DAPT in STEMI

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ACS with ST-Elevation STEMI
ACS without ST-Elevation NSTEMI / Unstable A.p.

Troponin & CK elevated
Troponins elevated or not

Adapted from Michael D
P2Y_{12} Inhibitors

<table>
<thead>
<tr>
<th>Class</th>
<th>Clopidogrel</th>
<th>Prasugrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binding</td>
<td>Thienopyridine</td>
<td>Thienopyridine</td>
<td>Triazolopyrimidine</td>
</tr>
<tr>
<td>Activation</td>
<td>Irreversible</td>
<td>Irreversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>Prodrug</td>
<td>Prodrug, limited by metabolism</td>
<td>Prodrug, not limited by metabolism</td>
<td>Active drug</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Onset of Effect</td>
<td>2–4 h</td>
<td>30 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Duration of Effect</td>
<td>3–10 days</td>
<td>5–10 days</td>
<td>3–4 days</td>
</tr>
<tr>
<td>Withdrawal Before Major Surgery</td>
<td>5 days</td>
<td>7 days</td>
<td>5 days</td>
</tr>
</tbody>
</table>


Early and Late Effects of Clopidogrel

CURE

Event-free survival

0 bis 30 days

31 days bis 12 months

Comforted endpoint: death, AMI, stroke

PCI CURE - Study

Hazard rates

Death / Myocardial Infarction

ASA
ASA + Clopidogrel

P=0.002

Delay to PCI: 10 days
82% : 81% Stents
21% : 27% GPIIb/IIIa

Day of follow-up

S. Mehta. et.al. The Lancet 2001

Antiplatelet Effect Clopidogrel vs. Prasugrel

IPA, %

Prasugrel 60 mg

Clopidogrel 300 mg

Time After Administration, h
Prasugrel versus Clopidogrel in Patients with Acute Coronary Syndromes

Stephen D. Wiviott, M.D., Eugene Braunwald, M.D., Carolyn H. McCabe, B.S., Gilles Montalescot, M.D., Ph.D., Witold Ruzyllo, M.D., Shmuel Gottlieb, M.D., Franz-Joseph Neumann, M.D., Diego Ardissino, M.D., Stefano De Servi, M.D., Sabina A. Murphy, M.P.H., Jeffrey Riesmeyer, M.D., Govinda Weerakkody, Ph.D., C. Michael Gibson, M.D., and Elliott M. Antman, M.D., for the TRITON–TIMI 38 Investigators

Wiviott et al. NEJM 2007; 357; 2001f

Balance of Efficacy and Safety

\[ \text{HR} = 0.81 \]
\[ (0.73-0.90) \]
\[ P=0.0004 \]
\[ \text{NNT} = 46 \]

\[ \text{HR} = 1.32 \]
\[ (1.03-1.68) \]
\[ P=0.03 \]
\[ \text{NNH} = 167 \]
**Stent Thrombosis**

*ARC Definite + Probable*

- **Any Stent at Index PCI**
  - N=14,844

- **Clopidogrel**
  - 2.4 (142)

- **Prasugrel**
  - 1.1 (68)

*HR 0.48*  
*P < 0.00001*  
*NNT= 77*

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**TRITON TIMI-38 STEMI cohort**

**Primary EP** (CV death, MI and stroke at 15 months)

- **Clopidogrel**
  - 12.4

- **Prasugrel**
  - 10.0

*p=0.02*  
*RRR=21%*

*p=0.002*  
*RRR=32%*

**HR=0.79 (0.65–0.97) NNT=42**

*Age-adjusted HR=0.81 (0.66–0.99)*

Montalescot et al. ESC 2008
Antiplatelet drug pathways

**Ticagrelor** is an *active drug*

Biotransformation and mode of action of clopidogrel, prasugrel, and ticagrelor.
Ticagrelor the first novel reversible P2Y\textsubscript{12} inhibitor

* Direct acting
  - Not a pro-drug; does not require metabolic activation
  - Rapid onset of inhibitory effect on the P2Y\textsubscript{12} receptor
  - Greater inhibition of platelet aggregation than clopidogrel

* Reversibly bound
  - Degree of inhibition reflects plasma concentration
  - Faster offset of effect than clopidogrel
  - Functional recovery of circulating platelets within ~48 hours, needs to be withdrawn only 5 days before surgery

Brilinta prescribing information (updated March 2013)

**Expert Opinion**

**Ticagrelor: the first novel reversible P2Y\textsubscript{12} inhibitor**

Wah Wah Han & Steven R Steinshubl
Geisinger Medical Center, Department of Cardiology, Danville, PA, USA

**Expert opinion:** Ticagrelor 180 mg loading dose followed by 90 mg b.i.d. is significantly more efficacious and, in general, as safe as clopidogrel in the treatment of all patients with an ACS regardless of treatment strategy. In addition, besides aspirin compared to placebo, it is the only pharmaceutical intervention shown to have a cardiovascular mortality benefit within 1 year in a broad ACS population. Whether this surprising benefit is realized in other populations is currently being tested.
Antiplatelet Effect Clopidogrel vs. Ticagrelor

Inhibition of Platelet Aggregation (IPA) %

Time [Hours]

Loading Dose

Maintenance Dose

Offset

Guttes, Circulation

The NEW ENGLAND JOURNAL of MEDICINE

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

Lars Wallentin, M.D., Ph.D., Richard C. Becker, M.D., Andrzej Budaj, M.D., Ph.D., Christopher P. Cannon, M.D., Håkan Emanuelsson, M.D., Ph.D., Claes Held, M.D., Ph.D., Jay Horrow, M.D., Steen Husted, M.D., D.Sc., Stefan James, M.D., Ph.D., Hugo Katus, M.D., Kenneth W. Mahaffey, M.D., Benjamin M. Scirica, M.D., M.P.H., Allan Skene, Ph.D., Philippe Gabriel Steg, M.D., Robert F. Storey, M.D., D.M., and Robert A. Harrington, M.D., for the PLATO Investigators"
**PLATO study design**

**PLAtelet inhibition and patient Outcomes**

Ticagrelor versus Clopidogrel in Patients with Acute Coronary Syndromes

NSTEMI (moderate-to-high risk) STEMI (if primary PCI)

Clopidogrel-treated or -naive; randomised within 24 hours of index event (N=18,624)

Clopidogrel

- If pre-treated, no additional loading dose;
- If naive, standard 300 mg loading dose, then 75 mg qd maintenance;
  (additional 300 mg allowed pre PCI)

Ticagrelor

- 180 mg loading dose, then 90 mg bid maintenance;
  (additional 90 mg pre-PCI)

Primary endpoint: CV death + MI + Stroke
Primary safety endpoint: Total major bleeding


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**PLATO study design**

**PLATO inclusion criteria**

- Hospitalisation for STEMI or NSTEMI ACS, with onset during the previous 24 hours
- With STEMI, the following two inclusion criteria were required
  - Persistent STEMI or new LBBB
  - Primary PCI planned
- With NSTEMI ACS, at least two of the following three were required
  - ST-segment changes on ECG indicating ischaemia
  - Positive biomarker indicating myocardial necrosis
  - One of the following risk indicators
    - ≥60 years of age
    - Previous MI or CABG
    - CAD with ≥50% stenosis in ≥2 vessels
    - Previous ischaemic stroke, TIA, carotid stenosis (≥50%)
    - Diabetes mellitus
    - Peripheral artery disease
    - Chronic renal dysfunction (creatinine clearance <60 mL/min)

Primary efficacy endpoint over time (composite of CV death, MI or stroke)

Cumulative incidence (%)

Clopidogrel
Ticagrelor
4.77
5.43
HR 0.88 (95% CI 0.77–1.00), p=0.045

No. at risk
Clopidogrel
Ticagrelor
9,291
9,333
8,875
8,942
8,763
8,827

Days after randomisation (1 month)

Cumulative incidence (%)

Clopidogrel
Ticagrelor
5.28
6.60
HR 0.80 (95% CI 0.70–0.91), p<0.001

No. at risk
Clopidogrel
Ticagrelor
9,291
9,333
8,560
8,678
8,405
8,520
8,177

Days after randomisation* (1 year)

*Excludes patients with any primary event during the first 30 days


Secondary efficacy endpoints over time

Myocardial infarction

Cumulative incidence (%)

Clopidogrel
Ticagrelor
4.9
5.8
HR 0.84 (95% CI 0.75–0.95), p=0.005

No. at risk
Days after randomisation
Ticagrelor
9,934
8,626
8,678
8,405
8,793
5,480
8,409

Clopidogrel
9,391
8,626
8,678
8,405
8,793
5,480
8,409

Cardiovascular death

Cumulative incidence (%)

Clopidogrel
Ticagrelor
6.1
6.0
HR 0.79 (95% CI 0.69–0.91), p=0.001

No. at risk
Days after randomisation
Ticagrelor
9,934
8,626
8,678
8,405
8,793
5,480
8,409

Clopidogrel
9,391
8,626
8,678
8,405
8,793
5,480
8,409

Stent thrombosis

(evaluated in patients with any stent during the study)

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n=5,640)</th>
<th>Clopidogrel (n=5,649)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent thrombosis, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite</td>
<td>71 (1.3)</td>
<td>106 (1.9)</td>
<td>0.67 (0.50–0.91)</td>
<td>0.009</td>
</tr>
<tr>
<td>Probable or definite</td>
<td>118 (2.1)</td>
<td>158 (2.8)</td>
<td>0.75 (0.59–0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Possible, probable, definite</td>
<td>155 (2.8)</td>
<td>202 (3.5)</td>
<td>0.77 (0.62–0.95)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*Time-at-risk is calculated from first stent insertion in the study or date of randomisation


Time to major bleeding – primary safety event

![Graph showing time to major bleeding](image)

K-M estimated rate (% per year) vs. Days from first IP dose

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (923)</th>
<th>Clopidogrel (925)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7,246</td>
<td>6,826</td>
</tr>
<tr>
<td></td>
<td>6,545</td>
<td>5,129</td>
</tr>
<tr>
<td></td>
<td>3,783</td>
<td>3,433</td>
</tr>
<tr>
<td></td>
<td>3,841</td>
<td>3,479</td>
</tr>
</tbody>
</table>

HR 1.04 (95% CI 0.95–1.13), p=0.434

Total major bleeding

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATO major bleeding</td>
<td>11.0%</td>
<td>11.2%</td>
</tr>
<tr>
<td>TIMI major bleeding</td>
<td>11.9%</td>
<td>12.1%</td>
</tr>
<tr>
<td>Red cell transfusion</td>
<td>7.9%</td>
<td>7.7%</td>
</tr>
<tr>
<td>PLATO life-threatening/fatal bleeding</td>
<td>8.9%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Fatal bleeding</td>
<td>5.8%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

Non-CABG and CABG-related major bleeding

<table>
<thead>
<tr>
<th>Condition</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CABG PLATO major bleeding</td>
<td>4.3%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Non-CABG TIMI major bleeding</td>
<td>2.8%</td>
<td>2.2%</td>
</tr>
<tr>
<td>CABG PLATO major bleeding</td>
<td>7.4%</td>
<td>7.9%</td>
</tr>
<tr>
<td>CABG TIMI major bleeding</td>
<td>5.3%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

Holter monitoring & Bradycardia related events

<table>
<thead>
<tr>
<th>Holter monitoring at first week</th>
<th>Ticagrelor (n=1,451)</th>
<th>Clopidogrel (n=1,415)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular pauses ≥3 seconds, % (adenosine – related side effect)</td>
<td>5.8</td>
<td>3.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Ventricular pauses ≥5 seconds, %</td>
<td>2.0</td>
<td>1.2</td>
<td>0.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Holter monitoring at 30 days</th>
<th>Ticagrelor (n=969)</th>
<th>Clopidogrel (n=1,006)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventricular pauses ≥3 seconds, %</td>
<td>2.1</td>
<td>1.7</td>
<td>0.52</td>
</tr>
<tr>
<td>Ventricular pauses ≥5 seconds, %</td>
<td>0.8</td>
<td>0.6</td>
<td>0.60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bradycardia-related event, %</th>
<th>Ticagrelor (n=9,235)</th>
<th>Clopidogrel (n=9,186)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacemaker Insertion</td>
<td>0.9</td>
<td>0.9</td>
<td>0.87</td>
</tr>
<tr>
<td>Syncope</td>
<td>1.1</td>
<td>0.8</td>
<td>0.08</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4.4</td>
<td>4.0</td>
<td>0.21</td>
</tr>
<tr>
<td>Heart block</td>
<td>0.7</td>
<td>0.7</td>
<td>1.00</td>
</tr>
</tbody>
</table>

*Other findings*

<table>
<thead>
<tr>
<th>All patients</th>
<th>Ticagrelor (n=9,235)</th>
<th>Clopidogrel (n=9,186)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea, %</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(Adenosine- related side effect)</td>
<td>13.8</td>
<td>7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any</td>
<td>0.0</td>
<td>0.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

With discontinuation of study treatment

<table>
<thead>
<tr>
<th>Neoplasms arising during treatment, %</th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>1.4</td>
<td>1.7</td>
<td>0.17</td>
</tr>
<tr>
<td>Malignant</td>
<td>1.2</td>
<td>1.3</td>
<td>0.69</td>
</tr>
<tr>
<td>Benign</td>
<td>0.2</td>
<td>0.4</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*p values were calculated using Fischer’s exact test*


Therapeutic considerations

Based on 1,000 patients admitted to hospital for ACS, using **Ticagrelor instead of clopidogrel** for 12 months resulted in:

- 14 fewer deaths
- 11 fewer myocardial infarctions
- 6–8 fewer cases with stent thrombosis
- No increase in bleedings requiring transfusion
- Treating 54 patients with ticagrelor instead of clopidogrel for one year will prevent one event of CV death, MI or stroke

![Outcomes with “Novel” P2Y12 Antagonists](chart.png)
Choice of Antiplatelet Therapy

Bleeding

Thrombosis

Predictors of bleeding in acute coronary syndrome

Variables
- Age (per 10-year increase)
- Female sex
- History of renal insufficiency
- History of bleeding
- Mean arterial pressure (per 20 mmHg decrease)
- Diuretics
- LMWH only
- Thrombolytics only
- GP IIb/IIIa blockers only
- Thrombolytics and GP IIb/IIIa blockers
- IV inotropic agents
- Other vasodilators
- Right-heart catheterization
- Percutaneous coronary intervention

Adjusted odds ratio
- 1.50
- 1.90
- 1.90
- 1.60
- 0.50

95% CI
- 1.30
- 1.70
- 1.00
- 0.80
- 0.40

P-value
- <0.0001

- Age
- Female sex
- Renal insufficiency
- History of bleeding
- Lower body weight
- Long invasive procedures

are powerful predictors of bleeding in ACS

Clopidogrel is preferably used when Prasugrel or Ticagrelor are either not available or contraindicated.

Dosing of antiplatelet drugs

DAPT MUST be continued for up to **12 months** with or without a stent

**ESC Guidelines**

Ticagrelor is recommended for all patients at moderate to high risk of ischaemic events **regardless of initial treatment strategy**

**ESC Guidelines**
**Ticagrelor**

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).

- First choice P2Y12 for troponin-positive ACS according to 2011 NSTE-ACS GL
- Loading dose 180 mg
- Maintenance dose 90 mg twice daily

**Prasugrel**

Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended for P2Y12-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.

- in P2Y12-inhibitor-naïve patients
- proceeding to PCI
- especially diabetics
Take Home Message

- Antiplatelet therapy is the cornerstone management in patients with ACS.
- There are well established drugs and new drugs for specific indications.
- Which drug for which patient needs more studies.
The use of Ticagrelor, the novel reversible, more intense P2Y<sub>12</sub> receptor inhibitor for one year in comparison to clopidogrel in a broad population with ST- and non-ST-elevation ACS provides:

- Superior Reduction in myocardial infarction (RRR=16%)
- Superior reduction in stent thrombosis (RRR=23%)
- Superior Reduction in cardiovascular and total mortality (RRR=16%)
- No change in the overall risk of major bleeding

Ticagrelor is a more effective alternative than clopidogrel for the continuous prevention of ischaemic events, stent thrombosis and death in the acute and long-term treatment of patients with ACS.


Take Home Message

Thank You