Outcomes with CYP2C19 Genotyping for Clopidogrel Response: An Update from the IGNITE Network

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Clopidogrel Pharmacokinetics

Sangkuh K et al. "Clopidogrel pathway" Pharmacogenet Genomics (2010). Copyright to PharmGKB.
**CYP2C19**

**Gene alleles**

<table>
<thead>
<tr>
<th>Allele</th>
<th>SNP</th>
<th>CYP2C19 Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1</td>
<td>N/A</td>
<td>Normal function</td>
</tr>
<tr>
<td>*2</td>
<td>681G&gt;A</td>
<td>No function/loss of function</td>
</tr>
<tr>
<td>*3</td>
<td>636G&gt;A</td>
<td>No function/loss of function</td>
</tr>
<tr>
<td>*17</td>
<td>-808C&gt;T</td>
<td>Increased function</td>
</tr>
</tbody>
</table>

**Phenotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>*1/*1</td>
<td>Normal Metabolizer (NM)</td>
</tr>
<tr>
<td>*1/*2, *1/*3</td>
<td>Intermediate Metabolizer (IM)</td>
</tr>
<tr>
<td>*2/*2, *2/*3</td>
<td>Poor Metabolizer (PM)</td>
</tr>
<tr>
<td>*1/*17</td>
<td>Rapid Metabolizer (RM)</td>
</tr>
<tr>
<td>*17/*17</td>
<td>Ultra-rapid Metabolizer (UM)</td>
</tr>
</tbody>
</table>
### Outcomes Based on RCT and Registry Post-Hoc Analyses

Meta-analysis of 9 trials and 9685 clopidogrel-treated high risk patients

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LOF vs no LOF</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE*</td>
<td>HR 1.57 (1.13-2.16)</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>HR 2.81 (1.81-4.37)</td>
</tr>
</tbody>
</table>

*Major adverse cardiovascular events (CV death, MI, or stroke)

LOF = Loss of function

Outcomes Based on Post-Hoc Analyses or TRITON-TIMI 38 and PLATO Trials

Occurrence of MACE

<table>
<thead>
<tr>
<th>CYP2C19 Genotype</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOF</td>
<td>8.5%</td>
<td>8.6%</td>
</tr>
<tr>
<td>No LOF</td>
<td>9.6%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

LOF = Loss of function

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)
CPIC Guidelines for Clopidogrel

ACS/PCI Patients

CYP2C19 Genotyping

RM (*1/*17)
UM (*17/*17)

NM (*1/*1)

IM (e.g. *1/*2)

PM (e.g. *2/*2)

Clopidogrel at a standard dose

Alternative antiplatelet (Prasugrel or Ticagrelor)
CYP2C19-Clopidogrel Implementation at UF Health

- Implemented in June 2012 as part of routine clinical practice
  - Test added to standard order set
  - Run in UF Health Pathology Labs
  - *CYP2C19* genotype placed in the electronic medical record

- Recommendations for alternative therapy provided for no-function/LOF allele carriers.

- Built clinical decision support.
**TAILOR-PCI**

ClinicalTrials.gov Identifier: NCT01742117

<table>
<thead>
<tr>
<th>Est. enrollment</th>
<th>5,270</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion criteria</td>
<td>PCI</td>
</tr>
<tr>
<td>Arms</td>
<td>Genotype-guided strategy (Ticagrelor for <em>CYP2C19</em>2 or *3 allele) versus clopidogrel</td>
</tr>
<tr>
<td>Outcomes</td>
<td>MACE at 1 year</td>
</tr>
<tr>
<td>Est. completion</td>
<td>3/2020</td>
</tr>
</tbody>
</table>

- **TAILOR-PCI**: Tailored Antiplatelet Initiation to Lesson Outcomes Due to Decreased Clopidogrel Response After Percutaneous Coronary Intervention
CYP2C19-Clopidogrel Outcomes at UF Health

• Reviewed medical records for patients who underwent PCI and genotyping in first 2 years of program
• Collected data on Major Adverse Cardiovascular Events (MACE) through 6 months after PCI
  - Composite of cardiovascular death, myocardial infarction, stroke, or stent thrombosis
  - Compared between patients with a LOF allele treated with alternative antiplatelet, e.g. ticagrelor, prasugrel vs. clopidogrel

CYP2C19-Clopidogrel Outcomes at UF Health

- n=408 total patients
- n=126 (31%) with LOF allele
- n=68 (54%) with LOF allele on alternative therapy

CYP2C19-Clopidogrel Outcomes at UF Health

**Survival Rate (%)**

- LOF alternative
- non-LOF
- LOF clopidogrel

**Number at risk**

<table>
<thead>
<tr>
<th>LOF alternative</th>
<th>68</th>
<th>59</th>
<th>54</th>
<th>51</th>
<th>47</th>
<th>45</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-LOF</td>
<td>282</td>
<td>213</td>
<td>191</td>
<td>181</td>
<td>167</td>
<td>153</td>
<td>144</td>
</tr>
<tr>
<td>LOF clopidogrel</td>
<td>58</td>
<td>37</td>
<td>32</td>
<td>29</td>
<td>26</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>408</td>
<td>309</td>
<td>277</td>
<td>261</td>
<td>240</td>
<td>222</td>
<td>206</td>
</tr>
</tbody>
</table>

LOF alternative vs LOF clopidogrel: p=0.012
LOF alternative vs Non-LOF: p=0.345

IGNITE Pharmacogenetics Working Group

• Part of the NIH-funded Implementing GeNomics In pracTicE (IGNITE) network

• Purpose
  – Engage institutions implementing pharmacogenetic testing into practice to collectively disseminate data on healthcare-related outcomes, utilization, and cost with genotype-guided drug therapy
Prospective Clinical Implementation of CYP2C19 Genotype Guided Antiplatelet Therapy After PCI: a Multi Site Investigation of MACE Outcomes in a Real-World Setting

NIH IGNITE Pharmacogenetics Working Group

Sanford Health
Sioux Falls, SD
Fargo, ND

University of Illinois
Chicago, IL

Indiana University
Indianapolis, IN

University of Pittsburgh
Pittsburgh, PA

University of Maryland
Baltimore, MD

Vanderbilt University
Nashville, TN

University of North Carolina
Chapel Hill, NC

University of Florida
Gainesville, FL

University of Alabama
Birmingham, AL
Specific Aims

In patients undergoing CYP2C19-guided antiplatelet therapy post-PCI, compare risk for major adverse cardiovascular events (MACE)

Aim 1

LOF-ALTERNATIVE (LOF on alternative therapy)* vs LOF-CLOPIDOGREL (LOF on clopidogrel 75 mg/day)

Aim 2

LOF-ALTERNATIVE vs non-LOF (no LOF allele)

*Prasugrel, ticagrelor, high dose clopidogrel
LOF = Loss of function
Study Design

Prospective multi-center investigation of clinical CYP2C19 genotype-guided antiplatelet therapy post-PCI

- Alternative antiplatelet therapy recommended in CYP2C19 LOF
- No genotype-guided recommendations in NON-LOF
- 7 sites contributed data on patients who underwent PCI and genotyping for primary analysis
Data Collection

Data manually abstracted from the electronic medical record using a common data collection tool

Review of patient encounters

- Death or hospitalizations for cardiovascular events

Data curated at University of Florida
Primary Endpoint

Major Adverse Cardiac Events (MACE)

- Death, myocardial infarction, or stroke within 12 months following index PCI

Antiplatelet therapy (CLOP or ALT) assessed at time of event or last encounter

Patients without MACE were censored at the time of last encounter
Statistical Analysis

Kaplan-Meier analysis to compare time to MACE
- LOF-ALTERNATIVE vs LOF-CLOPIDOGREL
- LOF-ALTERNATIVE vs NON-LOF

Logistic regression to build exposure propensity score

Cox proportional hazard model with propensity score adjustment
P2Y12 Inhibitor Therapy

Total Cohort
n=1815

LOF
n=572 (31.5%)

Clopidogrel
n=226 (39.5%)

Alternative
n=346 (60.5%)*

non-LOF
n=1243 (68.5%)

Clopidogrel n=1050 (84.5%)
Alternative n=193 (15.5%)†

*p<0.0001 for ALTERNATIVE between LOF and NON-LOF groups
†Prasugrel comprised >60% of ALTERNATIVE therapy
### Patient Characteristics (n=1,815)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LOF-ALT (n=346)</th>
<th>LOF-CLOP (n=226)</th>
<th>Non-LOF (n=1243)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean±SD</td>
<td>61±11</td>
<td>64±12*</td>
<td>63±12*</td>
</tr>
<tr>
<td>Male (%)</td>
<td>71</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>White (%)</td>
<td>77</td>
<td>76</td>
<td>79*</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>32</td>
<td>41*</td>
<td>39*</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>25</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Stroke or TIA (%)</td>
<td>7</td>
<td>16*</td>
<td>10</td>
</tr>
<tr>
<td>PCI indication (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>22</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Non-STEMI</td>
<td>28</td>
<td>32</td>
<td>28</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>19</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Stable disease</td>
<td>29</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Other/unknown</td>
<td>2</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
## Implementation Metrics in LOF

<table>
<thead>
<tr>
<th></th>
<th>n=572</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to genotype results, median (IQR)</td>
<td>1 (1-3) day</td>
</tr>
<tr>
<td>Time to alternative therapy, median (IQR)*</td>
<td>1 (1-6) day</td>
</tr>
</tbody>
</table>

*Data available for all but 4 patients*
Kaplan-Meier Survival Curve

Log-rank p=0.016

LOF = Loss of function

Circulation 2016;134:e711-712
Kaplan-Meier Survival Curve

Adjusted Hazard Ratio
LOF-CLOP vs LOF ALT: 2.21 (1.13-4.33)  p=0.021
LOF-ALT vs non-LOF: 0.81 (0.48-1.35)  p=0.41

Log-rank p=0.016
Log-rank p=0.15

Circulation 2016;134:e711-712
Summary

In data collected in a real-world setting with *CYP2C19* genotyping as part of clinical care, higher risk for MACE in *CYP2C19* LOF who were prescribed clopidogrel versus alternative antiplatelet therapy

Validation of findings at 2 additional sites is underway
Conclusion

Genotype-guided approach to antiplatelet therapy in the real world is feasible

In patients with CYP2C19 LOF, CV outcomes can be improved when clinical genotype made available and alternative therapy prescribed early after PCI
Next Steps

Economic analysis based on outcomes data.

Manuscript describing implementation strategies across sites.
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