Clopidogrel and CYP2C19 in Acute Coronary Syndrome
Should Pharmacogenetic Testing be Standard of Care?

September 22, 2017

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PGY1 Pharmacy Resident
Seton Healthcare Family
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ASCENSION TEXAS

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Conflict of Interest

• The author of this presentation has no conflicts of interest to disclose

Objectives

• Review oral antiplatelet agents

• Explain the FDA black box warning for clopidogrel pharmacogenetics

• Analyze the clinical impact of CYP2C19 polymorphisms on clopidogrel efficacy

• Evaluate the evidence for genotype-guided antiplatelet therapy

Meet the patient…

• A 75 year old Chinese female weighing 55 kg presents with an NSTEMI and is scheduled to undergo PCI

• Of note, the patient is taking St. John’s Wort

Antiplatelet Therapy in ACS

• 2013 ACCF/AHA STEMI Guidelines
  - P2Y12 inhibitor load for PCI with stenting, then continued for at least 12 months
    • Clopidogrel, prasugrel, or ticagrelor (LOE B)

• 2014 AHA/ACC NSTEMI Guidelines
  - P2Y12 inhibitor for at least 12 months for PCI with stenting
    • Clopidogrel, prasugrel, or ticagrelor (class I, LOE B)
  - Ticagrelor over clopidogrel in for early invasive or ischemia-guided strategy (class IIa, LOE B)

Acute Coronary Syndrome (ACS)

• Life-threatening situation from destabilization of atherosclerotic plaque
  - Includes STEMI, NSTEMI, and UA

• ACS occurs every 25 seconds in the United States

• 1.4 million patients hospitalized for ACS each year in the United States
  - 810,000 for MI

Meet the patient…

• Life-threatening situation from destabilization of atherosclerotic plaque

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Comparison of Oral Antiplatelet Agents

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<tr>
<td>Dose</td>
<td>LD: 300 or 600 mg MD: 75 mg/d</td>
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<td>Cost</td>
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<td>$$$</td>
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</tr>
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<td>Metabolism</td>
<td>Prodrug; CYP2C19 (major), CYP3A4 (minor)</td>
<td>Prodrug; CYP2B6 (major), CYP3A4 (minor)</td>
<td>CYP3A4 (major)</td>
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<td>Contraindications</td>
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Clopidogrel FDA Warning

**WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS**

See full prescribing information for complete based 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)

Clopidogrel Metabolism and Mechanism of Action

- **Clopidogrel**
  - CYP1A2, CYP2B6, CYP2C19
  - 2-oxo-clopidogrel
  - Active metabolite
  - Inhibits P2RY12 on platelet

  - CYP2C9, CYP2B6, CYP3A4, CYP3A5, CYP2C19, PON1

CYP2C19 Variant Alleles and Frequencies

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Clopidogrel Polymorphisms and Clopidogrel

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Pharmacokinetic Response to Clopidogrel Based on CYP2C19 Phenotype

Clopidogrel active metabolite formation

- **Pharmacokinetic Response**
  - **Clopidogrel, 100 mg**
  - **Clopidogrel, 75 mg**
Pharmacodynamic Response to Clopidogrel Based on CYP2C19 Phenotype

Reduction in platelet aggregation 24 hours after clopidogrel

CYP2C19 Genotype and Outcomes

Composite: death from cardiovascular causes, MI, or stroke

HR 1.53 (p = 0.01)

CYP2C19 Genotype and Stent Thrombosis

LOF Carriers (IMs + PMs)
Noncarriers

12.1%
8.0%

HR 1.53 (p = 0.01)

How does clopidogrel compare to other antiplatelet agents?

Clopidogrel vs. Prasugrel – TRITON-TIMI 38

13,608 patients with moderate-to-high-risk ACS with scheduled PCI

Prasugrel 60 mg load then 10 mg/day
Clopidogrel 300 mg load then 75 mg/day

Primary: composite death from CV causes, MI, or stroke

9.9%
12.1%
HR 0.81 (p < 0.001)

Safety: non-CABG related major hemorrhage

2.4%
1.8%
HR 1.32 (p = 0.03)

TRITON-TIMI 38 Genetic Substudy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Cardiovascular death, MI, and stroke</td>
<td>9.5%</td>
<td>9.8%</td>
<td>0.98 (0.80-1.20)</td>
</tr>
<tr>
<td>LOF carrier</td>
<td>8.5%</td>
<td>15.0%</td>
<td>0.57 (0.39-0.83)</td>
</tr>
<tr>
<td>Major or minor bleeding</td>
<td>4.7%</td>
<td>3.4%</td>
<td>1.38 (1.00-1.93)</td>
</tr>
<tr>
<td>LOF carrier</td>
<td>5.5%</td>
<td>3.5%</td>
<td>1.60 (0.80-3.10)</td>
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Conclusion

CYP2C19 genotype can distinguish which patients will receive extensive benefit from prasugrel over clopidogrel

*Estimates of outcome risks over 15 months for patients with UA or NSTEMI scheduled for PCI (excluded STEMI patients)
What do guidelines say about testing?

- 2011 ACCF/AHA/SCAI PCI Guidelines
  - Testing might be considered to identify patients at high risk for poor clinical outcomes
  - If PM status identified, consider alternate P2Y12 therapy
  - Routine genetic testing not recommended

- 2013 ACCF/AHA STEMI Guidelines
  - Acknowledges possibility of relationship between CYP2C19 polymorphisms and clopidogrel
  - No mention of pharmacogenetic testing

- 2014 AHA/ACC NSTEMI Guidelines
  - Routine genetic testing not recommended

What We Know

- CYP2C19 intermediate and poor metabolizer status associated worse outcomes with clopidogrel
  - Black box warning / FDA safety alert

- Prasugrel and ticagrelor are much more expensive and cannot be used in certain patients

- Guidelines still do not recommend testing

Does pharmacogenetic testing improve outcomes?

RAPID Gene Study

**Study Design**
- Single-center, prospective, randomized, blinded, N=200
- Rapid genotyping vs. standard treatment

**Patient Population**
- Inclusion: age 18-75 undergoing PCI for NSTEMI or stable ACS
- Exclusion: warfarin or dabigatran use, history of stroke or TIA, weight < 60 kg, platelets < 100,000, known bleeding diathesis, Hct < 30%, severe liver dysfunction, or CrCl < 30 ml/min

**Primary Outcome**
- Proportion of CYP2C19*2 carriers with high on-treatment platelet reactivity (P2Y12 reactivity units (PRU) > 234) after 1 week of dual antiplatelet therapy
RAPID Gene Study

Authors’ Conclusions

• Point-of-care genetic testing after PCI can be done effectively at the bedside
• Treatment of CYP2C19*2 carriers with prasugrel can reduce high on-treatment platelet reactivity

Strengths

• Prospective
• Genotype-guided vs. traditional selection
• Compared LOF carriers to LOF carriers

Weaknesses

• Universal clopidogrel load
• Only tested for CYP2C19*2
• Surrogate endpoint
• Primary outcome timing
• 95% of study population of western European ancestry

Genotyping-Approach vs. Conventional Approach in Chinese Patients

Study Design

• Single-center, prospective, randomized, open-label, N=132
• CYP2C19 genotype-guided P2Y12 antiplatelet therapy in ACS

Patient Population

• Inclusion: ACS (STEMI, UA/NSTEMI) +/- PCI, Chinese
• Exclusion: P2Y12 blocker w/in 6 months, chronic renal failure on HD or plan for HD, serious hepatic disease, CI to clopidogrel or ticagrelor, pregnant

Primary Outcome

• Platelet reactivity at 24 hours and 1 month after first loading dose of clopidogrel
### Genotyping-Approach vs. Conventional Approach in Chinese Patients

<table>
<thead>
<tr>
<th></th>
<th>On-treatment platelet reactivity</th>
<th>Genotype-guided</th>
<th>Standard</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTPR at 24 hours</td>
<td>6/65 (9.2%)</td>
<td>27/67 (40.3%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>HTPR at 1 month</td>
<td>4/62 (6.5%)</td>
<td>20/62 (32.3%)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate metabolizers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTPR at 24 hours</td>
<td>0/33 (0.0%)</td>
<td>12/27 (44.4%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>HTPR at 1 month</td>
<td>0/31 (0.0%)</td>
<td>10/27 (37.0%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td><strong>Poor metabolizers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTPR at 24 hours</td>
<td>0/7 (0.0%)</td>
<td>5/8 (62.5%)</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>HTPR at 1 month</td>
<td>0/6 (0.0%)</td>
<td>5/7 (71.4%)</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

HTPR: high on-treatment platelet reactivity = P2Y12 reaction units > 208

NR: not reported

### Authors’ conclusions

- Rapid genotyping-guided approach for selecting P2Y12 blockers is feasible
- Genotype-guided approach reduces the incidence of high on-treatment platelet reactivity

### Strengths
- Prospective
- Use of genotype-guidance randomized
- High risk patient population

### Weaknesses
- Surrogate endpoint
- PRU cutoff > 208
- Small sample size
- Patient population not generalizable
- LOF patients loaded with clopidogrel and ticagrelor

#### Study Design
- Prospective, multicenter
- CYP2C19 genotype-guided antiplatelet therapy post-PCI

#### Patient Population
- Average patient: early 60s, male, white, unstable ACS w/PCI
- 54 PMs + 518 IMs → 572 (31.5%) actionable genotypes

#### Primary Outcome
- Major adverse cardiac events (MACE): death, MI, or stroke within 12 months following index PCI

#### Prospective Clinical Implementation of CYP2C19 Genotype Guided Antiplatelet Therapy After PCI

* p<0.0001 for alternative therapy between LOF and NON-LOF groups

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** APPENDIX K

Prospective Clinical Implementation of CYP2C19 Genotype Guided Antiplatelet Therapy After PCI

Authors’ conclusions

• Genotype-guided approach feasible
• Higher risk for MACE in CYP2C19 LOF treated with clopidogrel vs. alternative
• Genotyping can improve clinical outcomes after PCI

Strengths

• Genotype-guided antiplatelet selection
• Prospective
• Real world setting
• Antiplatelet selection up to physician

Limitations

• Use of genotype-guidance not randomized
• High dose clopidogrel
• Outcomes based on carrier status
• Limited study information available

Summary of Evidence

<table>
<thead>
<tr>
<th>Trial</th>
<th>Overall Conclusion</th>
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<tr>
<td>Roberts, et al</td>
<td>Genotyping reduces high on-treatment platelet reactivity at day 7 in CYP2C19*2 carriers</td>
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<td>Tam, et al</td>
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<tr>
<td>Cavallari, et al</td>
<td>Genotyping reduces risk for MACE outcomes</td>
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Ongoing Trial

2700 STEMI patients undergoing PCI

CYP2C19 genotyping

2C19 LOF → prasugrel or ticagrelor

Wild-type → clopidogrel

Routine ticagrelor or prasugrel

POPular Genetics Study

POPular Genetics Study Endpoints

• Clinical benefit
  - Death, recurrent MI, definite stent thrombosis, stroke, platelet inhibition and patient outcomes
• Safety
  - Clinical benefit and major or minor bleeding
• Cost-effectiveness
• Quality of life
• A 75 year old Chinese female weighing 55 kg presents with an NSTEMI and is scheduled to undergo PCI
• Of note, the patient is taking St. John’s Wort
• Which antiplatelet option would you recommend?
  • A. Clopidogrel
  • B. Ticagrelor
  • C. Prasugrel
  • D. Order CYP2C19 genetic test

Back to the patient…

Recommendation
• Data not strong enough to support testing everyone
• Use genetic information when available
• Consider testing higher risk ethnicities

Conclusion
• Antiplatelet agents are not one size fits all
• Clopidogrel response variation can be partly explained by CYP2C19 polymorphisms
• CYP2C19 LOF carriers at higher risk for poor outcomes
• Evidence to support genotyping all patients is still limited - surrogate endpoints, small sample size, focused on feasibility
• Watch for results of the POPular Genetics Study

Acknowledgements

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Clinical Pharmacy Specialist – Internal Medicine
Seton Northwest Hospital

Kelsey Melloy, PharmD
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Appendix A: Abbreviations

Appendix B: Comparison of Oral Antiplatelet Agents

Appendix C: Clopidogrel FDA Warning

Appendix D: Clopidogrel Metabolism and Mechanism of Action

Appendix E: CYP2C19 Variant Alleles and Frequencies

Appendix F: CYP2C19 Polymorphisms and Clopidogrel

Appendix G: Pharmacokinetic Response to Clopidogrel Based on CYP2C19 Phenotype

Appendix H: Pharmacodynamic Response to Clopidogrel Based on CYP2C19 Phenotype

Appendix I: CYP2C19 Genotype and Outcomes

Appendix J: CYP2C19 Genotype and Stent Thrombosis

Appendix K: Cumulative MACE Rate Based on CYP2C19 Phenotype
Appendix A: Abbreviations

- ACCF: American College of Cardiology Foundation
- ACS: acute coronary syndrome
- AHA: American Heart Association
- ALT: alternative
- CABG: coronary artery bypass grafting
- CLOP: clopidogrel
- CV: cardiovascular
- CYP: cytochrome P450
- EM: extensive metabolizer (normal metabolizer)
- FDA: Federal Drug Administration
- HD: hemodialysis
- HR: hazard ratio
- HTPR: high on-treatment platelet reactivity
- IM: intermediate metabolizer
- LD: loading dose
- LOE: level of evidence
- LOF: loss of function
- MACE: major adverse cardiac events
- MD: maintenance dose
- MI: myocardial infarction
- MPA: maximal platelet aggregation
- NR: not reported
- NSTEMI non-ST elevated myocardial infarction
- PCI: percutaneous coronary intervention
- PM: poor metabolizer
- PRU: P2Y12 reactivity units
- STEMI: ST elevated myocardial infarction
- TIA: transient ischemic attack
- UA: unstable angina
- UM: ultra-rapid metabolizer
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Active metabolite
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Sangkuhl Katrin, Klein Teri E, Altman Russ B. Pharmacogenetics and genomics (2010).
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Clopidogrel active metabolite formation

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Reduction in platelet aggregation 24 hours after clopidogrel

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Composite: death from cardiovascular causes, MI, or stroke

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Noncarriers 8.0%

HR 1.53 (p = 0.01)

Appendix J: CYP2C19 Genotype and Stent Thrombosis


LOF Carriers (IMs + PMs) 2.6%
Noncarriers 0.8%
HR 3.09 (p = 0.02)
Appendix K: Prospective Clinical Implementation of CYP2C19 Genotype Guided Antiplatelet Therapy After PCI

LOF = loss of function carrier
CLOP = clopidogrel
ALT = alternative