Clopidogrel Pharmacogenetics: Can We Impact Clinical Practice?

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Disclosure

Relevant financial relationship(s) with industry

None

Off-label usage

Ticagrelor
Objectives

- Clopidogrel-CYP2C19 as a drug-gene pair
- Review CYP2C19 genetic variation
- CYP2C19 genetic variation and its impact on clopidogrel PK, PD and clinical outcomes
- Why haven’t we had an impact on clinical practice?
- TAILOR-PCI
  - Design
  - Pilot Study
  - Impact
Importance

One of the “most important unresolved issues in interventional cardiology”

JACC 2013
Clopidogrel

- CAD affects 7.6 million people in the U.S.
- 2.5 to 3 million clopidogrel prescriptions are written per month
- 2010 sales were $6.1 billion
- Thienopyridine P2Y$_{12}$ADP receptor antagonist
- FDA indications
  - Myocardial infarction
  - Thrombotic CVA
  - Peripheral arterial disease
  - Percutaneous coronary intervention
Clopidogrel metabolism

Clopidogrel metabolism involves several steps:

1. **Intestinal cell**: Absorption of Clopidogrel across the apical membrane, facilitated by the ABCB1 transporter.
2. **Liver cell**: Metabolism of Clopidogrel to its active metabolite, 2-Oxo-clopidogrel, by enzymes such as CYP2C19, CYP1A2, CYP286, CYP3A4, and CYP3A5.
3. **Platelet**: Activation of the active metabolite to an irreversible inhibitor of the P2Ry12 receptor on platelets, leading to inhibition of platelet aggregation.
4. **Elimination**: Excretion of the inactive metabolite through the kidneys (urine) and feces.

The process is further influenced by enzymes such as CES1 and CYP2C9, which play a role in the metabolism of Clopidogrel.
Genetic variation in CYP2C19
# CYP2C19 polymorphisms

<table>
<thead>
<tr>
<th>Allele</th>
<th>African</th>
<th>American</th>
<th>East Asian</th>
<th>European</th>
</tr>
</thead>
<tbody>
<tr>
<td>*13</td>
<td>0.68</td>
<td>0.69</td>
<td>0.6</td>
<td>0.63</td>
</tr>
<tr>
<td>*2</td>
<td>0.15</td>
<td>0.12</td>
<td>0.29</td>
<td>0.15</td>
</tr>
<tr>
<td>*3</td>
<td>0.0052</td>
<td>0.00028</td>
<td>0.089</td>
<td>0.0042</td>
</tr>
<tr>
<td>*4</td>
<td>0.00093</td>
<td>0.0024</td>
<td>0.00049</td>
<td>0.0025</td>
</tr>
<tr>
<td>*5</td>
<td>ND</td>
<td>0.00</td>
<td>0.00062</td>
<td>0.000073</td>
</tr>
<tr>
<td>*6</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00017</td>
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<tr>
<td>*7</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>0.00</td>
</tr>
<tr>
<td>*8</td>
<td>0.00</td>
<td>0.0012</td>
<td>0.00</td>
<td>0.0035</td>
</tr>
<tr>
<td>*17</td>
<td>0.16</td>
<td>0.18</td>
<td>0.027</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Does genetic variation in \textit{CYP2C19} affect clopidogrel outcomes?
# Meta analysis

CV death, MI, or stroke – *CYP2C19* genotype

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Events/No. individuals at Risk</th>
<th>Hazard ratio (95% CI)</th>
<th>Increased Risk in Non-carriers</th>
<th>Increased Risk in Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clarity-TIMI 28</td>
<td>8/77</td>
<td>1.56 (0.61-3.94)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXCELSIOR</td>
<td>5/243</td>
<td>1.63 (0.52-5.14)</td>
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</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>46/395</td>
<td>1.53 (1.07-2.19)</td>
<td></td>
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<tr>
<td>AFIJI</td>
<td>15/73</td>
<td>5.38 (2.32-12.47)</td>
<td></td>
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<tr>
<td>FAST-MI</td>
<td>63/635</td>
<td>0.79 (0.59-1.06)</td>
<td></td>
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</tr>
<tr>
<td>RECLOSE</td>
<td>15/247</td>
<td>2.32 (1.12-4.81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISAR</td>
<td>55/680</td>
<td>1.23 (0.89-1.70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLEAR-PLATELETS</td>
<td>6/68</td>
<td>3.95 (1.11-14.02)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermountain</td>
<td>68/344</td>
<td>1.29 (0.97-1.72)</td>
<td></td>
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</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>281/2762</strong></td>
<td><strong>1.57 (1.13-2.16)</strong></td>
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</tr>
</tbody>
</table>

**P = 0.006**

Hazard Ratio (95% CI)
CYP2C19 Clinical Outcomes
A meta-analysis

- 91% of patients had PCI performed
- 55% of patients had ACS
- Common genetic variation is associated with 1 in 3 patients developing ischemic events when treated with standard clopidogrel therapy for PCI

JAMA 2010
Clopidogrel: Black-box warning

PLAVIX® (clopidogrel bisulfate) tablets
Initial U.S. Approval: 1997

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)
ACCF/AHA Clopidogrel Clinical Alert: Approaches to the FDA "Boxed Warning": A Report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association

Writing Committee Members, David R. Holmes, Jr, Gregory J. Dehmer, Sanjay Kaul, Dana Leifer, Patrick T. O'Gara and C. Michael Stein

*Circulation* 2010;122;537-557; originally published online Jun 28, 2010;
The evidence base is insufficient to recommend either routine genetic or platelet function testing at the present time. There is no information that routine testing improves outcome in large subgroups of patients.
When Plavix Challange FDA on Plavix

By RON WINSLOW

Many doctors are questioning whether the Food and Drug Administration should require patients taking the popular anti-clotting drug Plavix to undergo a genetic test each year based on the test, a leading cardiology. Some patients' genetic markers suggest they are already taking the drug. This could cast doubt on the drug's effectiveness.

A new study casts doubt on whether patients taking the popular anti-clotting drug Plavix should undergo a genetic test each year based on the test, a leading cardiology. Some patients' genetic markers suggest they already take the drug. This could cast doubt on the drug's effectiveness.

Heart Patients May Face a New Drug Dilemma

By RON WINSLOW

The newly low cost of Plavix, one of the biggest-selling drugs, is intensifying debate among cardiologists over how to make sure patients get optimal benefit from any blood-thinning medication.

A generic version of Plavix became available this month so there is an incentive to switch patients to it.

But, nearly a third of patients prescribed a blood thinner to prevent heart attack or stroke have a genetic variation that limits their ability to benefit from it. This could cast doubt on the drug's effectiveness.

Global sales of Plavix, in billions of dollars:

<table>
<thead>
<tr>
<th>Year</th>
<th>Sales</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>$1.9</td>
</tr>
<tr>
<td>2011</td>
<td>$1.5</td>
</tr>
<tr>
<td>2012</td>
<td>$1.2</td>
</tr>
</tbody>
</table>

Source: Bristol-Myers Squibb
6.1.2. Clopidogrel Genetic Testing: Recommendations

**CLASS III: NO BENEFIT**

1. The routine clinical use of genetic testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended (829). *(Level of Evidence: C)*

**CLASS III: NO BENEFIT**

1. The routine clinical use of platelet function testing to screen patients treated with clopidogrel who are undergoing PCI is not recommended (829). *(Level of Evidence: C)*

Maintenance doses and duration of therapy

**DES placed: Continue therapy for 1 y with:**
- Clopidogrel: 75 mg daily
- Prasugrel: 10 mg daily
- Ticagrelor: 90 mg twice a day*

**BMS† placed: Continue therapy for 1 y with:**
- Clopidogrel: 75 mg daily
- Prasugrel: 10 mg daily
- Ticagrelor: 90 mg twice a day*
The black box warning has not gone away
The gap in clinical evidence remains

Does altering therapy based on CYP2C19 status affect clinical outcomes?
TAILOR-PCI

TAILORED ANTIPLATELET INITIATION TO LESSEN OUTCOMES DUE TO DECREASED CLOPIDOGREL RESPONSE AFTER PERCUTANEOUS CORONARY INTERVENTION
TAILOR-PCI study design

Coronary Angiography / PCI Referrals

Screen & Consent

No PCI

PCI

Screen Failures

Enrolled RANDOMIZED

5,270 patients at 40 centers

1-year follow-up

Conventional Arm

Clopidogrel 75 mg daily

12 month/Retrospective genotyping

WT CYP2C19

CYP2C19*2 & *3

Prospective Genotyping Arm

CYP2C19*2 & *3

Ticagrelor 90 mg BID

WT CYP2C19

Clopidogrel 75 mg daily

Primary outcomes: non-fatal MI, non-fatal stroke, CV death, urgent revascularization, stent thrombosis (if not captured above)
Study design

- Randomized clinical trial to evaluate the importance of modifying anti-platelet therapy based on CYP2C19 genotype and its impact on clinical outcomes

- Estimated 1 year event rate for the LOF allele subjects of the intervention group is 8% and 12% for the control group

- Sample size calculated based on 2-sided log-rank test, power of 0.8, $\alpha$ of 0.05, HR 0.65 and LOF allele prevalence of 30% in North America and 50% in Korea

- Patients with ACS only are being recruited from the Canadian and Korean sites. US sites are recruiting ACS and stable patients.
# TAILOR PCI versus POPular Genetics

<table>
<thead>
<tr>
<th></th>
<th>TAILOR-PCI</th>
<th>POPular</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial design</strong></td>
<td>RCT – Superiority genetic Rx over conventional Rx i.e. clopidogrel</td>
<td>RCT – Non-inferiority of genetic Rx compared to ticagrelor/prasugrel</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>Post-PCI – ACS, AMI, stable CAD</td>
<td>Post-PCI – STEMI (20-30% of ACS patients)</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>5,270</td>
<td>2,700</td>
</tr>
<tr>
<td><strong>End points</strong></td>
<td>CV death, stroke, MI, ST, urgent revascularization</td>
<td>Death, stroke, MI, ST, urgent revascularization, bleeding</td>
</tr>
<tr>
<td><strong>Event rate</strong></td>
<td>8% in genetic arm versus 12% in clopidogrel arm</td>
<td>16.9% in genetic arm versus 18.8% in ticagrelor/prasugrel</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td>Telephone calls</td>
<td>Questionnaires</td>
</tr>
<tr>
<td><strong>Genotyping</strong></td>
<td>Point of care - Spartan</td>
<td>Multiple different platforms</td>
</tr>
</tbody>
</table>
TAILOR-PCI milestones

- US, Canadian and Korean partnership
- Randomized 2746 patients with 29 centers (3/05/16)
- Innovative trial design to address FDA regulatory issues and feasibility
- Novel “point of care” genotyping platform:
  - Spartan point of care testing
- No Pharma support
Pilot study – data

2746 subjects enrolled

Conventional therapy N=1371

Prospective genotyping N=1375

Wild type N=799

Reduced function allele N=397

NA/Unknown/Withdrawn
# Pilot study – baseline characteristics

## Summary of Patients Enrolled in TAILOR-PCI Pilot

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (min, max)</strong></td>
<td>62 (26, 95)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2098 (76%)</td>
</tr>
<tr>
<td><strong>BMI, median (min, max)</strong></td>
<td>27.8 (10.2, 67.3)</td>
</tr>
<tr>
<td><strong>Ethnicity, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1710 (66%)</td>
</tr>
<tr>
<td>Asian</td>
<td>743 (29%)</td>
</tr>
<tr>
<td>Black</td>
<td>43 (2%)</td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>97 (4%)</td>
</tr>
<tr>
<td><strong>Hospital presentation, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Stable, asymptomatic</td>
<td>532 (19%)</td>
</tr>
<tr>
<td>STEMI, acute coronary syndromes</td>
<td>2214 (81%)</td>
</tr>
<tr>
<td><strong>Cardiac history</strong></td>
<td></td>
</tr>
<tr>
<td>History of MI (excluding index event), n (%)</td>
<td>389 (15%)</td>
</tr>
<tr>
<td>History of PCI, n (%)</td>
<td>634 (24%)</td>
</tr>
<tr>
<td>History of CABG, n (%)</td>
<td>195 (8%)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>684 (26%)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>604 (23%)</td>
</tr>
<tr>
<td>Peripheral Artery Disease, n (%)</td>
<td>61 (2%)</td>
</tr>
<tr>
<td>Stroke / TIA, n (%)</td>
<td>71 (3%)</td>
</tr>
<tr>
<td>Currently on dialysis, n (%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td><strong>Cardiac anatomy and function</strong></td>
<td></td>
</tr>
<tr>
<td>MVD, n (%)</td>
<td>990 (39%)</td>
</tr>
<tr>
<td>LMCA &gt;=70% stenosis, n (%)</td>
<td>81 (3%)</td>
</tr>
<tr>
<td>High/C lesion complexity, n (%)</td>
<td>514 (20%)</td>
</tr>
</tbody>
</table>
NIH Grant Approved

May 2016
TAILOR-PCI

- High impact on a highly prevalent disease
- Addresses an unresolved practice issue by using research methodology
- Immediate applicability of genotyping to clinical practice worldwide
- Pharmacoeconomic analysis
- Potential application to other disease states
- Creates a biobank for studies like GWAS
- Creates an infrastructure for other pragmatic cost effective multicenter studies
Summary

- Pharmacogenetic application of CYP2C19 to clopidogrel, one of the most commonly prescribed drugs in the U.S., remains unresolved

- FDA cautions use of clopidogrel in CYP2C19 poor metabolizers

- ACC/AHA/ESC recommend against routine genotyping in the absence of a prospective clinical trial

- TAILOR-PCI designed and conducted to address this gap
Thank you!

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