Potent Platelet Inhibition in Korean AMI Patients
The Korean Society of Cardiology
COI Disclosure

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The authors have no financial conflicts of interest to disclose concerning the presentation
P2Y$_{12}$ inhibitors in real clinical practices

In the U.S.
- Clopidogrel, 72% (n = 46,864)
- Prasugrel, 20% (n = 12,596)
- Ticagrelor, 8% (n = 5,140)

In Korea

![Graph showing the distribution of P2Y$_{12}$ inhibitors in Korea]
Treatment Paradox of Potent P2Y$_{12}$ inhibitors in “Real Clinical Practice”

In a real-world practice, there was an underutilization of potent P2Y$_{12}$ inhibitors which was more pronounced in higher-risk subsets.
Ethnic Differences of Ticagrelor

33% ~ 48% higher plasma concentration in Japanese compared with Caucasian.
After adjusting body weight, 20% of difference still persists.
Ticagrelor 90mg vs. 60mg in PEGASUS

Ticagrelor 60mg bid achieved similar PD efficacy despite lower plasma concentration vs. Ticagrelor 90mg bid.
Bleeding Risks Associated With P2Y$_{12}$ Inhibitors

Higher Platelet Inhibition = Higher Bleeding Risks
### Factors related to ischemic/bleeding risks

<table>
<thead>
<tr>
<th>Increased ischemic/ST risks</th>
<th>Increased Bleeding risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased ischemic risk</strong></td>
<td>History of prior bleeding</td>
</tr>
<tr>
<td>ACS</td>
<td>OAC</td>
</tr>
<tr>
<td>Multiple prior MIs</td>
<td>Female</td>
</tr>
<tr>
<td>Extensive CAD</td>
<td><strong>Advanced age</strong></td>
</tr>
<tr>
<td>DM</td>
<td>Low body weight</td>
</tr>
<tr>
<td>CKD</td>
<td><strong>Advanced age</strong></td>
</tr>
<tr>
<td><strong>Increased risk of ST</strong></td>
<td>CKD</td>
</tr>
<tr>
<td>ACS</td>
<td>DM</td>
</tr>
<tr>
<td>DM</td>
<td>Anemia</td>
</tr>
<tr>
<td>LVEF &lt;40%</td>
<td>Chronic steroid or NSAIDs</td>
</tr>
<tr>
<td>1G DES</td>
<td></td>
</tr>
<tr>
<td>Stent under-sizing/under-deployment</td>
<td></td>
</tr>
<tr>
<td>Small stent diameter</td>
<td></td>
</tr>
<tr>
<td>Greater stent length</td>
<td></td>
</tr>
<tr>
<td>Bifurcation stent</td>
<td></td>
</tr>
<tr>
<td>ISR</td>
<td></td>
</tr>
</tbody>
</table>

**High ischemic risk = High bleeding risk**
Impact of MI vs. Bleeding on mortality

<table>
<thead>
<tr>
<th>MI versus Bleeding</th>
<th>Adjusted Hazard Ratios</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MI vs. Minor Bleeding</strong></td>
<td>5.36/1.70</td>
<td>0.001</td>
</tr>
<tr>
<td><em>(BARC 2)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MI vs. Major Bleeding</strong></td>
<td>5.36/5.73</td>
<td>0.747</td>
</tr>
<tr>
<td><em>(BARC 3)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MI vs. Major Bleeding</strong></td>
<td>6.15/2.77</td>
<td>0.001</td>
</tr>
<tr>
<td><em>(BARC 3a)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MI vs. Major Bleeding</strong></td>
<td>6.15/4.51</td>
<td>0.242</td>
</tr>
<tr>
<td><em>(BARC 3b)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MI vs. Major Bleeding</strong></td>
<td>6.15/28.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><em>(BARC 3c)</em></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MI**

= BARC 3b
= TIMI Major
= GUSTO severe
= PLATO Major
# Temporal Trends in the Incidence and In-Hospital Mortality of AMI in Western and Asian Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Period</th>
<th>Gender</th>
<th>Incidence</th>
<th>In-hospital Mortality</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>1987 – 2008</td>
<td>Male (White)</td>
<td>-4.3%/year</td>
<td>-3.5%/year</td>
<td>Circulation 2012;125:1848-57</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female (White)</td>
<td>-3.8%/year</td>
<td>-3.0%/year</td>
<td>N Engl J Med 2010;362:2155-65</td>
</tr>
<tr>
<td>USA</td>
<td>1999 – 2008</td>
<td>Overall</td>
<td>274 → 208*</td>
<td>10.5% → 7.8%</td>
<td>BMJ 2012;344: e356</td>
</tr>
<tr>
<td>Denmark</td>
<td>1984 – 2008</td>
<td>Male</td>
<td>410 → 213*</td>
<td>31.4% → 14.8%</td>
<td>Heart 2015; 101:1413-21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>209 → 131*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Six EU countries</td>
<td>1985 – 2010</td>
<td>Male</td>
<td>-4.0%/year</td>
<td>-6.0%/year</td>
<td>J Am Heart Assoc 2014;3: e001066</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>-4.2%/year</td>
<td>-6.3%/year</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>1999 – 2008</td>
<td>Male</td>
<td>41.8 → 62.5*</td>
<td>20% → 8%</td>
<td>Circ J 2010;74: 93-100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>13.5 → 26.0*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>1979 – 2008</td>
<td>Male</td>
<td>18.7 → 46.4*</td>
<td>21.4% → 6.3%</td>
<td>Circ J 2017;81:520-8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>4.2 → 9.6*</td>
<td>19.4% → 12.2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>17.7 → 12.2*</td>
<td>9.1% → 9.9%</td>
<td></td>
</tr>
<tr>
<td>Korea</td>
<td>2006 – 2010</td>
<td>Male</td>
<td>60.1 → 40.9*</td>
<td>15.2% → 12.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td>3.16 → 17.6*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CHF After AMI: a Lost Battle

In-hospital (fully colored bars) and Post-AMI discharge (light-colored bars) heart failure

1 year mortality
How to Prevent CHF after AMI

Infarction

Wound Healing

Infarct Expansion & Pathologic remodeling
Platelet Inhibition and LV Remodeling

A

Rupture incidence (%)

50 40 30 20 10 0

Infarct Size (%)

60

Untreated, n=52

Clo-H, n=39

Clo-L, n=16

PD, n=20

Drug delivery

0 1 2 3 4 5 6 7

Days after infarction

B

LVDd (mm)

5.5

4.5

Untreated

Clopidogrel

P<0.05

Baseline

1wk

2wk

4wk

LV Area (cm²)

2.0

1.5

Baseline

wk-2

wk-2

P<0.05

Novel role of platelet reactivity in adverse left ventricular remodelling after ST-segment elevation myocardial infarction: The REMODELING Trial

Primary Endpoint:
✓ the prevalence of LVR in relation to quartile distribution of platelet reactivity measured by PRU.

Secondary Endpoints:
1) the correlation between prevalence of LVR and inflammatory marker indicated by hs-CRP;
2) the determinants of adverse LVR; and
3) performance of different models associated with LVR.
Prevalence of LV Remodeling

**A. PRU criteria**

- 1st quartile (29 - 177): 10.8%
- 2nd quartile (178 - 236): 23.1%
- 3rd quartile (237 - 293): 27.0%
- 4th quartile (294 - ): 35.1%

*p for trend = 0.015*

**B. hs-CRP criteria**

- 1st quartile (0.1 - 0.5): 12.5%
- 2nd quartile (0.6 - 1.1): 16.7%
- 3rd quartile (1.2 - 3.0): 35.1%
- 4th quartile (3.1 - ): 32.4%

*p for trend = 0.012*
# Predictors of LV Remodeling

<table>
<thead>
<tr>
<th>Predictors</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>1.93 (0.61 – 6.10)</td>
<td>0.517</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>5.15 (0.99 – 26.82)</td>
<td>0.052</td>
</tr>
<tr>
<td>PRU ≥ 248</td>
<td>3.15 (1.13 – 8.78)</td>
<td>0.028</td>
</tr>
<tr>
<td>hs-CRP ≥ 1.4 mg/L</td>
<td>7.12 (2.27 – 22.37)</td>
<td>0.001</td>
</tr>
<tr>
<td>Infarction size (CK AUC ≥ 80 kU/l)</td>
<td>15.03 (3.83 – 59.01)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>E/e' ≥ 15</td>
<td>1.08 (0.55 – 7.17)</td>
<td>0.298</td>
</tr>
<tr>
<td>LVEDVI ≤ 50 mL/m²</td>
<td>5.67 (1.57 – 20.42)</td>
<td>0.008</td>
</tr>
<tr>
<td>LVESVI ≥ 20 mL/m²</td>
<td>7.21 (1.70 – 30.61)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

### Predictors OR (95% CI) P

- **Female**
  - OR: 1.86 (0.58 – 5.95)
  - P: 0.296

- **Chronic kidney disease**
  - OR: 4.61 (0.91 – 23.20)
  - P: 0.064

- **PRU < 248 and hs-CRP < 1.4 mg/L vs.**
  - **PRU ≥ 248 and hs-CRP < 1.4 mg/L**
    - OR: 7.59 (1.67 – 34.44)
    - P: 0.009
  - **PRU < 248 and hs-CRP ≥ 1.4 mg/L**
    - OR: 17.95 (3.44 – 93.81)
    - P: 0.001
  - **PRU ≥ 248 and hs-CRP ≥ 1.4 mg/L**
    - OR: 21.49 (4.56 – 101.30)
    - P: < 0.001

- **Infarction size (CK AUC ≥ 80 kU/l)**
  - OR: 17.63 (4.11 – 75.65)
  - P: < 0.001

- **E/e' ≥ 15**
  - OR: 2.65 (0.57 – 7.39)
  - P: 0.271

- **LVEDVI ≤ 50 mL/m²**
  - OR: 5.23 (1.42 – 19.33)
  - P: 0.013

- **LVESVI ≥ 20 mL/m²**
  - OR: 9.90 (2.04 – 47.55)
  - P: 0.004
Myocardial Damage vs. Healing

![Graph showing sensitivity vs. 100-specificity for different models: Myocardial damage, Myocardial healing, and Combined.]

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial-damage model</td>
<td>0.796</td>
<td>0.723 – 0.857</td>
<td>Reference value</td>
</tr>
<tr>
<td>(LVEDVI ≤ 50 mL/m², LVESVI ≤ 20 mL/m², CK AUC ≥ 80 kU*h/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial-healing model</td>
<td>0.704</td>
<td>0.625 – 0.776</td>
<td>0.213*</td>
</tr>
<tr>
<td>(PRU ≥ 248, hs-CRP ≥ 1.4 mg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined model</td>
<td>0.874</td>
<td>0.810 – 0.922</td>
<td>0.015**/0.002†</td>
</tr>
<tr>
<td>(Myocardial-damage model + myocardial-healing model)</td>
<td></td>
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</tr>
</tbody>
</table>
Ticagrelor Versus Clopidogrel in Left Ventricular Remodeling After ST-segment Elevation Myocardial Infarction (HEALING-AMI)

This study is currently recruiting participants. (see Contacts and Locations)

Verified November 2016 by Gyeongsang National University Hospital

Sponsor:
Gyeongsang National University Hospital

Collaborators:
Chinese PLA General Hospital
Chungnam National University Hospital
Pusan National University Yangsan Hospital
National University Heart Centre, Singapore
Ulsan University Hospital
Kyungpook National University
Samsung Changwon Hospital
Kyunghee University Medical Center
Chungbuk National University Hospital
Chonnam National University Hospital
Seoul National University Bundang Hospital

Information provided by (Responsible Party):
Yongwi Park, Gyeongsang National University Hospital

ClinicalTrials.gov Identifier:
NCT02224534

First received: August 20, 2014
Last updated: November 14, 2016
Last verified: November 2016

History of Changes
Summary of the REMODELING study

- Enhanced levels of platelet activation and inflammation determined the incidence of adverse LV expansion after STEMI.

- Combining the measurements of these risk factors increased risk stratification of LVR.

- The role of intensified antiplatelet therapy in wound healing of infarcted myocardium is under investigation in the HEALING-AMI trial.
PCI in Patients at Hypercoagulable Condition

Platelet Rich vs. Fibrin Rich

Arterial Thrombosis ➔ Antiplatelet
Venous Thrombosis ➔ Anticoagulation

Atrial Fibrillation ➔ Arterial + Venous Thrombosis ➔ Antiplatelet + Anticoagulant
Risk of Bleeding With Single, Dual, or Triple Therapy

Bleeding Risk Reduction
1. OAC → NOAC
2. Anticoagulant + Single antiplatelet agent
3. Lower dose NOAC
Cross-talk Between Platelet Activation and Coagulation in AF

A (%)

- Low CHA₂DS₂-VASc score (≤2)
- High CHA₂DS₂-VASc score (>2)

- ADP
- TRAP
- Coll
- AA

B

- vWF:Ag (IU/dL)
- Fib (mg/dL)
- hs-CRP (μg/dL)
- D-dimer (ng/mL)

r = 0.322, p = 0.012
r = 0.393, p = 0.008
r = 0.088, p = 0.502
r = 0.081, p = 0.540

Omission of ASA: WOEST

- Triple therapy group vs Double therapy group
  - Days 0 to 365
  - Cumulative incidence of bleeding
  - P < 0.001
  - HR = 0.36, 95% CI [0.26-0.50]

- Cumulative incidence
  - P = 0.025
  - HR = 0.60, 95% CI [0.38-0.94]
Antithrombotic Therapy in MI Patients

AF patient in need of OAC after elective PCI with stent

Bleeding risk low compared to risk for ACS or stent thrombosis

Bleeding risk high compared to risk for ACS or stent thrombosis

Time from PCI

0
1 month
3 months
6 months
12 months
lifelong

Triple therapy (IIaB)

Dual therapy (IIaC)

OAC monotherapy (IB)

OAC monotherapy (IB)

Ischemic Risk?

OAC

Aspirin 75–100 mg daily

Clopidogrel 75 mg daily
PIONEER AF-PCI

Safety Endpoint

Efficacy Endpoint

Group 1: Rivaroxaban 15 (10) mg qd + Clopidogrel/Ticagrelor/Prasugrel for 12 months

Group 2: Rivaroxaban 2.5 mg bid + DAPT for 1, 6, or 12 months → Rivaroxaban 15 (10) mg qd + ASA for the remain

Group 3: OAC + DAPT for 1, 6, 12 months → OAC + ASA for the remain

Gyeongsang National University Changwon Hospital

GEMINI-ACS-1

- ACS Event
- STEMI*
- Non-STEMI
- UA

- At least 48 hours†
- Up to 10 days

- Rivaroxaban 2.5mg bid
  + pre-randomization P2Y12 inhibitor**

- ASA 100mg
  + pre-randomization P2Y12 inhibitor**

- 5.5 days (3.4, 7.6)

- ≥6 months duration of therapy

- 291 days (284,354)

* capped at 50%
† 24 hours if no PCI

** Ticagrelor 90mg bid or Clopidogrel 75mg daily
GEMINI-ACS-1

**Safety Endpoint**

HR = 1.09 (95% CI 0.80-1.50); P = 0.5840

**Efficacy Endpoint**

HR = 1.06 (95% CI 0.77-1.46); P = 0.7316

Lancet. 2017 Mar 17. e-pub, ASA Rivaroxaban
GEMINI-ACS-1: Analysis by P2Y\textsubscript{12} Strata

**Safety Endpoint**

**Efficacy Endpoint**

- Ticagrelor + ASA = 3.9%;
- Ticagrelor + Rivaroxaban = 4.7%;
- Clopidogrel + Rivaroxaban = 5.4%; and
- Clopidogrel + ASA = 5.9%
GEMINI-ACS-1: 30-day Landmark Analysis

Efficacy Endpoint
Summary

1. Potent platelet inhibitors are underutilized in Korean MI patients.
2. This may be mainly due to the fear of the inherent bleeding risk by potent platelet inhibition.
3. Korean MI patients have a similar in-hospital mortality with Western patients, which underlines more wide acceptance of potent P2Y$_{12}$ inhibitors.
4. Enhanced platelet inhibition may prevent the development of heart failure after MI.
5. Low dose rivaroxaban with a P2Y$_{12}$ inhibitor may be a possible option for MI patients at hypercoagulable state.
6. Potent platelet inhibition definitely reduced a ischemic risk and increased a bleeding risk in MI patients.
Conclusion

• Historical clopidogrel based DAPT may be a decent antiplatelet agent, but high proportion of Korean MI patients need a better antiplatelet care.
감사합니다