Case Presentation

Why and How Should We Switch Clopidogrel to Prasugrel?

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Case Description

- A 67 Y. Old Pt. admitted to IM with anginal CP.
- **DM, HTN, HLP.**
- First Tn I – negative.
- Clopidogrel 600 mg.
- **Second TnI – elevated.**
- Transferred to Cardiology Dept on the afternoon, Scheduled for cath the next morning.
TRITON-TIMI 38: Diabetic Subgroup Analysis (n=3,146)

CABG=Coronary Artery Bypass Graft surgery; CV=Cardiovascular; HR=Hazard Ratio; MI=Myocardial Infarction; NNT=Number Needed to Treat; TIMI=Thrombolysis In Myocardial Infarction
Clopidogrel Response Variability: Increase the Dose (300 mg vs. 600 mg)

What should the cardiology fellow do?

- Continue clop. MD & wait for cath results
- Load immediately with prasugrel 60 mg
- Load immediately with prasugrel 30 mg
- Start prasugrel 10 mg w/o loading
- Ticagrelor?
Trials Comparing IPA Following the Switch from Clopidogrel to **Prasugrel** or to **Ticagrelor**

- TABF (healthy volunteers)
- PRINCIPLE-TIMI 44 (elective PCI)
- ACAPULCO (NSTE-ACS patients undergoing PCI)
- SWAP (recent ACS history)
- TRIPLET (ACS patients undergoing PCI)

- **RESPOND**

- **PLATO (pre specified subgroup analysis)**

*There have been no studies powered to evaluate the clinical safety and efficacy of switching from clopidogrel to prasugrel*

- No IPA data available
Study Design

LD Phase
- Planned elective PCI
- Baseline laboratory measures
- Clopidogrel Naïve
- No planned GP IIb/IIIa
- Clopidogrel 600 mg
- Prasugrel 60 mg
- 0.5 hour post-LD labs; coronary angiography and post-angiography labs
- PCI
- No PCI
- 6 hoursa labs, 15 day events

MD Phase
- Clopidogrel 150 mg x 14 day
- Prasugrel 10 mg x 14 day
- 6 hoursa, 18-24 hours labs
- 15 day clinical events, labb, crossover
- 29 day clinical events, labb
- Prasugrel 10 mg x 14 day
- Clopidogrel 150 mg x 14 day

Primary end points: aLD phase 6 hours IPA (20 μM ADP); bMD phase 15 day and 29 day IPA (20 μM ADP). ADP=Adenosine Diphosphate; GP=Glycoprotein; IPA=Inhibition of Platelet Aggregation; LD=Loading Dose; MD=Maintenance Dose; PCI=Percutaneous Coronary Intervention

Wiviott SD et al. Circulation 2007;116:2923-2932
PRIMARY EP Acute Phase:
IPA 20 μM ADP

P<0.0001 for each

Prasugrel 60 mg

Clopidogrel 600 mg

Wiviott SD et al, Circulation 2007
Maximal Platelet Aggregation (MPA)

$P < 0.0001$ for each

MPA ($\% ; 20 \mu\text{M ADP}$)

- **Clopidogrel 600 mg**
  - Hours 0: 72.5
  - Hours 4: 60.7
  - Hours 24: 51.1

- **Prasugrel 60 mg**
  - Hours 0: 52.4
  - Hours 4: 26.8
  - Hours 24: 23.2

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Wiviott SD et al, Circulation 2007

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PRINCIPLE-TIMI 44: Inhibition of platelet aggregation with loading and maintenance doses


*P < 0.0001 vs clopidogrel
IPA = inhibition of platelet aggregation


**PRIMARY EP Chronic Phase:**

IPA 20 μM ADP

*Difference Between Treatments: 14.9 [95% CI 10.6 – 19.3], P<0.0001*

![Graph showing the difference in IPA (%; 20 μM ADP) between Prasugrel 10 mg and Clopidogrel 150 mg over 30 days. The graph demonstrates a statistically significant difference in platelet inhibition between the two treatments.](image-url)

Wiviott SD et al, Circulation 2007

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SWitching Anti Platelet Study (SWAP)

Patient eligible for enrollment 30 – 330 days post an ACS (Must be prescribed clopidogrel 75 mg qd)

Clopidogrel 75 mg qd x 13 -15 days
Baseline platelet function studies at end of clopidogrel run-in

N=33
Clopidogrel 75mg qd x 13-15 days

N=31
Prasugrel 60 mg loading, 10 mg qd x 13-15 days

N=36
Prasugrel 10 mg qd x 13-15 days

Platelet function studies at 2 hours, 24 hours, 7 and 14 days
SWAP: SWITCHING ANTIPLATELET THERAPY

Maximum Platelet Aggregation (20 μM ADP)

Similar findings obtained with MPA to 5 μM ADP, VASP PRI, and Verify Now® PRU

Angiolillo DJ et al. J Am Coll Cardiol 2010; 56:1017-23
SWAP: Poor Response Rates

Placebo LD/Clopidogrel 75 mg MD (N=33)
Placebo LD/Prasugrel 10 mg MD (N=36)
Prasugrel 60 mg LD/Prasugrel 10 mg MD (N=31)

P = 0.014

Poor response was defined as patients with MPA > 65% to 20 μM ADP assessed by light transmission aggregometry.
LD=Loading Dose; MD=Maintenance Dose; MPA=Maximal Platelet Aggregation.
Study Design

ACS-PCI Patient

ASA

Clopidogrel Placebo  Clopidogrel 600 mg  Clopidogrel 600 mg

Diagnostic Angiogram

If proceeding to PCI → VN-P2Y12 PRU Baseline, Genomics sample

Prasugrel 60 mg  Prasugrel 60 mg  Prasugrel 30 mg

VN-P2Y12 PRU: 2 ± 1 hr, 6 ± 1 hr, 24 ± 4 hr

Prasugrel 10 mg qd  Prasugrel 10 mg qd  Prasugrel 10 mg qd

VN-P2Y12 PRU: 72 ± 24 hr

IPA=Inhibition of Platelet Aggregation; LD=Loading Dose; PRU=P2Y12 Reaction Units
Adapted from http://www.clinicaltrials.gov/ trial number NCT0115738
Safety of Reloading Prasugrel in Addition to Clopidogrel Loading in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

Joshua P. Loh, MBBS, Lakshmana K. Pendyala, MD, Hironori Kitabata, MD, PhD, Rebecca Torguson, MPH, Fang Chen, PhD, Kenneth M. Kent, MD, PhD, Lowell F. Satler, MD, William O. Suddath, MD, Augusto D. Pichard, MD, and Ron Waksman, MD*

Patients with acute coronary syndrome undergoing percutaneous coronary intervention (PCI) commonly receive a loading dose of either clopidogrel or prasugrel, in addition to aspirin. The present study aimed to assess the safety of reloading prasugrel in patients who had initially received a loading dose of clopidogrel compared to prasugrel loading alone. The study included a cohort of 606 consecutive patients with acute coronary syndrome who had received a 60-mg loading dose of prasugrel before PCI. These patients were then categorized into clopidogrel preloading (300 or 600 mg) followed by prasugrel reloading (CP-load group, n = 90) and prasugrel loading only (P-load group, n = 516). Both groups received a 10-mg maintenance dose of prasugrel after PCI. The primary endpoint was in-hospital Thrombolysis In Myocardial Infarction-defined major bleeding. The secondary endpoints were other in-hospital bleeding complications and major cardiovascular events. Patients in the CP-load group compared to the P-load group were younger, with lower rates of cardiovascular risk factors. Significantly more patients in the CP-load group presented with biomarker-positive myocardial infarction (80.0% vs 30.6%, p ≤ 0.001) and cardiogenic shock (5.6% vs 1.4%, p = 0.022). No significant differences (p = NS) were seen in Thrombolysis In Myocardial Infarction major bleeding (2.6% vs 2.8%), Thrombolysis In Myocardial Infarction major or minor bleeding (12.2% vs 7.0%), the need for blood transfusion (2.6% vs 2.1%), and vascular complications (1.3% vs 2.0%) between groups. The CP-load group experienced more in-hospital major adverse cardiac events (5.6% vs 1.6%, p = 0.031), urgent coronary artery bypass grafting (3.3% vs 0.2%, p = 0.011), and longer hospital and intensive care unit stays. In conclusion, preloading with clopidogrel should not be prohibitive to reloading with prasugrel in patients presenting with acute coronary syndrome and undergoing PCI with respect to bleeding and vascular complications. © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;111:841–845)
**Time Course: Pharmacodynamic Population**

**PRU (LS mean), PD population**

![Graph showing PRU levels over time for different treatment groups.]

**% Inhibition (LS mean), PD population**

![Graph showing % inhibition levels over time for different treatment groups.]

- Placebo and Prasugrel 60 mg/10 mg
- Clopidogrel 600 mg and Prasugrel 60 mg/10 mg
- Clopidogrel 600 mg and Prasugrel 30 mg/10 mg

*P=NS at each time point vs. placebo/prasugrel 60 mg, **P=0.049 between the placebo/prasugrel 60 mg group and the clopidogrel 600 mg/prasugrel 60 mg group

Euro PCR. 2012
Transferring from Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome Patients: High on-Treatment Platelet Reactivity Analysis of the TRIPLET Trial
Safety Outcomes

Figure 1. In-hospital bleeding and vascular complications.
TRILOGY ACS Study Design

Medically Managed UA/NSTEMI Patients

Randomization Stratified by:
Age, Country, Prior Clopidogrel Treatment
(Primary analysis cohort — Age < 75 years)

Medical Management Decision ≤72 hrs
(No prior clopidogrel given) — 4% of total

- **Clopidogrel**
  - 300 mg LD
  - 75 mg MD

Medical Management Decision ≤10 days
(Clopidogrel started ≤ 72 hrs in-hospital OR on chronic clopidogrel) — 96% of total

- **Prasugrel**
  - 30 mg LD
  - 5 or 10 mg MD

- **Clopidogrel**
  - 75 mg MD

- **Prasugrel**
  - 5 or 10 mg MD

Minimum Rx Duration: 6 months; Maximum Rx Duration: 30 months

Primary Efficacy Endpoint: CV Death, MI, Stroke

1. All patients were on aspirin and low-dose aspirin (< 100 mg) was strongly recommended. For patients <60 kg or ≥75 years, 5 mg MD of prasugrel was given. Adapted from Chin CT et al. Am Heart J 2010;160:16-22.e1.
Platelet Function Substudy Design

UA/NSTEMI (N = 9326, 52 countries) planned medical management without revascularization

**Prasugrel** vs. **Clopidogrel**

- **Prasugrel**
  - 10 mg (< 75 years and ≥ 60 kg)
  - 5 mg (≥ 75 years; < 75 years and < 60 kg)

- **Clopidogrel**
  - 75 mg (for all)

**Aspirin** ≤ 100 mg (strongly recommended) for all

**PFS**: 2690 (28% of total) participants from 25 countries

**VerifyNow P2Y₁₂ Assay**
- At baseline, at 2 h, and at 1, 3, 6, 12, 18, 24, and 30 mos after randomization

- 126 without valid PRU measurement excluded from analysis

**2564 participants** (**prasugrel, n = 1286** and **clopidogrel, n = 1278**) included in final analysis

**Primary efficacy endpoint:**
- Composite of CV death, MI, and stroke through 30 months

**Key secondary endpoints:**
- All-cause death
- MI
Median On-Treatment PRU Through 30 Months

< 75 years and ≥ 60 kg
Clopidogrel 75 mg/day vs. Prasugrel 10 mg/day
Frequency of High Platelet Reactivity (HPR) > 208 PRU Cut-Point

[Graph showing the percentage of patients with HPR at various time points: Baseline, Hour 2, Month 1, Month 3, Month 6, Month 12, Month 18, Month 24, Month 30. The bars represent clopidogrel and prasugrel treatments.]
Primary Efficacy Endpoint to 30 Months  
(Age < 75 years)

HR (95% CI) ≤ 1 Year:  
0.99 (0.84, 1.16)  
HR (95% CI) > 1 Year:  
0.72 (0.54, 0.97)

HR (95% CI):  
0.91 (0.79, 1.05)  
P = 0.21

Interaction P = 0.07

No. at risk:  
Prasugrel: 3620, 3248, 2359, 1611, 953, 389  
Clopidogrel: 3623, 3244, 2390, 1596, 946, 399
TIMI Major Bleeding to 30 Months  
(Age < 75 years)

HR (95% CI):  
1.31 (0.81, 2.11)  
P = 0.27

No. at risk:  
Prasugrel:  3590  3072  2244  1499  885  427  
Clopidogrel: 3590  3116  2303  1552  925  425
PLATO study design

NSTE-ACS (moderate-to-high risk) STEMI (if PPCI planned)
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

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

PCI = percutaneous coronary intervention; ASA = acetylsalicylic acid;
CV = cardiovascular; TIA = transient ischaemic attack
## Study medication

<table>
<thead>
<tr>
<th>Medication</th>
<th>Ticagrelor (n=9,333)</th>
<th>Clopidogrel (n=9,291)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Start of randomised treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time after start of chest pain, h, median</td>
<td>11.3</td>
<td>11.3</td>
</tr>
<tr>
<td><strong>Randomised treatment compliance, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Premature discontinuation of study drug</td>
<td>23.4</td>
<td>21.5</td>
</tr>
<tr>
<td><strong>Clopidogrel start-up, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel in hospital before randomisation</td>
<td>46.0</td>
<td>46.1</td>
</tr>
<tr>
<td><strong>Invasive procedures at index hospitalisation, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Planned invasive treatment</td>
<td>72.1</td>
<td>71.9</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td>81.4</td>
<td>81.5</td>
</tr>
<tr>
<td>PCI during index hospitalisation</td>
<td>60.9</td>
<td>61.1</td>
</tr>
<tr>
<td>Cardiac surgery</td>
<td>4.3</td>
<td>4.7</td>
</tr>
</tbody>
</table>
## Primary efficacy endpoint in **selected** pre-defined subgroups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard Ratio (95% CI)</th>
<th>Total Patients</th>
<th>KM % at Month 12</th>
<th>HR (95% CI)</th>
<th>p-value (Interaction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall treatment effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td></td>
<td>8,430</td>
<td>9.3 11.0</td>
<td>0.85 (0.74, 0.97)</td>
<td></td>
</tr>
<tr>
<td>Definition of STEMI*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>Persist. ST-segment elev.</td>
<td></td>
<td>6,284</td>
<td>8.9 10.4</td>
<td>0.87 (0.74, 1.02)</td>
<td></td>
</tr>
<tr>
<td>LBBB</td>
<td></td>
<td>720</td>
<td>14.5 14.5</td>
<td>0.89 (0.59, 1.34)</td>
<td></td>
</tr>
<tr>
<td>Final diagnosis (only)</td>
<td></td>
<td>886</td>
<td>8.4 12.5</td>
<td>0.67 (0.44, 1.02)</td>
<td></td>
</tr>
<tr>
<td>Intended clop dose ≤24h post first dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.90</td>
</tr>
<tr>
<td>300 mg</td>
<td></td>
<td>5,505</td>
<td>10.1 11.9</td>
<td>0.84 (0.71, 0.99)</td>
<td></td>
</tr>
<tr>
<td>600 mg</td>
<td></td>
<td>2,922</td>
<td>7.9 9.3</td>
<td>0.86 (0.67, 1.11)</td>
<td></td>
</tr>
<tr>
<td>Time from index event to therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.89</td>
</tr>
<tr>
<td>&lt;12 hours</td>
<td></td>
<td>6,072</td>
<td>8.3 9.5</td>
<td>0.86 (0.73, 1.03)</td>
<td></td>
</tr>
<tr>
<td>≥12 hours</td>
<td></td>
<td>2,270</td>
<td>12.0 14.2</td>
<td>0.85 (0.67, 1.07)</td>
<td></td>
</tr>
</tbody>
</table>

*Patients with LBBB and ST-elevation were classified as LBBB.

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5 μM ADP-Induced Aggregation
8 hrs After Loading Dose

**p-values between genotypes**
(UM, EM, IM, PM)
TIG = 0.152, CLP = 0.289

**p-values between genotypes**
(LOF, Non-LOF)
TIG = 0.518, CLP = 0.078

**p-values between genotypes**
(GOF, LOF, EM)
TIG = 0.117, CLP = 0.168

UM = ultra rapid metabolizer
Extensive metabolizer
Intermediate metabolizer
Poor metabolizer

Wallentin et al. The Lancet 2010; DOI:10.1016/S0140-6736(10)61274-3
What should the cardiology fellow do?

- Continue clop. MD & wait for cath results
- Load immediately with prasugrel 60 mg
- Load immediately with prasugrel 30 mg
- Start prasugrel 10 mg w/o loading
- Ticagrelor?
Addendum

- The patient was loaded with 60 mg prasugrel on admission.
- Taken to cath lab the next morning.
- PCI to LCX with DES.
- Discharge next day.
Thank you for your attention