CYP2C19 Genotype-Guided Escalation and De-Escalation Switching of Antiplatelet Therapy After Percutaneous Coronary Intervention in a Real-World Setting

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ANTIPLATELET THERAPY AND SWITCHING

Percutaneous Coronary Intervention (PCI) 600K per year

Dual Antiplatelet Therapy (DAPT)
Aspirin + P2Y\textsubscript{12} Inhibitor

- **Benefit**: Reduce Ischemic Events
- **Risk**: Increase Bleeding Events

P2Y\textsubscript{12} Inhibitor **Switching** After PCI is Common

De-Escalation
- Prasugrel ↔ Ticagrelor
- Clopidogrel

Escalation
CYP2C19-Mediated Activation

1 in 3 patients are 
*CYP2C19* nonfunctional allele carriers

**Genotype**
- Nonfunctional Allele Carriers
  - Any *2 or *3 allele
  - No Nonfunctional Alleles
    - *1 and *17 genotypes
- IM/PM
- Intermediate/poor metabolizer
- UM/RM/NM
- Ultrarapid/rapid/normal metabolizer

**Phenotype**
- **CYP2C19**-Mediated Activation
  - Active Metabolite
  - Platelet Activation & Aggregation

**UNC Genotype-Guided Algorithm**

- **Initial clopidogrel**
- **Order CYP2C19 genotype**
- **Result**
  - UM, RM, or NM
  - IM or PM

- **Initial prasugrel or ticagrelor**
- **CYP2C19 maintenance therapy**
- **Prasugrel or ticagrelor maintenance therapy**
- **CONTINUE**
- **DESCALE**

CPIC guidelines for CYP2C19 genotype and clopidogrel therapy
### STUDY AIMS AND METHODS

#### AIM

1. Describe **frequency and timing** of switches between P2Y\textsubscript{12} inhibitors.

2. Evaluate **impact of CYP2C19 results** on escalation and de-escalation.

3. Examine the relationship between escalation and de-escalation, CYP2C19 status, and **clinical outcomes** post-PCI.

#### METHODS

**DESIGN**

Single-center, retrospective cohort of 1,063 genotyped patients who underwent PCI and received DAPT at UNC between 2012 and 2014.

**ENDPOINT**

- **Switch**: change in P2Y\textsubscript{12} inhibitor after initial therapy.
- **Clinical Outcome**: MACCE* or clinically significant bleeding event†.

**ANALYSIS**

- **Demographic/Clinical Factors**: t-test, chi-square, or Fisher's exact test.
- **Time-to-Switch**: Wilcoxon signed rank test.
- **Time-to-Event**: Cox proportional hazards regression in patients with follow-up after PCI (N=928), following stratification by initial antiplatelet therapy and adjusting for covariates. p<0.05 significant.

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* MACCE: major adverse cardiovascular or cerebrovascular event. Composite of death, MI, stent thrombosis, hospitalization for ACS/UA, ischemic stroke, or TIA.

† Clinically significant bleeding: GUSTO moderate or severe/life-threatening
In the overall population, patients are primarily male, white, and older, with multiple comorbidities. ACS makes up over half of index PCI indication. Two-thirds of patients were initiated on clopidogrel.

* Elevated bleeding risk: composite defined as one or more of: age ≥75 yrs; wt <60 kg; hx TIA or stroke; hx significant bleeding; current end-stage renal disease requiring dialysis; or, anticoagulant prescribed at discharge.
**Maintenance Therapy Selection**

- **No Switch** (81%)
  - Continue Clopidogrel: 582 patients
  - Continue Pras/Ticag: 282 patients

- **Switch** (19%)
  - Escalation to Pras/Ticag: 115 patients
  - De-escalation to Clopidogrel: 84 patients

**Median [IQR] Time-to-Switch**
- Escalation: 4 [2-17] days
- De-escalation: 20 [2-39] days

*p=0.001

*CYP2C19*-guided switching was common, observed in approximately 1 in 5 patients. De-escalation occurred significantly later after PCI on average than escalation.
IMPACT OF CYP2C19

Switches in P2Y<sub>12</sub> Therapy by CYP2C19 Status

1. Among IM/PMs initiated on clopidogrel, 101 (51%) were escalated to prasugrel or ticagrelor.
2. Among UM/RM/NMs initiated on prasugrel/ticagrelor, 77 (33%) were de-escalated to clopidogrel.

Consistent with genotype-guided prescribing, escalations occurred almost exclusively in IM/PMs and de-escalations occurred primarily in UM/RM/NMs.
**CLINICAL OUTCOMES – INITIAL CLOPIDOGREL**

**Patients initiated on Clopidogrel**
- N=612 (66%)
  - UM / RM / NM
    - N=435 (71%)
  - IM / PM
    - N=177 (29%)

- Continued Clopidogrel
  - N=424 (69%)
- Switched to Pras/Ticag
  - N=11 (2%)*

- Continued Clopidogrel
  - N=87 (14%)
- Switched to Pras/Ticag
  - N=90 (15%)

**Cumulative event rate (%)**
- Log-rank (unadjusted): P=0.007
  - Clop - IM/PM
  - Clop - U/R/NM
  - Alt - IM/PM (escalation)

*Due to rare occurrence, UM/RM/NMs escalated to prasugrel or ticagrelor were not included in the analysis.*
**CLINICAL OUTCOMES – INITIAL PRAS/ TICAG**

**Patients initiated on Pras/Ticag**
N=316 (34%)

- UM / RM / NM N=200 (63%)
- IM / PM N=116 (37%)

- **Switched to Clopidogrel**
  N=69 (22%)
  - Clop - U/R/NM (de-escalation)
  - Alt - U/R/NM

- **Continued Pras/Ticag**
  N=131 (42%)
  - Switched to Clopidogrel
    N=4 (1%)*
  - Continued Pras/Ticag
    N=127 (39%)
  - Alt - IPM/PM

<table>
<thead>
<tr>
<th>Group</th>
<th>Events No. (%)</th>
<th>Event Rate (per 100 pt- yrs)</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clop- U/R/NM</td>
<td>10 (15%)</td>
<td>21</td>
<td>1.1 (0.5 - 2.3)</td>
<td>0.75</td>
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<tr>
<td>Alt- U/R/NM</td>
<td>17 (13%)</td>
<td>20</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Alt- IM/PM</td>
<td>13 (12%)</td>
<td>18</td>
<td>Reference</td>
<td></td>
</tr>
</tbody>
</table>

*Due to rare occurrence, IMs de-escalated to clopidogrel were not included in the analysis.*
SUMMARY AND CLINICAL PERSPECTIVE

• FREQUENCY: *CYP2C19*-guided switching was common, observed in approximately 1 in 5 patients

• IMPACT OF GENOTYPE & TIMING: escalation primarily in *CYP2C19* nonfunctional allele carriers (88%), while de-escalation significantly later and primarily in patients without a nonfunctional allele (92%)

1. genotype-guided escalation to prasugrel or ticagrelor mitigates the risk of adverse cardiovascular outcomes conferred by clopidogrel use in *CYP2C19* nonfunctional allele carriers

2. use of genotype to selectively guide de-escalation to clopidogrel in patients without a *CYP2C19* nonfunctional allele appeared safe and effective