\( P_{2Y_{12}} \) Receptor Inhibitors

Clopidogrel, Prasugrel and Ticagrelor

Which Drug and for Whom?

Cheol Whan Lee, MD

Professor of Medicine, University of Ulsan College of Medicine, Heart Institute, Asan Medical Center, Seoul, Korea
A Miracle Drug!

The Great Journey
P2Y<sub>12</sub> Receptor Blockers
P2Y_{12} Receptor: A Key Player

PLATELET ACTIVATION

Amplification

Alpha granule

Coagulation factors
Inflammatory mediators

Shape change

Thrombin generation

Thrombin

Coagulation

Thromboxane

PAR4

PAR1

TP_{\alpha}

GPVI

5HT_{2A}

P2Y_1

P2X_1

ADP

5HT

ATP

Dense granule

P2Y_{12}

Aggregation

\alpha_{\text{IIb}}\beta_3

\alpha_{\text{IIb}}\beta_3

\alpha_{\text{IIb}}\beta_3

Fibrinogen

Currents and Pharm Des 2006;12:1255
Circulation 2010;121:171
The Inventor of Ticlopidine
Jean-Pierre Maffrand, 1972 (retire 2008)

In the early 1970’s Sanofi’s predecessor company (which will be referred to as “Sanofi” for simplicity) invented a “thienopyridine” compound named ticlopidine which was shown to have anti-thrombotic therapeutic benefit in that it inhibited blood platelet aggregation. The Sanofi inventor was Jean Pierre Maffrand, Ph.D. Ticlopidine, in the form of a hydrochloride salt, was marketed as a pharmaceutical in Europe beginning in 1978, and has the following structure (shown as a base, without any salt anion):
Cumulative Risk of Stoke, MI or Vascular Death in Patients in the CAPRIE Trial

19,185 patients with atherosclerotic disease

Event rate/year

Aspirin 5.83%

Clopidogrel 5.32%

Aspirin 8.7% *

Overall Relative Risk Reduction

No major safety differences

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Plavix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any bleed</td>
<td>9.28%</td>
<td>9.27%</td>
</tr>
<tr>
<td>ICH</td>
<td>0.49%</td>
<td>0.35%</td>
</tr>
<tr>
<td>GI bleed*</td>
<td>2.66%</td>
<td>1.99%</td>
</tr>
</tbody>
</table>

*p<0.05

Lancet 1996;348:1329
Dual anti-platelet therapy

**STARS:** P2Y12 Receptor Inhibitor

After coronary stenting, aspirin & ticlopidine should be considered for the prevention of the serious complication of stent thrombosis.

ASA alone 3.5% vs. Dual 0.5% (ST 86% ↓)

NEJM 1998;339:1665
Superior Efficacy of ADP Receptor Antagonists in Coronary Stenting

Clopidogrel

- Dual therapy (aspirin & clopidogrel)
  - PCI: BMS (1 month), DES (12 months)
  - ACS: 12 months
    A P2Y12 inhibitor should be added to aspirin as soon as possible and maintained over 12 months in ACS patients unless contraindication (IA, ESC2011)

- An alternative to aspirin
The Challenge
Which one is better?
**P2Y\textsubscript{12} Antagonists**

**Evolution**
- Ticlopidine
- Clopidogrel

**Revolution**
- Prasugrel

**AZD6140**
(CPTP: Cyclo-Pentyl-Triazolo-Pyrimidine; orally active)
TRITON – TIMI 38

ACS (STEMI or UA/NSTEMI) & Planned PCI (99%)

ASA \[\downarrow\] N = 13,000

Double-blind

PRASUGREL  CLOPIDOGREL

Median duration of therapy – 12 months

1° endpoint: CV death, MI, Stroke
2° endpoints: CV death, MI, Stroke, Rehosp Re-isch CV death, MI, UTVR
TRITON-TIMI 38 Prasugrel Lowers Events but Ups Bleeding versus Clopidogrel in ACS

13,608 ACS patients scheduled for PCI (STEMI 26%)

- **Cardiovascular death/MI/stroke**
  - HR 0.81 (0.73 - 0.90), p<0.001

- **Nonfatal MI**
  - HR 0.76 (0.67 - 0.85), p<0.001

- **Stent thrombosis (1.1% vs. 2.4%)**
  - HR 0.48 (0.36 - 0.64), p<0.001

- **Fatal bleeding (0.4% vs 0.1%)**
  - HR 4.19 (1.58 - 11.11), p=0.002

- **TIMI major/minor bleeding**
  - HR 1.31 (1.11 - 1.56), p=0.002

Risk groups: age>75 & lean<60kg or history of stroke/TIA
**TRITON: Study Limitations**

**Prasugrel in ACS**

NSS-ACS, ACCF/AHA Guideline 2011

It is not our recommendation that prasugrel be administered routinely before angiography, such as in an emergency department, or be used in patients who have not undergone PCI.

ACS, ESC Guideline 2011

**Prasugrel in, Clopidogrel out for STEMI**

Prasugrel (60-mg loading dose, 10-mg daily dose) is recommended for P2Y<sub>12</sub>-inhibitor-naïve patients (especially diabetics) in whom coronary anatomy is known and who are proceeding to PCI unless there is a high risk of life-threatening bleeding or other contraindications.\textsuperscript{d}
TRILOGY – ACS

Medically Managed NSTE-ACS

Low-dose ASA
N = 10,300 (<75y: ~7800)

Randomization within 10 days of index event
Stratified by age (75y), BWt (60kg), clopidogrel treatment
(300mg LD within 72h of index event & daily MD; or MD ≥ 5 days)

PRASUGREL
5 or 10mg/day

CLOPIDOGREL
75mg/day

Duration of therapy: minimum 6m, maximum 30m

1º endpoint: CV death, MI, Stroke
PLATO: A Study of PLATelet Inhibition & Patient Outcomes

ACS (STEMI/NSTEMI) (<24 h after chest pain)

ASA ↓ N = 18,624

Double-blind

IIB/IIA 27%

Ticagrelor

Clopidogrel

Median duration of therapy: 6-12 months

1º endpoint: CV death, MI, Stroke (15% RRR)
2º endpoints: Death, CV death, MI, stroke, recurrent ischemia, arterial thrombotic events
In 1000 ACS patients, replacing clopidogrel with ticagrelor for 12 months,

- 14 fewer deaths  
  (absolute risk reduction 1.4%)
- 11 fewer MI
- 6~8 fewer cases of stent thrombosis
- no increase in bleeding requiring transfusion.
# Major Bleeding

## Ticagrelor in ACS

<table>
<thead>
<tr>
<th>ESC2011</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticagrelor (180-mg loading dose, 90 mg twice daily) is recommended for all patients at moderate-to-high risk of ischaemic events (e.g. elevated troponins), regardless of initial treatment strategy and including those pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced).</td>
<td>I</td>
</tr>
<tr>
<td>Clopidogrel (300-mg loading dose, 75-mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel.</td>
<td>I</td>
</tr>
</tbody>
</table>
The PLATO trial: do you believe in magic?

Victor L. Serebruany and Dan Atar

Adenosine Hypothesis?
- vasodilation
- preconditioning
- immunomodulation
- dyspnea
- heart block
- renal function
IC Adenosine for Myocardial Salvage in Patients With STEMI

- Adenosine 4mg
- CMRI on day 2-3
- Salvage index = necrotic area / risk area

<table>
<thead>
<tr>
<th></th>
<th>Adenosine</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>50</td>
<td>44</td>
</tr>
<tr>
<td>Median</td>
<td>41.3</td>
<td>47.8</td>
</tr>
<tr>
<td>(Min,Max)</td>
<td>(0,100)</td>
<td>(0.84)</td>
</tr>
<tr>
<td>(Q1,Q3)</td>
<td>(21.67)</td>
<td>(40,61)</td>
</tr>
</tbody>
</table>
AMI

Stable angina
Beyond Platelets

P2Y12 receptor inhibitors may have a dual anti-ischemic effect by inhibiting both platelet activation and plaque destabilization.
# P2Y12 Receptor Inhibitors

<table>
<thead>
<tr>
<th>Type</th>
<th>Clopidogrel Thienopyridine</th>
<th>Prasugrel Thienopyridine</th>
<th>Ticagrelor Cyclopentyltriazolopyrimidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prodrug</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Oral administration</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Loading dose (mg)</td>
<td>300</td>
<td>60</td>
<td>180</td>
</tr>
<tr>
<td>Maintenance dose (mg)</td>
<td>75</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>Once daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Onset of action</td>
<td>Delayed</td>
<td>Rapid</td>
<td>Rapid</td>
</tr>
<tr>
<td>Offset of action</td>
<td>Delayed</td>
<td>Delayed</td>
<td>Rapid</td>
</tr>
<tr>
<td>Individual variability</td>
<td>Large</td>
<td>Small</td>
<td>Small</td>
</tr>
<tr>
<td>CYP-450 activation</td>
<td>Yes (twice)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Irreversible P2Y12 inhibition</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Relative potency</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Mean platelet inhibition</td>
<td>~50%</td>
<td>~70%</td>
<td>~95%</td>
</tr>
<tr>
<td>Time to peak inhibition (h)</td>
<td>~12+</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Half-life</td>
<td>Life of platelet</td>
<td>Life of platelet</td>
<td>7–12 h</td>
</tr>
<tr>
<td>Days to hold before CABG surgery</td>
<td>&gt;5</td>
<td>&gt;7</td>
<td>&gt;3</td>
</tr>
</tbody>
</table>

*With 300 mg loading dose.*

Heart 2010;96:656
Unanswered Questions

- STEMI: thrombolytic or medical therapy
- AMI: 1 year after AMI (PEGASUS)
- Stable angina: after DES
- Ischemic stroke
- Primary prevention
The Dilemma
Bleeding is the key!

Risk for Ischemic Events

Risk for Bleeding
Safety: More Potent, More Bleeding!

- **CURE**
  - N=12,563
  - 1 year FU
  - CURE major bleed
  - NEJM 2001;345:494-502
  - P=0.001
  - ASA + Clopidogrel: 8.8%
  - ASA + Placebo: 6.7%

- **CREDO**
  - N=2,116
  - 1 year FU
  - TIMI major bleed
  - NEJM 2001;345:494-502
  - P=0.07
  - ASA + Clopidogrel: 6.7%
  - ASA + Placebo: 3.8%

- **CHARISMA**
  - N=15,603
  - 2.5 year FU
  - GUSTO major bleed + moderate bleed
  - NEJM 2001;345:494-502
  - P=0.001
  - ASA + Clopidogrel: 2.6%
  - ASA + Placebo: 3.8%
Intracranial Bleeding

- Patient history of stroke or TIA

- TRITON-TIMI 38: incidence of stroke in patients with a history of prior TIA or stroke greater with prasugrel + ASA (6.5% total: 4.2% thrombotic, 2.3% ICH) vs clopidogrel + ASA (1.2% total, all thrombotic)

- PLATO: Fatal ICH higher in ticagrelor vs clopidogrel (0.1 vs 0.01; $P=0.02$)
Bleeding (p<0.001): GUSTO severe (HR1.66), TMIMI major (HR1.53), ICH (HR3.39)
Total death: HR1.05 (P=0.52)
In pts with ACS, the addition of vorapaxar to standard therapy did not significantly reduce the primary endpoint but significantly increased the risk of major bleeding.
Evolution of Anti-platelet Therapy

- **Placebo**: +60%
- **Aspirin**: -22%
- **Aspirin + Clopidogrel**: -20%
- **Aspirin + Prasugrel**: -19%
- **Aspirin + Ticagrelol**: -15%
- **DAPT + Vorapaxar**: -8% (p=NS)

Reduction in ischemic events (%)
Small bleed becomes a big bleed!
Old Soldiers Never Die.

New $P_2Y_{12}$ receptor inhibitors will be the key players in CV medicine.

감사합니다.