AHA’s
Scientific Sessions

Tuesday, November 15, 2016
Prospective Clinical Implementation of CYP2C19 Genotype Guided Antiplatelet Therapy After PCI: a Multi Site Investigation of MACE Outcomes in a Real-World Setting

Larisa H. Cavallari, PharmD
on behalf of the IGNITE Pharmacogenetics Working Group Investigators
Background

Clopidogrel is a prodrug that requires bioactivation by CYP2C19

CYP2C19 loss-of-function (LOF) alleles

- Lead to reduced or absent enzyme activity
- Impair ability to activate clopidogrel
- Reduce effectiveness of clopidogrel after PCI
**Background**

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 non-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>

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

LOF=Loss of function

## Background

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

### MACE Outcome

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
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</thead>
<tbody>
<tr>
<td>LOF</td>
<td>8.5%</td>
<td>8.6%</td>
</tr>
<tr>
<td>Non-LOF</td>
<td>9.6%</td>
<td>8.8%</td>
</tr>
</tbody>
</table>

LOF=Loss of function

Specific Aims

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

Primary analysis

LOF-Alternative (CYP2C19 LOF on prasugrel, ticagrelor, high dose clopidogrel) vs LOF-Clopidogrel (CYP2C19 LOF on clopidogrel 75 mg/day)

Secondary analysis

LOF-Alternative vs non-LOF (no CYP2C19 LOF allele)

LOF = Loss of function
NIH Implementing GeNomics In practice (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
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

LOF = Loss of function
Data Collection

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

Review of patient encounters

- Medication use
- Death or hospitalizations for cardiovascular events though 12 months post PCI

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 (Clopidogrel or Alternative) 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 MACE
  • LOF-Alternative vs LOF-Clopidogrel
  • LOF-Alternative vs non-LOF

Logistic regression to summarize group differences into a propensity score

Cox regression with propensity score adjustment

LOF = Loss of function
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 therapy between LOF and NON-LOF groups
†Prasugrel comprised >60% of Alternative therapy
LOF = Loss of function
## Patient Characteristics (n=1,815)

<table>
<thead>
<tr>
<th></th>
<th>LOF-Alternative (n=346)</th>
<th>LOF-Clopidogrel (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, no. (%)</td>
<td>245 (71)</td>
<td>150 (66)</td>
<td>829 (67)</td>
</tr>
<tr>
<td>White, no. (%)</td>
<td>267 (77)</td>
<td>172 (76)</td>
<td>977 (79)*</td>
</tr>
<tr>
<td>Diabetes, no. (%)</td>
<td>110 (32)</td>
<td>93 (41)*</td>
<td>488 (39)*</td>
</tr>
<tr>
<td>Stroke or TIA, no. (%)</td>
<td>24 (7)</td>
<td>36 (16)*</td>
<td>123 (10)</td>
</tr>
<tr>
<td>PCI indication, no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>237 (68)</td>
<td>145 (64)</td>
<td>828 (67)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>99 (29)</td>
<td>70 (31)</td>
<td>384 (31)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (3)</td>
<td>11 (5)</td>
<td>31 (2)</td>
</tr>
</tbody>
</table>

*p<0.05
# 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

LOF = Loss of function
Kaplan-Meier Survival Curve

Log-rank p=0.016

NO. at risk
LOF_CLOP  226  112  89  76  63  39  3
LOF_ALT  346  245  221  195  161  112  9

LOF = Loss of function
Kaplan-Meier Survival Curve

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

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

NO. at risk
LOF_CLOP 226 112 89 76 63 39 3
NON-LOF 1243 759 636 577 451 293 28
LOF_ALT 346 245 221 195 161 112 9

LOF = Loss of function
Summary

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

Validation of findings at 2 additional sites is underway
Limitations

Genotype-guided therapy was not randomized

Antiplatelet therapy at the discretion of the physician

Death based on electronic health record documentation
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
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Back up slides
N= 1815 patients

Actionable genotypes:
PM: 54 (3.0%)
IM: 518 (28.5%)
Total: 572 (31.5%)
MACE

Total Cohort
n=1815

- LOF
  - Clopidogrel 39.5%
  - Alternative 60.5%
  - MACE (Death, MI, or Stroke) 8.0%
  - p=0.016

- Non-LOF
  - Clopidogrel 84.5%
  - Alternative 15.5%
  - MACE (Death, MI, or Stroke) 6.0%
  - p=0.156
MACE in LOF-Clopidogrel vs LOF-alternative

Propensity adjusted HR 2.21 (1.13-4.33) p=0.021

Clopidogrel better

Clopidogrel worse
MACE in LOF-alternative vs non-LOF

Propensity adjusted HR 0.81 (0.48-1.35)  
p=0.41