ANTIAGREGANTS
IN ACUTE CORONARY SYNDROME

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Dual Antiplatelet Therapy

- ASA + Clopidogrel
- I Class of evidence in treatment of ACS
- **Beneficial, effective and useful** in acute and long term treatment of ACS
- Current standard in patients after stent implantation

Possible problems:

- Increased risk of bleeding
- Risk of stent thrombosis and MI in poor responders
Stent thrombosis of LAD bifurcation
Thromboscution
Kissing balloon dilatation
Clopidogrel: Double (600mg and 150mg/d 1wk) vs Standard Dose (300mg) Definite Stent Thrombosis

- Clopidogrel Standard Dose
- Clopidogrel Double Dose

Cumulative Hazard

Days

- HR 0.58
- 95% CI 0.42-0.79
- P=0.001
Clopidogrel: Double vs Standard Dose

Primary Outcome: PCI Patients

CV Death, MI or Stroke

Cumulative Hazard

Clopidogrel Standard

Clopidogrel Double

HR 0.85
95% CI 0.74-0.99
P=0.036

15% RRR
# Clopidogrel Double vs Standard Dose

## Bleeding PCI Population

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel Standard N= 8684</th>
<th>Clopidogrel Double N=8548</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI Major</td>
<td>0.5</td>
<td>0.5</td>
<td>1.06</td>
<td>0.70-1.61</td>
<td>0.79</td>
</tr>
<tr>
<td>CURRENT Major</td>
<td>1.1</td>
<td>1.6</td>
<td>1.44</td>
<td>1.11-1.86</td>
<td>0.006</td>
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<tr>
<td>CURRENT Severe</td>
<td>0.8</td>
<td>1.1</td>
<td>1.39</td>
<td>1.02-1.90</td>
<td>0.034</td>
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<tr>
<td>Fatal</td>
<td>0.15</td>
<td>0.07</td>
<td>0.47</td>
<td>0.18-1.23</td>
<td>0.125</td>
</tr>
<tr>
<td>ICH</td>
<td>0.035</td>
<td>0.046</td>
<td>1.35</td>
<td>0.30-6.04</td>
<td>0.69</td>
</tr>
<tr>
<td>RBC transfusion ≥ 2U</td>
<td>0.91</td>
<td>1.35</td>
<td>1.49</td>
<td>1.11-1.98</td>
<td>0.007</td>
</tr>
<tr>
<td>CABG-related Major</td>
<td>0.1</td>
<td>0.1</td>
<td>1.69</td>
<td>0.61-4.7</td>
<td>0.31</td>
</tr>
</tbody>
</table>

1. ICH, Hb drop ≥ 5 g/dL (each unit of RBC transfusion counts as 1 g/dL drop) or fatal
2. Severe bleed + disabling or intraocular or requiring transfusion of 2-3 units
3. Fatal or ↓Hb ≥ 5 g/dL, sig hypotension + inotropes/surgery, ICH or txn of ≥ 4 units
Conclusions

1. Double-dose clopidogrel significantly reduced stent thrombosis and major CV events (CV death, MI or stroke) in PCI.

2. In patients not undergoing PCI, double dose clopidogrel was not significantly different from standard dose (70% had no significant CAD or stopped study drug early for CABG).

3. There was a modest excess in CURRENT-defined major bleeds but no difference in TIMI major bleeds, ICH, fatal bleeds or CABG-related bleeds.

4. No significant difference in efficacy or bleeding between ASA 300-325 mg and ASA 75-100 mg
Platelet Aggregation after Clopidogrel Loading

Maximal aggregation 5 μmol/L ADP (%)

Time from loading dose to catheterisation (h)

Hochholzer W et al, Circulation 2005
Survival free of cardiovascular death, infarction and stent thrombosis depending on platelet reactivity

GRAVITAS: Gauging Responsiveness With a VerifyNow assay - Impact On Thrombosis And Safety

PCIs with DES (n=5900) → VN P2Y12 → non-responders → responders

75-mg/day (N=980) → 30 day FU + platelet function testing → 6 month + 1 year FU

150-mg/day (N=980)

Primary Clinical Endpoint: 6-month cardiac death, non-fatal MI, stent thrombosis
Secondary Endpoint: 30-day & 1 year cardiac death, non-fatal MI, stent thrombosis
Primary Physiologic Endpoint: Change in PRU at 30 days

PI: Matthew J. Price, MD
Coordinating Site: Scripps Clinic
Inhibition of Platelet Aggregation

Loading dose (LD)

Maintenance dose (MD)

Mean IPA (%)

0 10 20 30 40 50 60 70

1/0 1/2 1/4 1/6 7/1 7/2 28/0 28/2 28/4 28/6

Day/Hour Post Dosing

Prasugrel (40 mg LD/5 mg MD)
Prasugrel (40 mg LD/7.5 mg MD)
Prasugrel (60 mg LD/10 mg MD)
Prasugrel (60 mg LD/15 mg MD)
Clopidogrel (300 mg LD/75 mg MD)

Jernberg, T et al EHJ 2006
ACS (STEMI or UA/NSTEMI) & Planned PCI

ASA

N = 13,608

Double-blind

CLOPIDOGREL
300 mg LD/75 mg MD

PRASUGREL
60 mg LD/10 mg MD

Duration of therapy: 6-15 months

1° endpoint: CV death, MI, Stroke
2° endpoint: Stent Thrombosis
Safety endpoints: TIMI major bleeds, Life-threatening bleeds

Wiviott SD, Antman EM et al AHJ 2006
Main Trial: Primary Results

CV Death / MI / Stroke

- Prasugrel: HR 0.81 (0.73-0.90) P=0.0004
- Clopidogrel: HR 1.32 (1.03-1.68) P=0.03

TIMI Major NonCABG Bleeds

Wiviott SD, Braunwald E, McCabe CH et al NEJM2007
Prasugrel in STEMI and UA/NSTEMI

Wiviott SD, Braunwald E, McCabe CH et al NEJM2007
Safety Profile of Prasugrel in STEMI vs UN/NSTEMI

15-month incidence of TIMI major non-CABG bleed (%)

- STEMI: 2.1 (NNH = 333)
- UA/NSTEMI: 1.7 (NNH = 142)

- Clopidogrel
- Prasugrel

P = 0.65
P = 0.01

Wiviott SD, Braunwald E, McCabe CH et al NEJM2007
Net Clinical Benefit in STEMI

Montalescot G et al. Lancet 2009
Diabetic Subgroup
N=3146

- CV Death / MI / Stroke
  - Clopidogrel: 17.0
  - Prasugrel: 12.2
  - HR 0.70, P<0.001, NNT = 21

- TIMI Major NonCABG Bleeds
  - Clopidogrel: 2.6
  - Prasugrel: 2.5

Wiviott et al NEJM 2007
Stent Thrombosis (Definite + Probable)

Any Stent at Index PCI
N= 12,844

Clopidogrel

Prasugrel

HR 0.48
P <0.0001
NNT= 77
Definite/Probable ST: Any Stent (N=12844)

**EARLY ST**

HR 0.41 [0.29-0.59]  
P<0.0001

**LATE ST**

HR 0.60 [0.37-0.97]  
P=0.03

- **CLOPIDOGREL**
  - 0.82%
  - 40%

- **PRASUGREL**
  - 0.49%

% of Subjects vs. DAYS
Death Following ST

Mortality During Follow up (%) Post-Stent Thrombosis

HR 13.1 (9.8 – 17.5)
P<0.0001

% of Subjects

Stent Thrombosis
N=210

No Stent Thrombosis
N=12634
Net Clinical Benefit

Bleeding Risk Subgroups

Post-hoc analysis

Prior Stroke / TIA

Yes

No

Risk (%)

+54

P_{int} = 0.006

-16

Age

>=75

< 75

P_{int} = 0.18

-16

Wgt

< 60 kg

>=60 kg

P_{int} = 0.36

+3

-14

OVERALL

0.5

1

2

HR

Prasugrel Better

Clopidogrel Better

Wiviott et al NEJM 2007
• Thienopyridines act by binding covalently to the P2Y12 receptor, causing a structural change, and rendering the receptors permanently inactivated

**DISPERSE-2 PK/PD Substudy:**
Suppression of Platelet Aggregation in Clopidogrel-Pretreated Patients (N=44)

- **Ticagrelor 90 mg (n=9)**
- **Ticagrelor 180 mg (n=7)**
- **Ticagrelor 270 mg (n=16)**
- **Clopidogrel 75 mg (n=12)**

*P<0.05 for AZD6140 vs clopidogrel.

PLATO study design

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

- NSTE-ACS (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)

6–12-month exposure

PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack
K-M estimate of time to first primary efficacy event (composite of CV death, MI or stroke)

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval
Secondary efficacy endpoints over time

**Myocardial infarction**
- Clopidogrel: 6.9%
- Ticagrelor: 5.8%
- HR 0.84 (95% CI 0.75–0.95), p=0.005

**Cardiovascular death**
- Clopidogrel: 5.1%
- Ticagrelor: 4.0%
- HR 0.79 (95% CI 0.69–0.91), p=0.001

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**No. at risk**

<table>
<thead>
<tr>
<th>Days after randomisation</th>
<th>Clopidogrel</th>
<th>Ticagrelor</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9,291</td>
<td>9,333</td>
</tr>
<tr>
<td>60</td>
<td>8,560</td>
<td>8,678</td>
</tr>
<tr>
<td>120</td>
<td>8,405</td>
<td>8,678</td>
</tr>
<tr>
<td>180</td>
<td>8,177</td>
<td>8,520</td>
</tr>
<tr>
<td>240</td>
<td>7,849</td>
<td>8,405</td>
</tr>
<tr>
<td>300</td>
<td>7,305</td>
<td>8,780</td>
</tr>
<tr>
<td>360</td>
<td>6,891</td>
<td>8,822</td>
</tr>
</tbody>
</table>

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**Cumulative incidence (%)**

**Secondary efficacy endpoints over time**
Stent thrombosis
(evaluated in patients with any stent during the study)

<table>
<thead>
<tr>
<th>Stent thrombosis, n (%)</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>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 (3.6)</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

HR 1.04 (95% CI 0.95–1.13), p=0.434

K-M estimated rate (% per year)

Days from first IP dose

No. at risk

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor</th>
<th>Clopidogrel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9,235</td>
<td>9,186</td>
</tr>
<tr>
<td>60</td>
<td>7,246</td>
<td>7,305</td>
</tr>
<tr>
<td>120</td>
<td>6,826</td>
<td>6,930</td>
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<tr>
<td>180</td>
<td>6,545</td>
<td>6,670</td>
</tr>
<tr>
<td>240</td>
<td>5,129</td>
<td>5,209</td>
</tr>
<tr>
<td>300</td>
<td>3,783</td>
<td>3,841</td>
</tr>
<tr>
<td>360</td>
<td>3,433</td>
<td>3,479</td>
</tr>
<tr>
<td>Study Period</td>
<td>Ticagrelor (n=1,451)</td>
<td>Clopidogrel (n=1,415)</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-----------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Holter monitoring at first week</td>
<td>5.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Ventricular pauses ≥3 seconds, %</td>
<td>2.0</td>
<td>1.2</td>
</tr>
<tr>
<td>Holter monitoring at 30 days</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Ventricular pauses ≥5 seconds, %</td>
<td>0.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Bradycardia-related event, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacemaker Insertion</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Syncope</td>
<td>1.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Heart block</td>
<td>0.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>
## Other findings

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor (n=9,235)</th>
<th>Clopidogrel (n=9,186)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnoea, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>13.8</td>
<td>7.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>With discontinuation of study treatment</td>
<td>0.9</td>
<td>0.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neoplasms arising during treatment, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<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
Conclusions

• Reversible, more intense P2Y$_{12}$ receptor inhibition for one year with ticagrelor in comparison with clopidogrel in a broad population with ST- and non-ST-elevation ACS provides
  – Reduction in myocardial infarction and stent thrombosis
  – Reduction in cardiovascular and total mortality
  – No change in the overall risk of major bleeding
Indirect comparison Prasugrel vs. Ticagrelor

Funnel plots comparing prasugrel vs. ticagrelor for the risk of key clinical events. Odds ratios (OR) <1.0 favor prasugrel, whereas odds ratios >1.0 favor ticagrelor.

Zoccai GB. EuroPCR 2010
# Guidelines on myocardial revascularization

The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

## NSTE-ACS

<table>
<thead>
<tr>
<th>Antiplatelet therapy</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Clopidogrel (with 600 mg loading dose as soon as possible)</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Clopidogrel (for 9–12 months after PCI)</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Prasugrel&lt;sup&gt;d&lt;/sup&gt;</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Ticagrelor&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

## STEMI

<table>
<thead>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Clopidogrel&lt;sup&gt;f&lt;/sup&gt;</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Prasugrel&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Ticagrelor&lt;sup&gt;d&lt;/sup&gt;</td>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>
CYP2C19 Polymorphism and Response to Clopidogrel

CYP2C19 Polymorphism and Response to Prasugrel

Cangrelor (AR-C69931MX)

- Parenteral ADP-P2Y\textsubscript{12} receptor antagonist
- ATP analogue
- Direct and Reversible P2Y\textsubscript{12} inhibitor
- More potent than clopidogrel ~90% inhibition of platelet aggregation at 1 - 4 mcg/kg/min iv
- Plasma half-life of 5-9 min.; 20 min. for return to normal platelet function
CHAMPION Trial: Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition PCI

INNOVATE PCI: treatment with oral and intravenous *Elinogrel* in setting of non-urgent PCI

- Second phase trial
- Evaluation of clinical effectiveness, safety and tolerability

Rao et al. *ESC Congress 2010*
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