“East-Asian Paradox”
De-Escalation Strategy of Ticagrelor

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Disclosure Statement of Financial Interest

- Research funding from Chong Kun Dang pharmaceutical Corp, AstraZeneca, Accumetrics, Daiichi Sankyo.
Contemporary P2Y12 Inhibitors

P2Y<sub>12</sub> inhibitors
- clopidogrel
- prasugrel
- ticagrelor

Diagram showing the inhibition of platelet aggregation with COX-1 inhibitors (aspirin) and various P2Y<sub>12</sub> inhibitors.
Fatal Case Series

74/F, ACS, PCI
Extensive subdural hemorrhage after ticagrelor use ➔ Expired

74/M, ACS, PCI
Acute ICH, pons after ticagrelor use ➔ Expired

70/M, ACS, PCI
Multiple SDH after ticagrelor use ➔ Vegetative state
Current European and US guidelines recommend that use of ticagrelor or prasugrel in preference to clopidogrel is reasonable for ACS patients with or without PCI.

However, several studies suggested that East Asian patients had differential ischemic and bleeding propensity in response to antithrombotic treatment compared with Western patients (the so-called ‘East Asian paradox’).
Optimal Antiplatelet Therapy: Ethnic Difference

Does one size fit all?
“East-Asian Paradox”

EXPERT CONSENSUS DOCUMENT

World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI

Glenn N. Levine, Young-Hoon Jeong, Shinya Goto, Jeffrey L. Anderson, Yong Huo, Jessica L. Mega, Kathryn Taubert and Sidney C. Smith Jr

Abstract | Guideline recommendations on the use of dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes and in those undergoing percutaneous coronary intervention (PCI) have been formulated by both the ACC/AHA and the ESC. These recommendations are based primarily on large, phase III, randomized, controlled trials of the P2Y$_{12}$ inhibitors clopidogrel, prasugrel, and ticagrelor. However, few East Asian patients have been included in the trials to assess the use of these agents, particularly the newer agents prasugrel and ticagrelor. Additionally, an increasing body of data suggests that East Asian patients have differing risk profiles for both thrombophilia and bleeding compared with white patients, and that a different ‘therapeutic window’ of on-treatment platelet reactivity might be appropriate in East Asian patients. Furthermore, a phenomenon referred to as the ‘East Asian paradox’ has been described, in which East Asian patients have a similar or even a lower rate of ischaemic events after PCI compared with white patients, despite a higher level of platelet reactivity during DAPT. Recognizing these concerns, the World Heart Federation has undertaken this evidence-based review and produced this expert consensus statement to determine the antiplatelet treatment strategies that are most appropriate for East Asian patients.
East-Asian Paradox

Which Dose Is Optimal for East-Asian Patients?

Figure 2 | Postulated differences in the optimal ‘therapeutic window’ of platelet reactivity between white and East Asian populations.
Clinical Phenotype of “East-Asian Paradox”
What It Is?

The ‘East Asian paradox’ describes a phenomenon in which, despite a higher level of platelet reactivity in response to antiplatelet therapy, East Asian patients have a similar or even lower rate of ischemic events and a higher rate of bleeding events after ACS or PCI compared with white patients.

Always “Under-Report of Events” critics from many, many reviewers for our submitted papers
Plausible Mechanisms of “East-Asian Paradox”

- A genetic differences in metabolic or pharmacodynamic features:
  - genetic polymorphisms (ie, CYP2C19 LOF alleles, factor V Leiden [G1691A] and prothrombin [G20210A] gene mutations),
  - plasma hemostatic factors (ie, fibrinogen, d-dimer, and factor VIII),
  - endothelial activation markers (ie, von Willebrand factor, intercellular adhesion molecule 1, and E-selectin)
- A relatively small body size and lower renal clearance in Asian patients
- Thus, the relative tradeoff “sweet spot” between ischemia & bleeding may be different
Clinical Evidences and Experiences of P2Y12 Inhibitors in East Asian Patients
This Hypothesis Was Realized in the Japanese Drug-Approval Trials

1. PRASFIT-ACS trials suggested the efficacy and safety profile of 20 mg loading and 3.75 mg maintenance dose of prasugrel (around 1/3 of US dose)

2. PHILO trial suggested ticagrelor (180 mg loading dose plus 90 mg twice daily maintenance dose) may be harmful for especially Japanese patients.

Primary Endpoint of PRASFIT-ACS and TRITON-TIMI 38

**PRASFIT-ACS**

- HR: 0.77, 95% CI [0.56-1.07]
- P-value: 0.12
- Follow-up: 24 weeks

- Prasugrel 20/3.75 mg (n = 685)
- Clopidogrel 300/75 mg (n = 678)

**TRITON-TIMI 38**

- HR: 0.81, 95% CI [0.73-0.90]
- P-value: < 0.001
- Follow-up: 15 months

- Prasugrel 60/10 mg (n = 6813)
- Clopidogrel 300/75 mg (n = 6795)

Cumulative incidence of MACE (%)
Non-CABG TIMI-Major Bleeding Events of PRASFIT-ACS and TRITON-TIMI 38

**PRASFIT-ACS**

- **Prasugrel 20/3.75 mg (n = 685)**
  - Incidence: 1.9%

- **Clopidogrel 300/75 mg (n = 678)**
  - Incidence: 2.2%

HR: 0.82, 95% CI [0.39-1.73]
P-value: 0.38
Follow-up: 48 weeks

**TRITON-TIMI 38**

- **Prasugrel 60/10 mg (n = 6813)**
  - Incidence: 2.2%

- **Clopidogrel 300/75 mg (n = 6795)**
  - Incidence: 1.7%

HR: 1.32, 95% CI [1.03-1.68]
P-value: 0.03
Follow-up: 15 months

Based on Safety Analysis Set
Incidence: (n / n) x 100%
PHILO trial with ticagrelor

- PHILO was designed to explore the consistency of the effects of ticagrelor in PLATO patients with patients from East Asian countries.

<table>
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<th>Clopidogrel</th>
<th>OR (95%CI)</th>
<th>P-value</th>
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<tr>
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<td>Composite end point</td>
<td>43</td>
<td>28</td>
<td>1.60(0.97–2.62)</td>
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<tr>
<td>Death</td>
<td>10</td>
<td>7</td>
<td>1.44(0.54–4.25)</td>
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<tr>
<td>Stroke</td>
<td>9</td>
<td>6</td>
<td>1.51(0.54–4.25)</td>
<td>0.60</td>
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<tr>
<td>MI</td>
<td>24</td>
<td>15</td>
<td>1.63(0.85–3.15)</td>
<td>0.19</td>
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<tr>
<td>Bleeding*</td>
<td>92</td>
<td>56</td>
<td>1.83(1.27–2.63)</td>
<td>0.001</td>
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<tr>
<td>Net clinical Benefit**</td>
<td>76</td>
<td>51</td>
<td>1.6(1.09–2.35)</td>
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MI (excluding silent), * PLATO defined, ** PLATO defined as CV death, MI, stroke, or CABG related or non CABG related major bleeding.
Patient Level Meta-Analysis (7 RCTs)

7 Randomized Clinical Trials

- **DES LATE**: 12m (n=2514) vs. 24m (n=2531)
- **EXCELLENT**: 6m (n=722) vs. 12m (n=721)
- **ITALIC**: 6m (n=953) vs. 24m (n=941)
- **OPTIMIZE**: 3m (n=1563) vs. 12m (n=1556)
- **PRODIGY**: 6m (n=751) vs. 24m (n=750)
- **RESET**: 3m (n=1059) vs. 12m (n=1058)
- **SECURITY**: 6m (n=682) vs. 12m (n=717)

Asian: n=8605
- Long duration DAPT n=4310
- Short duration DAPT n=4295

Non-Asian: n=7913
- Long duration DAPT n=3964
- Short duration DAPT n=3949

Individual patient data analysis

Courtesy by Dr. Park KW. submitted
Disparity in ischemia and bleeding risk (according to ethnicity)

A. Ischemic outcomes

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<th>Non-Asian</th>
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<td>6615</td>
<td>4671</td>
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<tr>
<td>400</td>
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HR 0.480, 95% CI 0.343-0.672, p<0.001
Log rank p<0.001

B. Bleeding outcomes

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HR 2.077, 95% CI 1.183-3.646, p=0.011
Log rank p=0.009
A Randomized Double-Blind Trial Evaluating Platelet Inhibition with Low-Dose Ticagrelor versus Standard-Dose Ticagrelor and Clopidogrel in Acute Coronary Syndromes: The OPTIMA Trial

Patients with ACS (Unstable Angina or NSTEMI) (N=60)

Stratified by
(1) clinical indication (UA vs. AMI)

- Low-dose Ticagrelor
  (LD 120mg, MD: 60mg bid)
  (N=20)

- Standard-dose Ticagrelor
  (LD 180mg, MD: 90mg bid)
  (N=20)

- Standard-dose clopidogrel
  (LD 600mg, MD: 75mg qd)
  (N=20)

- Platelet reactivity with the VerifyNow P2Y12 assay and the Multiplate Analyzer at 0, 0.5, 1, 2, 4, 8, 24h and 30d.

- PK sampling at 0, 0.5, 1, 2, 4, 8 and 10h on days 1.

- Clinical follow-up assessment at in-hospital, at discharge, and at 30 days

**Primary end point: PRU at 8hrs after loading and at 30 days during maintenance**

233 ACS patients assessed for eligibility

- 35 Already taking P2Y12 receptor antagonist
- 31 No obstructive CAD
- 50 Having at least one exclusion criteria
- 52 Declined to participate

65 ACS patients underwent randomisation

- 22 Randomised to receive low-dose ticagrelor
  - 22 Included in the primary analysis (≥1 follow-up sample)
  - 22 Completed blood sampling at 30-day time point
  - 1 Discontinued study drug

- 22 Randomised to receive standard-dose ticagrelor
  - 22 Included in the primary analysis (≥1 follow-up sample)
  - 21 Completed blood sampling at 30-day time point

- 21 Randomised to receive clopidogrel
  - 21 Included in the primary analysis (≥1 follow-up sample)
  - 20 Completed blood sampling at 30-day time point
  - 1 Withdrew consent

Primary Endpoint: P2Y12 - PRU

P2Y12 - % Inhibition

Low-dose ticagrelor 60 mg is as effective for adequate platelet inhibition in East Asia with ACS as standard-dose ticagrelor, but is remarkably more effective than clopidogrel.

A reduced dose of ticagrelor might be more appropriate in East Asian patients due to their differential bleeding and ischemic risk profiles (i.e., low BMI, more vulnerable to bleeding, genetic polymorphism).

However, an adequately powered RCT is required to confirm that adjusted-dose ticagrelor offers better safety and similar efficacy for East Asian patients with ACS.
"East-Asian Paradox"

How To Do ?

Different Dosing and Strategy Is Required for East-Asian Population !!!

All Hypothesis Should Be Confirmed via a Large-Sized RCTs
Antithrombotic Strategy after PCI

SIHD: 6 months
ACS: 12 months

2016 ACC/AHA Guideline
Antithrombotic Strategy after PCI

SIHD: 6 months
ACS: 12 months

2017 ESC Guideline
Current Hot Issue in PCI

New drugs
- Ticagrelor
- Prasugrel
- DOACs

New DES
- Ultra-thin strut DES
- BRS

Subjects
- High Bleeding risk
- Complex High risk

What is the OPTIMAL DAPT?
Complex High-Risk PCI

High-risk Patient
- Previous NSTEMI or STEMI
- Recurrent ischemic event on DAPT
- History of Stent thrombosis
- Chronic inflammatory disease
- Diabetes
- Chronic renal dysfunction

High-risk PCI
- >3 Stents
- Total stent length >60 mm
- Complex PCI: CTO, Complex Bifurcation, Multivessel PCI
- PCI with BRS

Continue Long-term DAPT

“Optimal DAPT duration of complex high-risk PCI is still unknown”

2017 ESC Guideline
Timing of ischemic versus bleeding event after PCI

Current evidence

• Complex High-risk PCI: more DAPT (duration or potency)

• Early Ischemic risk and Late bleeding risk

• The best DAPT may be *Escalation and De-escalation* strategy in Complex High-Risk PCI
TAILOred Versus COventional AntithRombotic StratEgy IntenDed for Complex HIgh-Risk PCI

TAILORED-CHIP trial

Duk-Woo Park, MD.
Heart institute, Asan Medical Center
What is TAILORED-CHIP trial?

To evaluate the **efficacy** and **safety** of **tailored antithrombotic therapy** with **early** (< 6-month post-PCI) **escalation** and **late** (> 6-month post-PCI) **de-escalation strategy** in patients **undergoing complex high-risk PCI** as compared with conventional DAPT (clopidogrel plus aspirin for 12 months).
Trial Hypothesis

Complex High-risk PCI

Ischemic

Bleeding

More Potent DAPT For Ischemic Risk “Ticagrelor + ASA”

Less Potent DAPT For Bleeding Risk “Clopidogrel Only”
2,000 Patients Undergoing Complex High-Risk PCI*

Stratified randomization by (1) trial center or (2) diabetes

Conventional Arm (N=1,000)
Clopidogrel + Aspirin 12 months

Tailored Arm (N=1,000)
Low-dose (60 mg) Ticagrelor + Aspirin
Early 6 months (Early Escalation)
Clopidogrel alone
Late 6 months (Late De-Escalation)

The primary endpoint was a composite outcome of death, MI, stroke, stent thrombosis, urgent revascularization, and clinically relevant bleeding (BARC 2, 3, or 5) at 12 months

*Complex High-Risk PCI
Left main PCI, chronic total occlusion, bifurcation requiring two-stent technique, severe calcification, diffuse long lesion (lesion length ≥ 30mm), multivessel PCI (≥ 2 vessels requiring stent implantation), ≥3 requiring stents implantation, ≥3 lesions will be treated, predicted total stent length for revascularization >60mm, diabetes, CKD (Cr-clearance <60ml/min) or severe LV dysfunction (EF <40%).
Primary

A net clinical outcome of all-cause death, MI, stroke, stent thrombosis, urgent revascularization and clinical relevant bleeding (BARC 2,3, or 5) at 12 months post-PCI
Study endpoints

Secondary

- Each component of primary outcome
- Composite of death (all or CV), MI, stroke, stent thrombosis or urgent revascularization
- Composite of death (all or CV), MI, or stroke
- Composite of death (all or CV) or MI
- Any revascularization
- BARC 3 or 5 bleeding
- Major or minor bleeding according to definition from TIMI
- Major or minor bleeding to definition from ISTH
Inclusion criteria

- Men or women aged ≥18 years
- Patients scheduled PCI with contemporary DES.
- Patients must have at least one of any features of complex high-risk anatomic, procedural and clinical-related factors.
  - Clinical factors; *diabetes, chronic kidney disease* (CrCl <60 mL/min), severe LV dysfunction (*LVEF* <40%)
  - Lesion- or procedure-related factors; *left main* lesion, bifurcation lesion requiring *two stent technique, CTO* lesion, severe *calcification, diffuse long* lesion (lesion length ≥ at least 30mm), multi-vessel PCI (*≥ 2 vessels requiring stent implantation*), *≥3 requiring stent* implantation, *≥3 lesions* will be treated, or predicted *total stent length > 60 mm*
Exclusion criteria

- Enzyme-positive ACS (NSTEMI or STEMI)
- Contraindication to aspirin or P2Y12 inhibitors (ticagrelor or clopidogrel)
- Cardiogenic shock at index admission
- Patients treated with only BMS or balloon angioplasty during index procedure
- Need for chronic oral anticoagulation (warfarin or NOAC)
- Active bleeding or extreme-risk for major bleeding (e.g. active PUD, GI pathology with high risk for bleeding, malignancy with high risk for bleeding)
Study Status

• AMC：①IRB 승인완료  
②MFDS 승인완료  
③ Brilinta 60 mg 입고

• 공동연구기관: 국내 22개 센터  
  → 22개 기관 IRB 초기 심의 진행 중
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The “East Asian paradox” describes a phenomenon of differential ischemic and bleeding response to antithrombotic therapies.

Despite a higher level of platelet reactivity to antithrombotic therapy, East Asian patients have a higher risk of bleeding events, but a similar or even lower risk of ischemic events as compared with White patients.
No definitive data are available to support the clinical superiority of the more potent P2Y12 inhibitors (prasugrel and ticagrelor) over clopidogrel as an adjunct to aspirin for DAPT in East Asian patients with ACS or those undergoing PCI.

Further studies are required to assess the efficacy and safety of potent P2Y12 inhibitors (ticagrelor or prasugrel) for ACS or PCI among East Asian patients.

The optimal antiplatelet therapy for east Asian population should be a balancing act between risk of ischemia and risk of bleeding.