Pharmacogenomics with Clopidogrel: Does One Size Fit All?

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Objectives

• Discuss the role of P2Y\textsubscript{12} inhibitors in cardiovascular pharmacotherapy
• Describe patient variability in response to P2Y\textsubscript{12} inhibitors
• Explore the role of pharmacogenomics in P2Y\textsubscript{12} inhibitor management
P2Y₁₂ Inhibitors

- Decrease platelet activation
  - Inhibit the P2Y₁₂ receptor responsible for platelet activation
- Reduce thrombosis in patients with cardiovascular disease
- Clopidogrel most prescribed

<table>
<thead>
<tr>
<th></th>
<th>Year</th>
<th>Prodrug?</th>
<th>Platelet Inhibition</th>
<th>Reversibility?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>1996</td>
<td>Yes</td>
<td>30-40%</td>
<td>No</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>2009</td>
<td>Yes</td>
<td>60-70%</td>
<td>No</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>2010</td>
<td>No</td>
<td>80-90%</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Response Variability with Clopidogrel

- **Responders**: 13%
- **Non-responders**: 87%

Total n=804

Response Variability with Clopidogrel

- Responders: 2.3% (n=699)
- Nonresponders: 8.6% (n=105)

p<0.001

Enter Pharmacogenomics

- The study of how genetics affect individual variation in response to drugs
Pharmacogenomic Terminology

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene</td>
<td>Unit of DNA that encodes a protein</td>
</tr>
<tr>
<td>Single-nucleotide polymorphism (SNP)</td>
<td>Genetic variation of a DNA “building block” (single nucleotide)</td>
</tr>
<tr>
<td>Allele</td>
<td>A variant form of a gene</td>
</tr>
<tr>
<td></td>
<td>Humans have two alleles for each gene</td>
</tr>
<tr>
<td>Genotype</td>
<td>Individual genetic constitution</td>
</tr>
<tr>
<td></td>
<td>(Describes combination of alleles)</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Observable properties of an organism</td>
</tr>
</tbody>
</table>
Clopidogrel Pharmacogenomics

• Prodrug activated primarily by CYP2C19
• The gene encoding CYP2C19 has many alleles
  – Some patients have decreased or loss of function alleles

↓ Drug activation  Platelets remain active  Risk for thrombosis

• CYP2C19 function does not affect other P2Y₁₂ inhibitors

## CYP2C19 Polymorphisms

<table>
<thead>
<tr>
<th>Allele</th>
<th>Phenotype</th>
<th>Clinical Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19*1</td>
<td>Wild-type</td>
<td></td>
</tr>
<tr>
<td>CYP2C19*2</td>
<td>Loss-of-function allele</td>
<td>Decreased efficacy</td>
</tr>
<tr>
<td>CYP2C19*3-8</td>
<td>Reduced/loss of function</td>
<td>Decreased efficacy</td>
</tr>
<tr>
<td>CYP2C19*17</td>
<td>Increased enzyme activity</td>
<td>Increased efficacy and increased bleeding</td>
</tr>
</tbody>
</table>

**Metabolizer Types:**

- **Poor metabolizer**: *2/*2 or *3/*3
- **Intermediate metabolizer**: *1/*2 or *1/*3 (Carrier)
- **Extensive metabolizer**: *1/*1 (Homozygous wild-type)
- **Rapid metabolizer**: *1/*17 (Carrier)
- **Ultra-rapid metabolizer**: *17/*27

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Clinical Outcomes in CYP2C19 Variants

<table>
<thead>
<tr>
<th>CYP2C19 Variant</th>
<th>HR† (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>One reduced function variant</td>
<td>1.57 (1.13-2.16)</td>
<td>0.006</td>
</tr>
<tr>
<td>Two reduced function variants</td>
<td>1.55 (1.11-2.17)</td>
<td>0.01</td>
</tr>
<tr>
<td>One or two reduced function variants</td>
<td>1.76 (1.24-2.50)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

n = 9685
† Cardiovascular Death, Myocardial Infarction, or Ischemic Stroke

Black Box Warning
“Consider alternate treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers”
Other Potential Polymorphisms

- **ABCB1**
  - Encodes P-glycoprotein efflux pump
  - >50 variants
- **Paraoxonase and other CYP450 enzymes**
  - Involved with clopidogrel activation
- **Carboxyesterase**
  - Deactivates clopidogrel
Identification of Variant Patients

- Laboratory-based methods
  - Time consuming and labor intensive

- Point-of-care assays
  - Spartan RX™ System
  - Verigene XP® System

<table>
<thead>
<tr>
<th></th>
<th>Verigene®</th>
<th>Spartan RX™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Medium</td>
<td>Whole blood</td>
<td>Buccal swab</td>
</tr>
<tr>
<td>Time to Result</td>
<td>2.5 hours</td>
<td>1 hour</td>
</tr>
</tbody>
</table>

Management Recommendations

- ACC/AHA Guidelines
  - Potential role in high-risk patients undergoing elective PCI

- Clinical Pharmacogenomics Consortium Guidelines

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Recommendation</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrarapid/extensive metabolizer</td>
<td>Clopidogrel</td>
<td>Strong</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>Alternative antiplatelet therapy</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>(prasugrel, ticagrelor)*</td>
<td></td>
</tr>
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*If no contraindication

ACC: American College of Cardiology, AHA: American Heart Association; PCI: Percutaneous Coronary Intervention
The RAPID STEMI Study

Genotype assessed by Spartan RX™

- CYP2C19*2 ABCB1TT
- Wild-type

- Clopidogrel 150 mg daily x 6 days then 75 mg daily (n=29)
- Prasugrel 10 mg daily (n=30)
- Clopidogrel (dosing per MD) (n=42)

Augmented-dose Clopidogrel

- On Treatment High Platelet Reactivity: 7(24.1)

Prasugrel 10 mg

- p-value: 0.046

# P2Y$_{12}$ Inhibitor Pharmacogenomics Programs

<table>
<thead>
<tr>
<th></th>
<th>VUMC</th>
<th>UFL</th>
<th>UMD</th>
<th>UNC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>LHC</td>
<td>PCI</td>
<td>LHC</td>
<td>High-risk PCI</td>
</tr>
<tr>
<td><strong>Assay</strong></td>
<td>Lab</td>
<td>Lab</td>
<td>Verigene$^\text{®}$</td>
<td>Lab</td>
</tr>
<tr>
<td><strong>Turnaround Time</strong></td>
<td>-</td>
<td>3.5 days</td>
<td>5 hours</td>
<td>24-48 hours</td>
</tr>
<tr>
<td><strong>Alert Method</strong></td>
<td>EMR Alert</td>
<td>EMR Alert</td>
<td>Provider Call</td>
<td>None</td>
</tr>
<tr>
<td><strong>Follow Up</strong></td>
<td>Nurse/RPh</td>
<td>RPh</td>
<td>MD/RPh</td>
<td>-</td>
</tr>
<tr>
<td><strong>Patients Screened</strong></td>
<td>2,165</td>
<td>291</td>
<td>166</td>
<td>229</td>
</tr>
<tr>
<td><strong>Therapy Change (n, %)</strong></td>
<td>-</td>
<td>56(19)</td>
<td>17(10)</td>
<td>49(19)</td>
</tr>
</tbody>
</table>

VUMC: Vanderbilt University Medical Center; UFL: University of Florida; UMD: University of Maryland; UNC: University of North Carolina
LHC: Left Heart Catheterization; PCI: Percutaneous Coronary Intervention; EMR: Electronic Medical Record

Lessons Learned

• Necessities
  – Interdisciplinary implementation team
  – Hospital leadership buy-in

• Barriers
  – Drug cost
  – Ongoing evidence review needed
  – Phlebotomy, nurse, clinician education
  – Information technology integration
  – Delay to results
Role of the Pharmacist

- Recommend pharmacogenomic testing
- Design personalized regimens based on the patient’s pharmacogenomic profile
- Educate patients, pharmacists, and other health care professionals
- Communicate and document interpretation and recommendations to the health care team
Summary and Conclusions

• Pharmacogenomic differences contribute to response variability of clopidogrel
• Genetic testing can be utilized to individualize therapy
• Pharmacists serve a key role in pharmacogenomic implementation
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