Pharmacodynamic Responses of Low Dose New P2Y12 Inhibitor in Korean

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1. PD of Low LD of Prasugrel *in Healthy Volunteer*
2. PD of Low vs High LD of Prasugrel *in CAD Patients*
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4. PD of Re-Loading of Prasugrel *in CAD Patients*
5. Low Dose (Single dose) of Ticagrelor Loading and Maintenance *in Healthy Volunteer*
6. Standard Dose of Prasugrel and Ticagrelor Loading *in STEMI Patients*
Clopidogrel vs. Prasugrel: Pharmacokinetics and Pharmacodynamics

TRITON-TIMI 38 Study
Prasugrel vs. Clopidogrel

TIMI Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel</th>
<th>Clopidogrel</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG</td>
<td>2.4%</td>
<td>1.8%</td>
<td>0.03</td>
</tr>
<tr>
<td>Major or Minor</td>
<td>4.0%</td>
<td>3.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG-related</td>
<td>13.4%</td>
<td>3.2%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

HR 0.81 (0.73-0.90)
P < 0.001

HR 1.32 (1.03-1.68)
P = 0.03

Consensus on the Definition of HPR and LPR

Old age, anemia, chronic renal failure, low BMI, DM, prior bleeding, triple antithrombotic therapy, ticagrelor or prasugrel therapy

Old age, anemia, Chronic renal failure, high BMI, DM, cardiac marker elevation, prior ACS, ST and CABG

Ethnic Difference of Prasugrel Loading

A

Prasugrel 60 mg LD

AM Concentration (ng/mL)

0.0 0.5 1.0 2.0 4.0

- Caucasian
- Japanese
- Chinese
- Korean

Low Dose Prasugrel and Clopidogrel mg in Japanese

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Healthy Volunteer

Screened subjects (n = 22)

- Refusal of consent (n = 2)
- Exclusion
  - Abnormal platelet function (n = 7)
  - Abnormal liver function (n = 1)

Enrolled subjects (n = 12)

- Pra-G
  - Prasugrel 30 mg (n = 6)
- Clo-G
  - Clopidogrel 600 mg (n = 6)

2 weeks washout period

- Prasugrel 30 mg (n = 6)
- Clopidogrel 600 mg (n = 6)

Platelet function test: Baseline 0.5, 2, 6, 24 hours

Clopidogrel 600mg vs Prasugrel 30mg Loading in Heathy Volunteer

- Graph 1: Inhibition of Platelet Aggregation (%)
- Graph 2: % Inhibition by VerifyNow
- Graph 3: % Inhibition by MEA

1. PD of Low LD of Prasugrel in Healthy Volunteer
2. **PD of Low vs High LD of Prasugrel in Suspected CAD Patients**
3. PD of Low MD Prasugrel *in CAD Patients*
4. PD of Re-Loading of Prasugrel *in CAD Patients*
5. Low Dose (Single dose) of Ticagrelor Loading and Maintenance *in Healthy Volunteer*
6. Standard Dose of Prasugrel and Ticagrelor Loading *in STEMI Patients*
* Suspected CAD patients

- Baseline PLT Function Test
  - Clopidogrel 600mg (n=8)
  - Prasugrel 30mg (n=9)
  - Prasugrel 60mg (n=9)

- PLT Function Test (post CAG or PCI)

* Platelet Function Measurement
  - light transmission aggregometry, VerifyNow, multiple electrode aggregometry
Methods – Time of Platelet Function Measurement

- Clopidogrel 600 mg
- Prasugrel 60 mg
- Prasugrel 30 mg

Time (hours)
Results

Mean Platelet Activity ±SD at Peak by LTA, VerifyNow and MEA

Lee DH et al. Korean Circ J. 2014;44:386-393
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Platelet Function Measurement:
light transmission aggregometry, VerifyNow, multiple electrode aggregometry.

Suspected CAD patients

MD of antiplatelet therapy (> 1 month)

Clopidogrel 75mg (n=34)  Prasugrel 10mg (n=34)  Prasugrel 5mg (n=34)

PLT Function Test (Maintenance treatment phase)
HPR by LTA(55) and MEA(46.8)
HPR by VerifyNow(208 and 240)

- Clopidogrel
- Prasugrel 5mg
- Prasugrel 10mg

Statistical significance:
- $p < 0.001$
- $p = 0.014$
LPR by VerifyNow(85) and MEA(19)

VerifyNow

MEA
Consensus on the Definition of HPR and LPR

Optimal Platelet Reactivity

MEA (19-46.8) and LTA (12-55)
Optimal Platelet Reactivity

VerifyNow (85 vs. 208 or 235)
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Comparison of prasugrel and clopidogrel reloading on high platelet reactivity in clopidogrel-loaded patients undergoing percutaneous coronary intervention (PRAISE-HPR): a study protocol for a prospective randomized controlled clinical trial

Dong-Hyun Lee¹, Moo Hyun Kim¹,², Tae-Ho Park¹, Jong Sung Park¹, Kyungil Park Jeong-Min Seo¹ and Michael S Lee³

PRAISE-HPR Study
NCT01609647
Mean Platelet Activity ±SD by VerifyNow at screening, post-PCI and 30 days
% Change in platelet reactivity during study course by VerifyNow
Primary Endpoint: The percentage of HPR and LPR at post-PCI

- **post-HPR**
  - Prasugrel: 30%
  - Clopidogrel: 32%
  - *p* = 0.002

- **post-LPR**
  - Prasugrel: 45%
  - Clopidogrel: 7%
  - *p* = 0.002

Legend:
- Prasugrel
- Clopidogrel
The percentage of HPR and LPR at 30 days

- **HPR at 30 days**: p = 0.149
- **LPR at 30 days**: p = 0.199

![Bar chart showing the percentage of HPR and LPR at 30 days for prasugrel and clopidogrel.](chart_image)
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Study design overview

Screened subjects (n=19)

Refusal of consent (n=2)

Exclusion Abnormal platelet function (n=5)

Enrolled subjects (n=12)

Tic-G
Ticagrelor 90mg LD, followed by 90mg MD daily for 5 days (n=6)

Clo-G
Clopidogrel 600mg LD, followed by 75mg MD daily for 5 days (n=6)

2 weeks washout period

Ticagrelor 90mg LD, followed by 90mg MD daily for 5 days (n=6)

Clopidogrel 600mg LD, followed by 75mg MD daily for 5 days (n=6)

Platelet function test: Baseline 0.5, 2, 6, 24, 26, 120, 122 hours
Lose Dose (Single Daily Dose) of Ticagrelor

The individual platelet function test values at variable time points

Lose Dose (Single Daily Dose) of Ticagrelor

Mean inhibition of platelet aggregation after LD and MD of ticagrelor or clopidogrel

Lose Dose (Single Daily Dose) of Ticagrelor

The percentage of HPR at different time points in the ticagrelor and clopidogrel groups

The percentage of LPR at different time points in the ticagrelor and clopidogrel groups

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Comparison of Prasugrel and Ticagrelor Antiplatelet Effects in Korean Patients Presenting with ST-segment Elevation Myocardial Infarction - PANTASTIC Trial

Cai De Jin, Moo Hyun Kim, Long Zhe Guo, Young-Rak Cho, Kyungil Park, Jong-Sung Park, Tea-Ho Park, Young-Dae Kim

Department of Cardiology
Regional Clinical Trial Center
College of Medicine, Dong-A University
STEMI patients undergoing primary PCI

Current therapy with antiplatelet agents

No

Randomized
(n=60)

Prasugrel 60mg LD (n=30)

Ticagrelor 180mg LD (n=30)

PRU & VASP index at baseline

MD:10mg/day * 30 days

Primary endpoint: incidence of HPR at 48 ± 12 hours after LD

MD:90mg bid *30 days

Clinical follow-up: In-hospital & 30 day ischemic events and bleeding (BARC ≥ 3) events
Platelet reactivity values assessed by VerifyNow (a) and VASP (b) at baseline and 48 hours after loading dose.
Stable patients with history of MI 1-3 yrs prior + ≥1 additional atherothrombosis risk factor*

RANDOMIZE DOUBLE BLIND

Ticagrelor 90mg bid

Ticagrelor 60mg bid

Placebo

Follow-up Visits Q4 mos for 1st yr, then Q6 mos,

Min 12 months of Follow Up Event-driven trial

Primary Efficacy Endpoint: CV Death, MI, or Stroke
Primary Safety Endpoint: TIMI Major Bleeding

*N~21,000

*Age ≥65 yrs, diabetes, 2nd prior MI, multivessel CAD, or chronic non-end stage renal dysfunction

Study Schema for PEGASUS-TIMI 54. CAD, Coronary artery disease; MI, myocardial infarction.
Our study suggests that compared to the high dose of prasugrel and ticagrelor, the pharmacodynamics effect of low loading and maintenance dose may be a better option in East-Asian CAD patients.
Thank You