The Pharmacogenetics of Clopidogrel

CANNeCTIN
Cutting-Edge Pharmacogenetics Symposium

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Disclosure Statement

Astra Zeneca (scientific advisory boards)
Bristol-Myers-Squibb (honoraria, scientific advisory boards)
Eli Lilly & Daiichi-Sankyo (honoraria)
Eisai (research grant)
sanofi-aventis (research grant, honoraria, scientific advisory boards)
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Outline

1. Mechanism of action and clinical benefit of clopidogrel
2. Variability in response to clopidogrel
3. Clopidogrel pharmacogenetic interactions
4. Potential therapeutic options
Outline

1. Mechanism of action and clinical benefit of clopidogrel

2. Variability in response to clopidogrel

3. Clopidogrel pharmacogenetic interactions

4. Potential therapeutic options
Role of Platelet Activation and Aggregation

Clopidogrel in STEMI

Double-blind, randomized, placebo-controlled trial in 3491 patients, age 18-75 yrs with STEMI < 12 hours

Fibrinolytic, ASA, Heparin

randomize

Clopidogrel

300 mg + 75 mg qd

Placebo

Coronary Angiogram

(2-8 days)

30-day clinical follow-up

Primary endpoint:
Occluded artery (TIMI Flow Grade 0/1) or D/MI by time of angio

Study Drug

Open-label clopidogrel per MD in both groups
Clopidogrel in STEMI

![Graph showing the comparison between Clopidogrel and Placebo in terms of Occluded Artery or Death/MI (%). The graph indicates a significant reduction in Occluded Artery or Death/MI with Clopidogrel compared to Placebo.]

- **Clopidogrel**: 15.0
- **Placebo**: 21.7
- **Change**: -6.7%
- **P-value**: <0.0001

![Graph showing the comparison between Clopidogrel and Placebo in terms of CV Death, MI, or Urgent Revascularization (%). The graph indicates a reduction in CV Death, MI, or Urgent Revascularization with Clopidogrel compared to Placebo.]

- **Placebo**: 20%
- **Clopidogrel**: 20%
- **Odds Ratio**: 0.80 (95% CI 0.65-0.97)
- **P-value**: 0.026

Sabatine MS et al. *NEJM* 2005; 352: 1179
**COMMIT: Clopidogrel (75 mg qd) in AMI**

45,851 Patients p/w AMI w/ in 24 hrs; ASA; lytic therapy (~1/2)

<table>
<thead>
<tr>
<th>Days</th>
<th>Placebo (10.1%)</th>
<th>Clopidogrel (9.3%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>14</td>
<td>7</td>
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<tr>
<td>21</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>28</td>
<td>5</td>
<td>5</td>
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</tbody>
</table>

9% relative risk reduction (P=.002)

<table>
<thead>
<tr>
<th>Days</th>
<th>Placebo (8.1%)</th>
<th>Clopidogrel (7.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
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</tr>
<tr>
<td>14</td>
<td>5</td>
<td>5</td>
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<tr>
<td>21</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>28</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

7% relative risk reduction (P=.03)

Clopidogrel in NSTE ACS: CURE

12,563 Pts, GP IIb/IIIa & early invasive approach discouraged

\[ \text{RR 0.80, } p<0.001 \]

CURE. *NEJM* 2001;345:494-502
Clopidogrel in Patients with Stable CAD or at High Risk for Atherothrombosis

Bhatt DL et al. *NEJM* 2006;354:1706-17

**CV Death, MI, Stroke (%)**

- **Placebo + ASA:** 7.3% (N=15,603)
- **Clopidogrel + ASA:** 6.8%

**RRR:** 7.1% [95% CI: -4.5%, 17.5%]  
P=0.22
CHARISMA — Prior MI Subgroup

N=3,846

Death, MI, Stroke (%)

Placebo + ASA

Clopidogrel + ASA

HR=0.774 (95% CI [0.613–0.978])
P=0.031

Thienopyridine Rx following PCI

STARS

- Aspirin
- Aspirin + warfarin
- Aspirin + ticlopidine

$P = 0.001$

CREDO

- Clopi x 28 d
- Clopi x 1 yr

$27\%$ RRR
$P = 0.02$

$0.0\%$ 
$0.5\%$
$1.0\%$
$1.5\%$
$2.0\%$
$2.5\%$
$3.0\%$
$3.5\%$
$4.0\%$

Cumulative Incidence of Primary End Point (%)

$0.0$ 
$2.0$ 
$4.0$ 
$6.0$ 
$8.0$ 
$10.0$ 
$12.0$

Death/MI/stroke

Days after Stenting

0 
2 
4 
6 
8 
10 
12 
14 
16 
18 
20 
22 
24 
26 
28 
30

Months after PCI
Outline

1. Mechanism of action and clinical benefit of clopidogrel

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4. Potential therapeutic options
24 Hours After 300mg Clopidogrel

Gurbel PA et al., Circulation 2003;107:2908-2913

"Resistance" = 31%

N=96, Elective PCI

Patients (%)

20

10

≤ -30 (-30, 20)
(-20, -10)
(0, 10)
(10, 20)
(20, 30)
(30, 40)
(40, 50)
(50, 60)
>60

△ Platelet Aggregation Before and After Clopidogrel (%)

"Resistance" = ≤10% △ platelet aggregation
Clopidogrel Responsiveness and Recurrent CV Events in STEMI

Clopidogrel Responsiveness and SAT


LTA: light-transmission aggregometry to 5 μmol/L ADP

VASP: ratio of vasodilator-stimulated phosphoprotein reactivity

P<0.001
P=0.03
Clinical Consequences of Stent Thrombosis

- Non-fatal MI: 69%
- Death: 24%
- Unstable Angina: 7%

Outline

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2. Variability in response to clopidogrel
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4. Potential therapeutic options
Clopidogrel Metabolism

**Clopidogrel** (prodrug)

**Intestinal absorption** (ABCB1)

**Esterases**

**Hepatic metabolism** (CYTPA4, CYTPA5, and CYTP2C19)

**Inactive metabolites** (85% of clopidogrel dose)

**Active metabolites** (15% of clopidogrel dose)

**Platelet**

**GPIIb/IIIa receptor**

**ITGB3**

**P2RY12 receptor**

**ADP**

**CYPs:** 3A2, 2B6, 2C9, 2C19

**Active Metabolite**

Cytochrome P450

Enzymes

- 57 human CYPs (18 families and 42 subfamilies)
- Account for >90% of drug transformations
- Major phase 1 biotransforming system (mono-oxygenation)

Genes

- Highly polymorphic
- Common-consensus star allele nomenclature (eg, *CYP2C19*2 refers to haplotype containing 681G>A)
- Certain alleles confer reduced enzymatic function (eg, splicing defect)
CYP2C19 and Platelet Inhibition

28 Healthy Volunteers Given Clopidogrel 75 mg/d x 7 days

Hulot et al. *Blood* 2006;108:2244
CYP2C19 and Platelet Inhibition

797 patients treated with clopidogrel 600 mg before PCI

Trenk et al. JACC 2008;51:1925
Genotyping and Gene Classification

Non-carriers of any reduced-function alleles (expected to be extensive metabolizers)

Carriers of ≥1 reduced-function allele (expected to be poor metabolizers)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Classification</th>
<th>Observed Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>Non-carrier</td>
<td>*17/*17, *1A/*17, *1A/*1A</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Non-carrier</td>
<td>*1A/*1A, *1A/*2A, *1A/*11A, *1A/*12</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Non-carrier</td>
<td>*1A/*1A, *1A/*1C, *1C/*1C</td>
</tr>
<tr>
<td></td>
<td>Carrier</td>
<td>*1A/*6, *1A/*9, *1C/*6/*1C/*9, *1C/*13, *6/*9, *9/*9</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>Non-carrier</td>
<td>*1A/*1A, *1A/*3A, *1A/*6, *2A/*3A</td>
</tr>
<tr>
<td></td>
<td>Carrier</td>
<td>*3A/*3A, *3A/*3F, *3A/*6</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Non-carrier</td>
<td>*1A/*1A, *1A/*1B</td>
</tr>
<tr>
<td></td>
<td>Carrier</td>
<td>None</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>Non-carrier</td>
<td>*1A/*1A, *1A/*1D, *1A/*1E, *1D/*1D, *1D/*1E, *1D/*1L, *1E/*1L, *1L/*1L</td>
</tr>
<tr>
<td></td>
<td>Carrier</td>
<td>*1A/*1C, *1C/*1D, *1C/*1E, *1C/*1C</td>
</tr>
</tbody>
</table>

Genotyping was performed using the Affymetrix Targeted Human DMET 1.0 Assay (98% of genotypes) and bi-directional sequencing or exon-specific PCR followed by RFLP in the case of CYP2C19*17 or a no-call on the DMET chip (2% of genotypes).
Methods: PK/PD

- **Subjects**: 162 healthy individuals, 6 studies

- **Pharmacokinetics (PK)**
  - Clopidogrel active metabolite measured by liquid chromatography with mass spectrometry
  - Computed $\text{AUC}_{0-t}$ from time of dose to last measurable concentration of active metabolite

- **Pharmacodynamics (PD)**
  - Response assessed using light transmission aggregometry in response to 20 µM ADP
  - Expressed as absolute reduction in maximal platelet aggregation from baseline ($\Delta\text{MPA}$)
  - Overall $\Delta\text{MPA} = 36.0\pm20.5\%$
Methods: Clinical Outcomes

- **Subjects:** 1,477 subjects with ACS and planned PCI in TRITON-TIMI 38 allocated to clopidogrel (300 mg load, 75 mg maintenance) with a median follow-up of 15 months

- **Clinical Outcomes**
  - CV Death, MI, Stroke
  - Stent Thrombosis (Def or Prob per ARC Definition)
  - TIMI Major or Minor Bleeding
CYP450 Genetic Variants & PK/PD

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Gene</th>
<th>% Difference in AUC&lt;sub&gt;0-t&lt;/sub&gt;</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-32.4</td>
<td>0.00006</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-6.8</td>
<td>0.59</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>-15.7</td>
<td>0.035</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>5.6</td>
<td>0.59</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>11.2</td>
<td>0.45</td>
</tr>
</tbody>
</table>

**Pharmacodynamics**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Absolute Difference in ΔMPA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-9.0</td>
<td>0.00054</td>
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<tr>
<td>CYP2C9</td>
<td>-0.6</td>
<td>0.86</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>-5.7</td>
<td>0.012</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>7.5</td>
<td>0.012</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>0.5</td>
<td>0.90</td>
</tr>
</tbody>
</table>

**CYP2C19 Extended Classification**

**Clopidogrel 300mg**

- UM (n=47)
- EM (n=43)
- IM (n=27)
- PM (n=3)

**Clopidogrel 75mg**

- UM (n=22)
- EM (n=31)
- IM (n=29)
- PM (n=8)

Reduction in MPA (%) at 24-hour

UM – Ultra
EM – Extensive
IM – Intermediate
PM – Poor

**CYP2C19 & Clinical Outcomes**

**CYP2C19 Reduced-Function Allele Carriers**

- **HR 1.53**
  - (95% CI 1.07-2.19)
  - P=0.014

**Number at Risk:**

<table>
<thead>
<tr>
<th>Days After Randomization</th>
<th>Non-carrier</th>
<th>Carrier</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1064</td>
<td>395</td>
</tr>
<tr>
<td></td>
<td>1009</td>
<td>364</td>
</tr>
<tr>
<td></td>
<td>999</td>
<td>360</td>
</tr>
<tr>
<td></td>
<td>980</td>
<td>348</td>
</tr>
<tr>
<td></td>
<td>870</td>
<td>306</td>
</tr>
<tr>
<td></td>
<td>755</td>
<td>270</td>
</tr>
<tr>
<td></td>
<td>542</td>
<td>181</td>
</tr>
</tbody>
</table>

* Carriers ~30% of the population

**CYP2C19 & Stent Thrombosis**

Hazard Ratio 3.09
(95% CI 1.19-8.00)
P=0.015

CYP2C19 Reduced-Function Allele Carriers

Non-carriers

N=1,389


* Carriers ~30% of the population
CYP2C19*2 Carriers

- The *2 allele accounted for 95% of the subjects classified as carriers of a CYP2C19 reduced-function allele.
- This *2 variant encodes a cryptic splice variant that leads to limited enzymatic activity.
- In clopidogrel treated patients:

<table>
<thead>
<tr>
<th>Event</th>
<th>KM Rates *2 Carriers vs. Non-carriers</th>
<th>HR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint</td>
<td>11.7 vs 8.3%</td>
<td>1.42</td>
<td>0.04</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>2.7 vs. 0.8%</td>
<td>3.33</td>
<td>0.004</td>
</tr>
</tbody>
</table>
# CYP450 Genotypes and Efficacy

<table>
<thead>
<tr>
<th>Gene</th>
<th>Carriers of Reduced Function Allele</th>
<th>Non-carriers</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2C19</td>
<td>12.1% (46/395)</td>
<td>8.0% (83/1064)</td>
<td>1.53 (1.07-2.19)</td>
<td>0.014</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>10.0% (22/230)</td>
<td>9.0% (107/1226)</td>
<td>1.09 (0.69-1.73)</td>
<td>0.41</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>10.0% (36/370)</td>
<td>9.0% (68/777)</td>
<td>1.11 (0.74-1.67)</td>
<td>0.78</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>8.7% (95/1130)</td>
<td>9.5% (14/151)</td>
<td>0.89 (0.51-1.57)</td>
<td>0.69</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>8.5% (5/59)</td>
<td>8.9% (95/1099)</td>
<td>0.97 (0.40-2.39)</td>
<td>0.96</td>
</tr>
</tbody>
</table>
## CYP450 Genotypes and Safety

<table>
<thead>
<tr>
<th>Gene</th>
<th>Carriers of Reduced Function Allele</th>
<th>Non-carriers</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>2.9%</td>
<td>3.0%</td>
<td>1.01 (0.51-2.01)</td>
<td>0.98</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>3.4%</td>
<td>2.9%</td>
<td>1.07 (0.47-2.40)</td>
<td>0.88</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>3.3%</td>
<td>3.1%</td>
<td>1.08 (0.53-2.18)</td>
<td>0.84</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>3.0%</td>
<td>3.3%</td>
<td>0.77 (0.30-1.97)</td>
<td>0.58</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>3.4%</td>
<td>3.0%</td>
<td>1.29 (0.31-5.38)</td>
<td>0.73</td>
</tr>
</tbody>
</table>
CYP2C19 and Clinical Events: AFIJI

259 young patients with MI treated with clopidogrel

Freedom from CV Death, MI, Urgent Revascularization (%)

Stent Thrombosis:
(HR 6.02, 95% CI 1.81-20.04, P=0.0009)

CYP2C19 and Clinical Events: FAST-MI

2208 patients with MI treated with clopidogrel

*ABCB1* (or *MDR1*) encodes P-glycoprotein (P-gp), an ATP-dependent efflux pump for xenobiotics that thus ↓ drug accumulation.
In 1,535 patients who underwent PCI, the \textit{MDR1} variant allele had no significant effect (P = 0.35).

CYP2C19 and Stent Thrombosis: ISAR

2485 patients undergoing PCI and treated with clopidogrel

HR 3.81 for *2 carriers vs. non-carriers (95% CI 1.45-10.02) P=0.007

**CYP2C19 and Stent Thrombosis: RECLOSE**

772 patients undergoing PCI and treated with clopidogrel


HR 2.59 for *2 carriers vs. non-carriers*

(95% CI 1.15-5.88)  
P=0.022
### CYP2C19, Plt Agg, & Stent Thrombosis

772 patients undergoing PCI and treated with clopidogrel

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariable*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>CYP2C19 *2 carrier</td>
<td>2.59 (1.15-5.88)</td>
<td>0.02</td>
</tr>
<tr>
<td>Residual plt aggregation ≥70%</td>
<td>3.17 (1.32-7.59)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* Model contained CYP2C19, platelet resistance, and clinical factors

CYP2C19 & Major Adverse Cardiac Events:

CLEAR PLATELETS 1 & 2: 227 patients undergoing elective PCI

Gurbel PA et al. ACC 2009.
Relation of On-Treatment Aggregation to CYP2C19*2 and Event Occurrence (n = 188)

20 µM ADP-Induced Aggregation (%)

-/-         -/*2        *2/*2

Without Events

With Events

p = 0.02

p = 0.004

Gurbel PA et al. ACC 2009.
### Relative Risk for Ischemic Event Occurrence:

**Cox Proportional Hazards Regression Analysis**

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>0.87</td>
<td>0.79-0.96</td>
<td>0.005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.29</td>
<td>1.19-4.39</td>
<td>0.01</td>
</tr>
<tr>
<td>Current Smoking</td>
<td>2.29</td>
<td>1.19-4.39</td>
<td>0.01</td>
</tr>
<tr>
<td>PPIs</td>
<td>2.07</td>
<td>0.82-5.20</td>
<td>0.12</td>
</tr>
<tr>
<td>IIb/IIa Inhibitor Use</td>
<td>1.27</td>
<td>0.84-1.93</td>
<td>0.25</td>
</tr>
<tr>
<td>Anticoagulant</td>
<td>1.09</td>
<td>0.39-3.01</td>
<td>0.87</td>
</tr>
<tr>
<td>Drug Eluting Stents</td>
<td>0.74</td>
<td>0.23-2.36</td>
<td>0.60</td>
</tr>
<tr>
<td>Lesion Diameter</td>
<td>0.99</td>
<td>0.33-3.01</td>
<td>0.99</td>
</tr>
<tr>
<td>Total No. of Vessels</td>
<td>1.07</td>
<td>0.44-2.57</td>
<td>0.87</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>0.97</td>
<td>0.94-1.02</td>
<td>0.18</td>
</tr>
<tr>
<td>CYP2C19*2</td>
<td>3.03</td>
<td>1.28-7.19</td>
<td>0.01</td>
</tr>
<tr>
<td>HPR (&gt;59%)</td>
<td>4.47</td>
<td>1.65-12.07</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Gurbel PA et al. ACC 2009.
CYP2C19 and MI:
Intermountain Heart Collaborative (IHC) Study Registry

1250 patients undergoing PCI w/ DES and Rx’d w/ clopidogrel

OR 1.50 (95% CI 1.00-2.24)
P=0.048

### Major Adverse Cardiovascular Events

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Z-Value</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLARITY-TIMI 28</td>
<td>1.390</td>
<td>0.598</td>
<td>3.230</td>
<td>0.765</td>
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<tr>
<td>EXCELSIOR</td>
<td>0.590</td>
<td>0.221</td>
<td>1.576</td>
<td>-1.052</td>
<td>0.293</td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>1.530</td>
<td>1.069</td>
<td>2.189</td>
<td>2.327</td>
<td>0.020</td>
</tr>
<tr>
<td>AFIJI</td>
<td>3.690</td>
<td>1.691</td>
<td>8.053</td>
<td>3.279</td>
<td>0.001</td>
</tr>
<tr>
<td>FAST-MI</td>
<td>0.860</td>
<td>0.676</td>
<td>1.094</td>
<td>-1.229</td>
<td>0.219</td>
</tr>
<tr>
<td>Giusti et al.</td>
<td>2.360</td>
<td>1.120</td>
<td>4.971</td>
<td>2.259</td>
<td>0.024</td>
</tr>
<tr>
<td>EHJ</td>
<td>1.140</td>
<td>0.826</td>
<td>1.573</td>
<td>0.798</td>
<td>0.425</td>
</tr>
<tr>
<td>CLEAR-PLATELETS</td>
<td>2.420</td>
<td>1.177</td>
<td>4.977</td>
<td>2.403</td>
<td>0.016</td>
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<tr>
<td>IHC</td>
<td>1.430</td>
<td>0.979</td>
<td>2.088</td>
<td>1.851</td>
<td>0.064</td>
</tr>
</tbody>
</table>

**Risk ratio and 95% CI**

- **CLARITY-TIMI 28**: Risk ratio 1.390, Lower limit 0.598, Upper limit 3.230, Z-Value 0.765, p-Value 0.444
- **EXCELSIOR**: Risk ratio 0.590, Lower limit 0.221, Upper limit 1.576, Z-Value -1.052, p-Value 0.293
- **TRITON-TIMI 38**: Risk ratio 1.530, Lower limit 1.069, Upper limit 2.189, Z-Value 2.327, p-Value 0.020
- **AFIJI**: Risk ratio 3.690, Lower limit 1.691, Upper limit 8.053, Z-Value 3.279, p-Value 0.001
- **FAST-MI**: Risk ratio 0.860, Lower limit 0.676, Upper limit 1.094, Z-Value -1.229, p-Value 0.219
- **Giusti et al.**: Risk ratio 2.360, Lower limit 1.120, Upper limit 4.971, Z-Value 2.259, p-Value 0.024
- **EHJ**: Risk ratio 1.140, Lower limit 0.826, Upper limit 1.573, Z-Value 0.798, p-Value 0.425
- **CLEAR-PLATELETS**: Risk ratio 2.420, Lower limit 1.177, Upper limit 4.977, Z-Value 2.403, p-Value 0.016
- **IHC**: Risk ratio 1.430, Lower limit 0.979, Upper limit 2.088, Z-Value 1.851, p-Value 0.064

**Meta Analysis**

**Preliminary Data**
## Stent Thrombosis

<table>
<thead>
<tr>
<th>Study name</th>
<th>Statistics for each study</th>
<th>Risk ratio and 95% CI</th>
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<tbody>
<tr>
<td></td>
<td>Risk ratio</td>
<td>Lower limit</td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>3.090</td>
<td>1.192</td>
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<tr>
<td>AFIJI</td>
<td>6.020</td>
<td>1.809</td>
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<tr>
<td>Giusti et al.</td>
<td>2.590</td>
<td>1.145</td>
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<tr>
<td>EHJ</td>
<td>3.810</td>
<td>1.449</td>
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<tr>
<td></td>
<td><strong>3.402</strong></td>
<td><strong>2.108</strong></td>
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</table>

Meta Analysis

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Preliminary Data
Pharmacogenetics

To date, the impact of CYP2C19 genotype on the pharmacokinetics of clopidogrel’s active metabolite has been evaluated in 227 subjects from 7 reported studies. Reduced CYP2C19 metabolism in intermediate and poor metabolizers decreased the $C_{\text{max}}$ and AUC of the active metabolite by 30-50% following 300- or 600 mg loading doses and 75 mg maintenance doses. Lower active metabolite exposure results in less platelet inhibition or higher residual platelet reactivity. To date, diminished antiplatelet responses to clopidogrel have been described for intermediate and poor metabolizers in 21 reported studies involving 4,520 subjects.

The association between CYP2C19 genotype and clopidogrel treatment outcome was evaluated in 2 post-hoc clinical trial analyses (substudies of CLARITY-TIMI 28$^{1}$ [n=465] and TRITON-TIMI 38$^{2}$ [n=1,477]) and 5 cohort studies (total n=6,489). In CLARITY-TIMI 28 and one of the cohort studies (n=765; Trenk$^{3}$), cardiovascular event rates did not differ significantly by genotype. In TRITON-TIMI 38 and 3 of the cohort studies (n= 3,516; Collet$^{4}$, Sibbing$^{5}$, Giusti$^{6}$), patients with an impaired metabolizer status (intermediate and poor combined) had a higher rate of cardiovascular events (death, myocardial infarction, and stroke) or stent thrombosis compared to extensive metabolizers. In the fifth cohort study (n=2,208; Simon$^{7}$), the increased event rate was observed only in poor metabolizers.

Pharmacogenetic testing can identify genotypes associated with variability in CYP2C19 activity. There may be genetic variants of other CYP450 enzymes with effects on the ability to form clopidogrel’s active metabolite.
Outline

1. Mechanism of action and clinical benefit of clopidogrel

2. Variability in response to clopidogrel

3. Clopidogrel pharmacogenetic interactions

4. Potential therapeutic options
Higher Clopidogrel Doses


Δ Aggregation (5 µM ADP-induced Aggregation) at 24 Hours

- **Resistance = 28% (300 mg)**
- **Resistance = 8% (600 mg)**
ISAR-CHOICE
Platelet Aggregation

ISAR-CHOICE 2: Doubling the Daily Dose of Clopidogrel After PCI Improves Inhibition at 30 Days

$P = 0.006$

ARMYDA-2 Trial: Primary Endpoint

255 patients with stable CAD or NSTEMI prior to PCI
13% received GP IIb/IIIa inhibitors
20% received drug-eluting stents

Randomized 4-8 Hours Pre-PCI

High Loading Dose of Clopidogrel
600 mg Pre-PCI

Standard Loading Dose of Clopidogrel
300 mg Pre-PCI

Primary composite of death, MI, or target vessel revascularization

\[ P = 0.041 \]

Plt Agg, Loading Dose, and CV Events

292 patients with NSTE ACS
Randomized to 600 mg vs. 300 mg of Clopidogrel ≥12 hrs before PCI

High post-Rx plt reactivity only independent predictor of CV events

Cuisset et al. JACC 2006;48:1339
Study Design

Patients with ACS (UA/NSTEMI or STEMI) planned for early invasive strategy, i.e. intend for PCI as early as possible within 72 hrs of randomization

- **Clopidogrel High Dose Group**
  - Clopidogrel 600mg loading dose Day 1 followed by 150mg from Day 2 to Day 7; 75mg from Day 8 to 30

- **Clopidogrel Standard Dose Group**
  - Clopidogrel 300mg (+placebo) Day 1 followed by 75mg (+placebo) from Day 2 to Day 7; 75mg from Day 8 to 30

- **ASA low dose group**
  - At least 300mg Day1; 75–100mg from D2 to D30

- **ASA high dose group**
  - At least 300mg Day1; 300mg–325mg from D2 to D30

- **ASA high dose group**
  - At least 300mg Day1; 300mg–325mg from D2 to D30
CYP2C19 and Clopidogrel Doses

Chemical structures of P2Y\textsubscript{12} Inhibitors

**Clopidogrel**

\[
\text{ClO} - \text{P} - \text{C} - \text{CH}_3
\]

**Ticagrelor**

\[
\text{HO} - \text{O} - \text{N} - \text{N} - \text{S} - \text{CF}_3
\]

**Prasugrel**

\[
\text{O} - \text{C} - \text{P} - \text{I} - \text{CH}_3
\]

**Cangrelor**

\[
\text{O} - \text{P} - \text{O} - \text{O} - \text{NO}_3
\]
Prasugrel vs. Clopidogrel: Speed of Onset and Non-responders

% IPA (20 μM ADP)

Time (Hr)

Prasugrel

Clopidogrel

Prasugrel vs. Clopidogrel

Brandt et al ACC 2005
13,608 Patients with ACS and Planned PCI Randomized to Prasugrel (60/10) vs. Clopidogrel (300/75)

**CV Death / MI / Stroke**

Prasugrel: HR 1.32 (1.03-1.68) P=0.03
Clopidogrel: HR 0.81 (0.73-0.90) P=0.0004

**TIMI Major Non-CABG Bleeds**

Prasugrel: HR 1.32 (1.03-1.68) P=0.03
Clopidogrel: HR 0.81 (0.73-0.90) P=0.0004

Wiviott SD et al. NEJM 2007;357:2001-15
In Vitro Antiplatelet Effects of Active Metabolites

Prasugrel AM (IC$_{50}$ = 26 μM)

Clopidogrel AM (IC$_{50}$ = 21 μM)

Platelet aggregation (%)

Concentration (μM)

* $P < 0.05$  ** $P < 0.01$ vs. control

Insights into Potency: Active Metabolite

Plasma Concentration (ng/ml)

Time in Hr

0 6 12 18 24

Prasugrel 60 mg
Clopidogrel 300 mg

ISTH 2005 Payne et al, P0952
Thienopyridine Metabolism

# CYP450 Genetic Variants & PK/PD

## 238 Healthy Subjects Treated with Prasugrel

### Pharmacokinetics

<table>
<thead>
<tr>
<th>Gene</th>
<th>% Difference in AUC(0-t)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-6.1</td>
<td>0.06</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-5.3</td>
<td>0.27</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>-0.4</td>
<td>0.90</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>-0.8</td>
<td>0.82</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>-3.5</td>
<td>0.47</td>
</tr>
</tbody>
</table>

### Pharmacodynamics

<table>
<thead>
<tr>
<th>Gene</th>
<th>Absolute Difference in (\Delta MPA)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>-1.3</td>
<td>0.63</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>-1.7</td>
<td>0.42</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>-0.6</td>
<td>0.65</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>1.3</td>
<td>0.38</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>-1.6</td>
<td>0.37</td>
</tr>
</tbody>
</table>

---

## CYP450 Genotypes and Efficacy

1466 Patients w/ ACS and Planned PCI Rx’d w/ Prasugrel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Carriers of Reduced Function Allele</th>
<th>Non-carriers</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2C19</td>
<td>8.5% (34/407)</td>
<td>9.8% (99/1048)</td>
<td>0.89 (0.60-1.31)</td>
<td>0.27</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>11.2% (25/234)</td>
<td>9.2% (108/1213)</td>
<td>1.20 (0.78-1.85)</td>
<td>0.58</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>11.2% (36/329)</td>
<td>8.1% (62/798)</td>
<td>1.45 (0.96-2.18)</td>
<td>0.15</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>9.3% (99/1095)</td>
<td>9.1% (14/157)</td>
<td>1.03 (0.59-1.80)</td>
<td>0.81</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>12.1% (9/75)</td>
<td>9.0% (94/1093)</td>
<td>1.42 (0.72-2.81)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

### CYP450 Genotypes and Safety

1466 Patients w/ ACS and Planned PCI Rx’d w/ Prasugrel

<table>
<thead>
<tr>
<th>Gene</th>
<th>Carriers of Reduced Function Allele</th>
<th>Non-carriers</th>
<th>Kaplan-Meier Event Rates for TIMI Major or Minor Bleeding</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CYP2C19</strong></td>
<td>4.5% (17/405)</td>
<td>3.8% (38/1047)</td>
<td>1.17 (0.66-2.07)</td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td><strong>CYP2C9</strong></td>
<td>5.5% (12/233)</td>
<td>3.7% (42/1211)</td>
<td>1.48 (0.78-2.82)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td><strong>CYP2B6</strong></td>
<td>2.3% (7/329)</td>
<td>4.2% (31/795)</td>
<td>0.55 (0.24-1.25)</td>
<td>0.15</td>
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</tr>
<tr>
<td><strong>CYP3A5</strong></td>
<td>3.7% (39/1092)</td>
<td>5.5% (8/157)</td>
<td>0.71 (0.33-1.52)</td>
<td>0.38</td>
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</tr>
<tr>
<td><strong>CYP1A2</strong></td>
<td>2.7% (2/75)</td>
<td>3.8% (39/1090)</td>
<td>0.77 (0.19-3.19)</td>
<td>0.72</td>
<td></td>
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</tbody>
</table>

**CYP2C19 & Clinical Outcomes**

1466 Patients w/ ACS and Planned PCI Rx’d w/ Prasugrel

---

**Non-carriers of a CYP2C19 reduced function allele**

- Hazard Ratio 0.89
- (95% CI 0.60-1.31)
- P=0.27

**Carriers**

- Hazard Ratio 0.58
- (95% CI 0.13-2.69)
- P=0.48

---

CLOPIDOGREL

Pharmacokinetics

Relative Percent Difference in $AUC_{0,t}$ (95% CI) in Carriers vs. Non-Carriers of a Reduced-Function CYP2C19 Allele

-32.4 0.00006

Pharmacodynamics

Absolute Difference in $\Delta MPA$ (95% CI) in Carriers vs. Non-Carriers of a Reduced-Function CYP2C19 Allele

-9.0 0.00054

Clinical Outcomes

Hazard Ratio for CV Death, MI, or Stroke (95% CI) in Carriers vs. Non-Carriers of a Reduced-Function CYP2C19 Allele

1.53 0.01

PRASUGREL

Pharmacokinetics

Relative Percent Difference in $AUC_{0,t}$ (95% CI) in Carriers vs. Non-Carriers of a Reduced-Function CYP2C19 Allele

-6.1 0.061 <0.0001

Pharmacodynamics

Absolute Difference in $\Delta MPA$ (95% CI) in Carriers vs. Non-Carriers of a Reduced-Function CYP2C19 Allele

-1.3 0.63 0.015

Clinical Outcomes

Hazard Ratio for CV Death, MI, or Stroke (95% CI) in Carriers vs. Non-Carriers of a Reduced-Function CYP2C19 Allele

0.89 0.27 0.046

Conclusions

• Clopidogrel, a P2Y$_{12}$ inhibitor, is one of the most widely prescribed drugs in the world and ↓ ischemic events and ↓↓ stent thrombosis

• Clopidogrel is a prodrug that requires biotransformation by CYP450 enzymes into an active metabolite

• ~30% of individuals harbor a reduced-function CYP2C19 allele; almost all of these are the *2 allele, which greatly ↓ function

• Carriers of a reduced-function CYP2C19 allele have lower levels of active metabolite, less platelet inhibition, and higher rates of ischemic events and stent thrombosis

• Higher doses of clopidogrel may improve platelet inhibition in carriers of reduced-function CYP2C19 alleles

• Pharmacologic and clinical efficacy of the 3$^{\text{rd}}$ generation P2Y$_{12}$ inhibitor prasugrel does not appear to be affected by common CYP450 genetic variation