the US required routine pharmacogenomic testing for patients enrolled and treated with clopidogrel due to concerns for inadequate platelet inhibition among patients randomized to rivaroxaban
Goals and Objectives of GEMINI-ACS Switching Substudy

- Characterize timing, patterns, and factors associated with P2Y12 inhibitor (clopidogrel or ticagrelor) switching during trial follow-up through 12 months
- Evaluate impact of mandatory testing and feedback of CYP2C19 metabolizer status on changes in initial P2Y12 inhibitor use, particularly clopidogrel, for patients included in the GEMINI-ACS trial
- Characterize ischemic and bleeding outcomes by CYP2C19 metabolizer status
GEMINI-ACS Trial Design

3037 patients (Ticagrelor = 1704, Clopidogrel = 1333 - physician choice)
P2Y12 inhibitor therapy provided, Adherence 95% during trial follow-up
Ticagrelor used in 85% in WE, 68% in NA, and ≤ 50% in other regions

ASA + Clopidogrel/Ticagrelor

Rivaroxaban 2.5 mg bid +
Clopidogrel 75 mg or Ticagrelor 90 mg bid

Aspirin 100 mg daily +
Clopidogrel 75 mg or Ticagrelor 90 mg bid

Median follow-up: 326 days (284–383)

Lancet 2017;389:1799-1808
Methods

• Mandatory testing and reporting of CYP2C19 metabolizer status to investigators ~ one week after randomization in 3,016 of 3,037 (99%) patients
  – Per CPIC guidelines, 34.4% were determined to be ultra-metabolizers (UM), 37.8% extensive metabolizers (EM), 24.5% intermediate metabolizers (IM), and 3.2% reduced/poor metabolizers (RM)
  – No recommendations were given regarding initial P2Y12 inhibitor therapy choices

• Investigator-reported reasons for switching initial P2Y12 inhibitor recorded
• Baseline characteristics associated with P2Y12 inhibitor switching assessed with multivariable modeling
• Clinical outcomes collected and adjudicated through 12 months
Pre-Randomization* Intent to Switch P2Y12 Inhibitor Based on CYP2C19 Metabolizer Status

- Clopidogrel to Ticagrelor (based on reduced metabolizer status)
  - 52% will not switch
  - 46% will switch

- Ticagrelor to Clopidogrel (based on ultra-metabolizer status)
  - 94% will not switch
  - 6% will switch

*Assessed at the time of randomization (rivaroxaban vs. aspirin) in each patient
Any P2Y12 Switching by Initial P2Y12 Inhibitor Choice

![Graph showing event rates](image)

- Clopidogrel
- Ticagrelor

Event Rates (%)

- Time to P2Y12 switch (months)

- p<0.001
# Reasons for and Timing of P2Y12 Inhibitor Switching

<table>
<thead>
<tr>
<th></th>
<th>N=3037</th>
<th>Time to Switch (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients who switched P2Y12</td>
<td>197/3037 (6.5%)</td>
<td>40 (24,118)</td>
</tr>
<tr>
<td>Ticagrelor to Clopidogrel</td>
<td>144/1704 (8.5%)*</td>
<td>62.5 (29,151.5)</td>
</tr>
<tr>
<td>Reasons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19 Metabolizer Status</td>
<td>1 (0.6%)</td>
<td>29</td>
</tr>
<tr>
<td>Non-Bleeding Adverse Event</td>
<td>81 (56.4%)</td>
<td>42 (28.94)</td>
</tr>
<tr>
<td>Other (including bleeding)</td>
<td>61 (42.4%)</td>
<td>102 (31,197)</td>
</tr>
<tr>
<td>Recurrent Ischemic Event</td>
<td>1 (0.6%)</td>
<td>133</td>
</tr>
<tr>
<td>Clopidogrel to Ticagrelor</td>
<td>53/1333 (4.0%)*</td>
<td>30 (10,40)</td>
</tr>
<tr>
<td>Reasons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19 Metabolizer Status</td>
<td>23 (43.4%)</td>
<td>29 (14,33)</td>
</tr>
<tr>
<td>Non-Bleeding Adverse Event</td>
<td>3 (5.7%)</td>
<td>91 (30,92)</td>
</tr>
<tr>
<td>Other (including bleeding)</td>
<td>17 (32.1%)</td>
<td>27 (2,34)</td>
</tr>
<tr>
<td>Recurrent Ischemic Event</td>
<td>10 (18.8%)</td>
<td>64 (3,77)</td>
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</table>

* Chi-square: 23.9, p<0.001
P2Y12 Switching by CYP2C19 Metabolizer Status: Clopidogrel to Ticagrelor

1333 clopidogrel-treated patients at randomization

465 patients
UM Phenotype

8 patients switched
(1.7%)

468 patients
EM Phenotype

11 patients switched
(2.4%)

343 patients
IM Phenotype

16 patients switched
(4.7%)

48 patients
RM Phenotype

16 patients switched
(33%)

p<0.001
P2Y12 Switching by CYP2C19 Metabolizer Status: Ticagrelor to Clopidogrel

1704 ticagrelor-treated patients at randomization

- 574 patients (UM Phenotype)
  - 49 patients switched (8.5%)

- 672 patients (EM Phenotype)
  - 50 patients switched (7.4%)

- 396 patients (IM Phenotype)
  - 42 patients switched (10.6%)

- 50 patients (RM Phenotype)
  - 5 patients switched (10%)

p=0.35
### Independent Factors Associated with P2Y12 Switching

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GRACE Risk Score, per 10 units</strong></td>
<td>1.13</td>
<td>(1.05-1.21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Overall effect of CYP2C19 metabolizer status</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Extensive vs Ultra</td>
<td>0.91</td>
<td>(0.62-1.35)</td>
<td></td>
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<tr>
<td>Intermediate vs Ultra</td>
<td>1.50</td>
<td>(1.02-2.22)</td>
<td></td>
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<tr>
<td>Reduced/Poor vs Ultra</td>
<td>5.28</td>
<td>(3.09-9.00)</td>
<td></td>
</tr>
<tr>
<td><strong>Initial P2Y12 inhibitor : interaction with time</strong></td>
<td></td>
<td></td>
<td>0.005</td>
</tr>
<tr>
<td>Ticagrelor vs Clopidogrel: 1 month</td>
<td>1.48</td>
<td>(1.12-1.96)</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor vs Clopidogrel: 6 months</td>
<td>1.83</td>
<td>(1.19-2.80)</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor vs Clopidogrel: 9 months</td>
<td>1.92</td>
<td>(1.21-3.03)</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor vs Clopidogrel: 12 months</td>
<td>1.98</td>
<td>(1.22-3.21)</td>
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<tr>
<td><strong>Overall effect of region</strong></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Asia/Pacific vs Western Europe</td>
<td>0.53</td>
<td>(0.23-1.20)</td>
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<tr>
<td>Central Europe vs Western Europe</td>
<td>0.52</td>
<td>(0.34-0.80)</td>
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<tr>
<td>Eastern Europe vs Western Europe</td>
<td>0.51</td>
<td>(0.32-0.81)</td>
<td></td>
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<tr>
<td>North America vs Western Europe</td>
<td>1.42</td>
<td>(0.90-2.25)</td>
<td></td>
</tr>
<tr>
<td>South America vs Western Europe</td>
<td>1.01</td>
<td>(0.58-1.77)</td>
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Ischemic and Bleeding Outcomes Through 12 Months by CYP2C19 Metabolizer Phenotype

Only 4 events occurred in the reduced/poor phenotype group:
2 CV deaths, 1 MI, 1 definite stent thrombosis
Limitations

• The GEMINI-ACS trial was not designed or powered to specifically assess P2Y12 inhibitor switching among patients who were reduced/poor CYP2C19 metabolizer so results are hypothesis generating
  – Only 3.2% of patients enrolled were reduced metabolizers
• Did not collect data on use of platelet function testing and its potential influence on P2Y12 inhibitor switching
• Low number of ischemic events in reduced/poor metabolizer group precluded analysis of the treatment effect of initial and switched P2Y12 inhibitor use, as well as rivaroxaban vs. aspirin
Conclusions

• In the context of this ACS trial, where P2Y12 therapy was provided and results of CYP2C19 metabolizer status were shared after randomization:
  – Only among half of the patients did investigators intend to switch to ticagrelor from clopidogrel based on metabolizer status
  – P2Y12 inhibitor switching was more frequent with ticagrelor vs. clopidogrel
  – Multiple factors, including reduced/poor metabolizer status, associated with switching
  – Only one-third of reduced/poor metabolizer patients treated with clopidogrel were switched to ticagrelor

• Findings do not support the utility of mandatory testing of CYP2C19 metabolizer status in this context, as majority of investigators did not act on the information

• Future studies should determine the clinical importance of tailored P2Y12 inhibitor therapy based upon prospective genotyping results