# The Effect of Pre-treatment with Prasugrel vs. Clopidogrel in Patients with STEMI Undergoing Primary PCI on Angiographic and Clinical Outcomes

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# Background

- Prasugrel is a 3rd generation theinopyridine shown to inhibit ADP-induced platelet aggregation more rapidly, more consistently and to a greater extent than clopidogrel.

- In the TRITON-TIMI 38 trial prasugrel was more effective than clopidogrel for prevention of ischemic events in patients with ACS, scheduled for PCI, although with an increased risk of bleeding

# Background

- In the TRITON-TIMI 38 trial the majority of patients received the study drug during the PCI, and not as pre-treatment.

- There is limited data on the efficacy of prasugrel in the setting of “real-life” all-comer patients with STEMI, treated with primary PCI

# Aim

- To compare the efficacy of prasugrel and clopidogrel pre-treatment in patients with STEMI treated with primary PCI.

# Methods

- We employed the primary PCI registry of the Rabin Medical Center which includes all patients with STEMI treated with primary PCI in our institution.
- From 2001 all patients with STEMI are entered into a clinical database (registry) and followed
- Excluded from the current analysis: were patients with cardiogenic shock, patients admitted more than 12 hrs after the beginning of chest pain

# Methods

- Only patients who received pre-treatment with clopidogrel or prasugrel, before being transferred to the catheterization laboratory, were included in the current analysis ($n_{total}$ = 1102)

- They were allocated into 2 groups:

1. Clopidogrel (300-600mg) pretreatment (n=965)
2. Prasugrel (60 mg) pretreatment (n=137)

# Methods

- Of note: In the past 2 years the majority of patients were treated with prasugrel, whereas clopidogrel was used mainly in the period before
- All patients were also pretreated with aspirin 200-325 mg
- PCI was performed according to standard practice. GP IIb/IIIa use and stent choice was at the discretion of the operator

# Methods

- Angiographic endpoints:  TIMI flow at the beginning of the PCI, TIMI myocardial perfusion grade (blush) at the end of the procedure
- Clinical endpoints:  death, nonfatal re-MI, target vessel revascularization (TVR), definite stent thrombosis (as defined by the ARC criteria)
- MACE: death, nonfatal MI or TVR

# Results – clinical characteristics

| Variable | Clopidogrel (n=965) | Prasugrel (n=137) | P value |
|---|---|---|---|
| **Age (years)** | **61±13** | **56±9** | **0.0001** |
| Women | 17.6% | 12.4% | 0.1 |
| **Diabetes** | **26%** | **17.5%** | **0.03** |
| Hypertension | 53.6% | 47.5% | 0.2 |
| Hyperlipidemia | 52% | 60% | 0.1 |
| Current smoker | 46.5% | 52.6% | 0.3 |
| Prior MI | 12.4% | 16% | 0.7 |
| S/P CABG | 2.8% | 2.9% | 0.9 |
| **Renal Insufficiency** | **12.4%** | **5.1%** | **0.01** |
| Anemia | 23.6% | 22% | 0.6 |
| **Anterior Wall MI** | **46%** | **41%** | **0.06** |
| LVEF < 40% | 39.6% | 34.3% | 0.2 |

# Results – time intervals

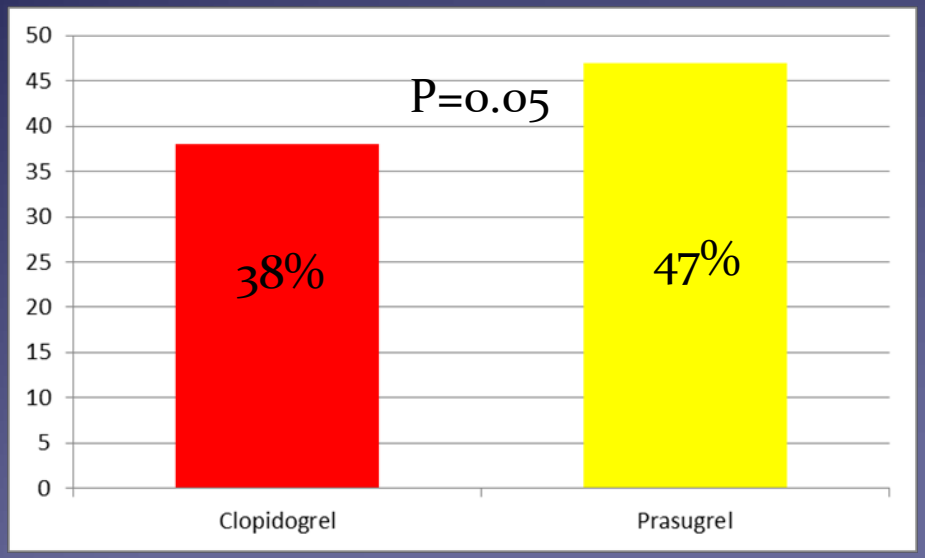
| | Clopidogrel (n=965) | Prasugrel (n=137) | P value |
|---|---|---|---|
| **Chest pain – emergency room (hrs)** | **3±2.6** | **2.4±2** | **0.004** |
| Emergency room – PCI (hrs) | 1.6±1.7 | 1.4±1 | 0.1 |

# Results – angiographic and PCI factors

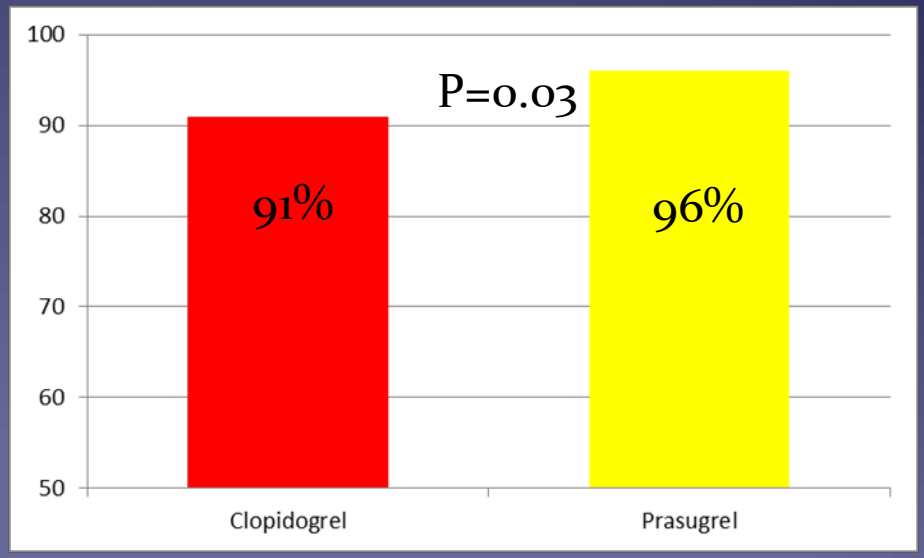
| Variable | Clopidogrel (n=965) | Prasugrel (n=137) | P value |
|---|---|---|---|
| Culprit vessel | | | 0.1 |
| LAD | 46.3% | 44% | |
| LCX | 15% | 15.3% | |
| RCA | 36.5% | 40% | |
| **Visible thrombus** | **83%** | **69%** | **0.004** |
| No reflow | 4.4% | 4.4% | 1 |
| **GP IIb/IIIa use** | **71%** | **57%** | **0.001** |
| **≥ 2 stents used** | **31%** | **40%** | **0.03** |
| **DES use** | **17.1%** | **33.6%** | **0.001** |
| Mean stent width (mm) | 3.1±0.5 | 3.1±0.5 | 0.1 |
| Total stent length (mm) | 19±6 | 18±6 | 0.1 |

# Results – angiographic outcomes

**Pre TIMI 2-3 flow**




**Post Blush grade 2-3**



# Results – clinical outcomes

| Variable | Clopidogrel (n=965) | Prasugrel (n=137) | P value |
|---|---|---|---|
| **30 days** | | | |
| **Death** | **2.7%** | **0** | **0.05** |
| Re-MI | 1.8% | 0.8% | 0,4 |
| Stent thrombosis | 1.2% | 0,8% | 0.6 |
| TVR | 2.6% | 0.8% | 0.2 |
| **MACE** | **6.3%** | **2.3%** | **0.05** |
| EF (%) | 43±10 | 45±10 | 0.053 |
| **6 months** | | | |
| **Death** | **4.2%** | **0** | **0.04** |
| Re-MI | 3.4% | 2.2% | 0.5 |
| Stent thrombosis | 2% | 1.7% | 0.5 |
| TVR | 7.8% | 3.7% | 0.4 |
| MACE | 13.6% | 5.8% | 0,1 |

# Results

- Multivariate logistic regression analysis showed that prasugrel treatment was associated with an odds ratio of 1.61 for pre TIMI flow 2-3 (1.1-2.35, p=0.01).

- The model was adjusted for age, sex, DM, Renal insufficiency, MI location and propensity score for clopidogrel/prasugrel.

# Results:

## Independent predictors of pre PCI TIMI flow 2-3 in multivariate analysis:

| Variable | OR | CI | P value |
|---|---|---|---|
| GFR<60 | 0.85 | 0.74-0.99 | 0.036 |
| Anterior MI | 0.8 | 0.68-0.95 | 0.01 |
| Prasugrel | 1.61 | 1.1-2.35 | 0.01 |

# Results

Regarding clinical outcomes,

- In multivariate analysis, no differences in mortality were found between the two study groups in 30d and 6m.

- Independent predictors of 6m mortality were age>65, GFR<60, Killip score>1 at presentation, EF<40%

# Limitations:

- Registry
- There were significant imbalances in clinical characteristics between the groups
- Different time intervals of recruitment
- Clopidogrel 300-600mg

# Conclusions

- In a “real-life” consecutive registry of patients with STEMI treated with primary PCI, pre-treatment with prasugrel appeared to be associated with better pre PCI TIMI flow, compared with clopidogrel.

# THANK YOU

**DIVISION OF CARDIOVASCULAR and RENAL PRODUCTS**

***Revised* Secondary CDTL Review**

Date: January 9, 2009

NDA: 22-307
EFFIENT™ (prasugrel hydrochloride) Tablets
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**Table 16. FDA Subgroup Analysis of Primary Endpoint by Timing of Loading Dose (Composite of CV Death, Nonfatal MI, or Nonfatal Stroke) (TAAL)**

| Timing of Loading Dose | UA/NSTEMI | | | STEMI | | | All ACS | | |
|---|---|---|---|---|---|---|---|---|---|
| | Prasugrel (N=5044) | Clopidogrel (N=5030) | HR 95% CI P-value | Prasugrel (N=1769) | Clopidogrel (N=1765) | HR 95% CI P-value | Prasugrel (N=6813) | Clopidogrel (N=6795) | HR 95% CI P-value |
| 0-2 hrs prior to PCI | N=1078 n=103 | N=1045 n=117 | 0.85 0.65, 1.11 0.3212 | N=432 n=52 | N=440 n=59 | 0.90 0.62, 1.30 0.5843 | N=1510 n=155 | N=1485 n=176 | 0.86 0.70, 1.08 0.2340 |
| 2-6 hrs prior to PCI | N=61 n=4 | N=67 n=5 | 0.9191 | N=9 n=1 | N=7 n=1 | NE | N=70 n=5 | N=74 n=6 | 0.90 0.28, 2.95 0.8927 |
| 6-12 hrs prior to PCI | N=16 n=3 | N=9 n=2 | 0.84 0.14, 5.08 0.8530 | N=4 n=0 | N=1 n=1 | NE | N=20 n=3 | N=10 n=3 | 0.46 0.09, 2.30 0.3263 |
| ≥12 hrs prior to PCI | N=102 n=15 | 84 12 | 1.01 0.47, 2.16 0.9651 | N=10 n=1 | N=5 n=1 | NE- | N=112 n=16 | N=89 n=13 | 1.01 0.47, 2.16 0.8358 |
| **During PCI** | **N=3660 n=329** | **3671 400** | **0.82 0.71, 0.95 0.0081** | **N=1221 n=110** | **N=1213 n=143** | **0.75 0.59, 0.97 0.0209** | **N=4881 n=439** | **N=4884 n=543** | **0.80 0.71, 0.91 0. 0005** |
| Post PCI | N=1078 n=103 | 1045 117 | 0.85 0.65, 1.11 0.3212 | N=15 n=2 | N=21 n=2 | NE | N=63 n=7 | N=68 n=16 | 0.43 0.18, 1.04 0.0391 |

ACS=acute coronary syndrome; CI=confidence interval, CV=cardiovascular, HR=hazard ratio; NE=not evaluated; NSTEMI=non-ST-elevation myocardial infarction; STEMI=ST-elevation myocardial infarction; UA=unstable angina.
N=number of subjects in subgroup; n=number of subjects experiencing the primary endpoint.
Analysis by Ququan Liu, M.D., M.S., Biometrics, FDA.

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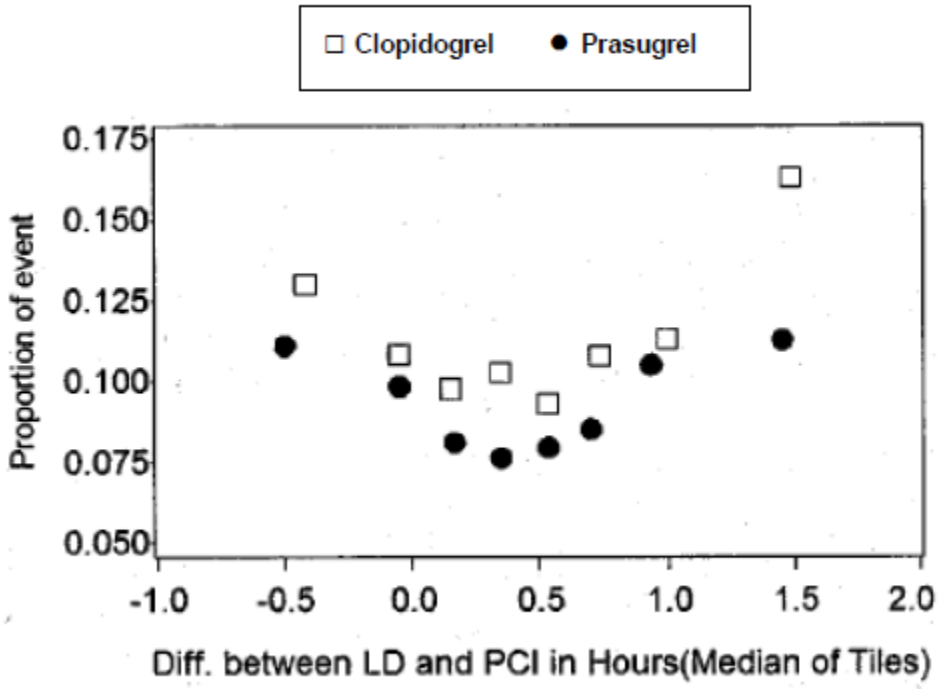
**Figure 11. Timing of Loading Dose and Effect on Primary Endpoint (TAAL)**




**(Analysis by Rajanikanth Madabushi, Ph.D., Pharmacometrics, FDA)**

# TRITON TIMI-38 subgroup analysis for ST elevation MI

## Montalescot et al, Lancet 2009 ;373

- Table 2: major efficacy and safety endpoints at 30d:

| | Clopidogrel | Prasugrel | Hazard ratio (95% CI) | p | Number needed to treat (95% CI)* |
|---|---|---|---|---|---|
| **Efficacy endpoints** | | | | | |
| Primary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) | | | | | |
| All STEMI cohort | 166 (9·5%) | 115 (6·5%) | 0·68 (0·54–0·87) | 0·0017 | 35 (24–84) |
| Primary PCI | 101 (8·2%) | 79 (6·6%) | 0·80 (0·60–1·08) | 0·1440 | .. |
| Secondary PCI | 65 (12·3%) | 36 (6·4%) | 0·50 (0·34–0·76) | 0·0008 | 17 (12–35) |

- Table 3: major efficacy and safety endpoints at 15m:

| | Clopidogrel | Prasugrel | Hazard ratio (95% CI) | p | Number needed to treat (95% CI)* |
|---|---|---|---|---|---|
| **Efficacy endpoints** | | | | | |
| Primary endpoint (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke) | | | | | |
| All STEMI cohort | 216 (12·4%) | 174 (10·0%) | 0·79 (0·65–0·97) | 0·0221 | 41 (24–266) |
| Primary PCI | 142 (11·6%) | 121 (10·2%) | 0·87 (0·68–1·11) | 0·2662 | .. |
| Secondary PCI | 74 (14·1%) | 53 (9·6%) | 0·65 (0·46–0·92) | 0·0154 | 21 (14–100) |

# Effect of *Clopidogrel* Pretreatment on Angiographic and Clinical Outcomes in Patients Undergoing Primary Percutaneous Coronary Intervention for ST-Elevation Acute Myocardial Infarction

Eli I. Lev, MD*, Ran Kornowski, MD, Hana Vaknin-Assa, MD, David Brosh, MD, Shmuel Fuchs, MD, Alexander Battler, MD, and Abid Assali, MD

Pretreatment with clopidogrel before elective primary percutaneous coronary intervention (PCI) has been shown to reduce ischemic complications. There are limited data about the value of clopidogrel pretreatment in the setting of PCI for ST-elevation myocardial infarction (STEMI). We aimed to examine the effect of clopidogrel preloading on angiographic and clinical outcomes in patients with STEMI who were treated with PCI. We conducted a prospective registry of all patients treated with primary PCI for STEMI from March 2003 to June 2006. Excluded were patients with cardiogenic shock. For the current analysis, patients (n = 292) were allocated into 2 groups. One group received clopidogrel loading dose before PCI (in the emergency department or coronary care unit, n = 165); the other,immediately after PCI (n = 127). TIMI myocardial perfusion (TMP) grade at the end of PCI and 30-day and 6-month clinical outcomes were assessed. Clinical characteristics were similar among the groups. However, patients pretreated with clopidogrel were more likely to receive aspirin and β blockers before the current admission. TMP grade 3 occurred in a higher proportion of patients in the clopidogrel pretreatment group than in the no-pretreatment group (85% vs 71%, p = 0.01). Multivariate logistic regression analysis showed that clopidogrel pretreatment was associated with an odds ratio of 2.2 for TMP grade 3 (1.2 to 3.9, p = 0.01). Furthermore, the incidence of reinfarction at 30 days was lower in the pretreatment group (0% vs 3.2%, respectively, p = 0.04). In conclusion, these findings support the early use of clopidogrel in patients with STEMI who are treated with primary PCI.  (Am J Cardiol 2008;101:435–439)