

eeting of 2014.12.12-13 Novotel Ambassador Busan, Korea

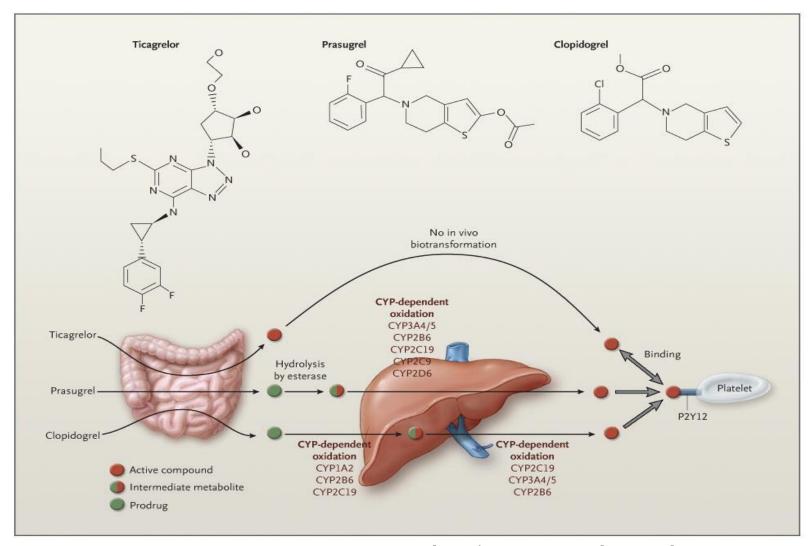
## New P2Y12 Receptor Inhibitors in Korean AMI Patients

Keun-Ho Park, M.D.

Chonnam National University Hospital



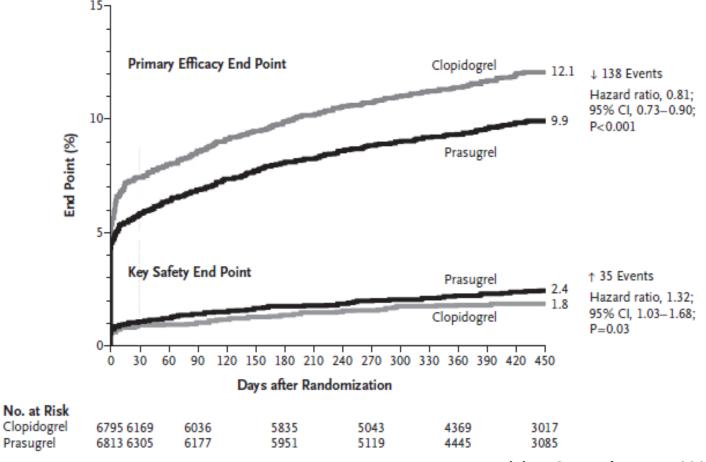
## Biotransformation and Mode of Action of Clopidogrel, Prasugrel, and Ticagrelor



Schömig A. N Engl J Med 2009;361:1108-1111.

### **TRITON-TIMI 38**

Superior efficacy of Prasugrel vs. clopidogrel : 19% RRR of primary efficacy endpoints, CV Death, MI, Stroke.



Wiviott SD et al. NEJM. 2007;357:2001-15

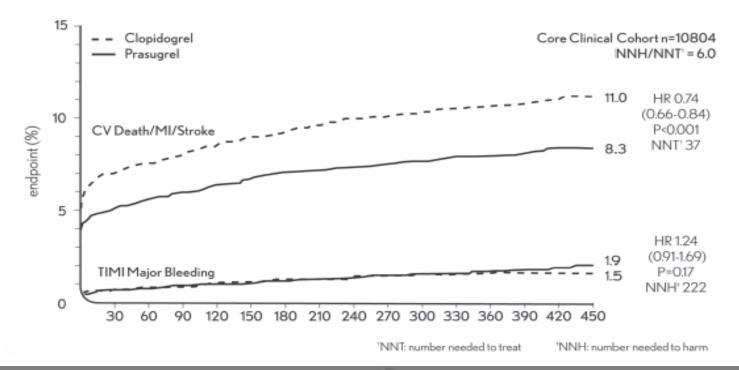


## **Prasugrel Core Clinical Cohort**

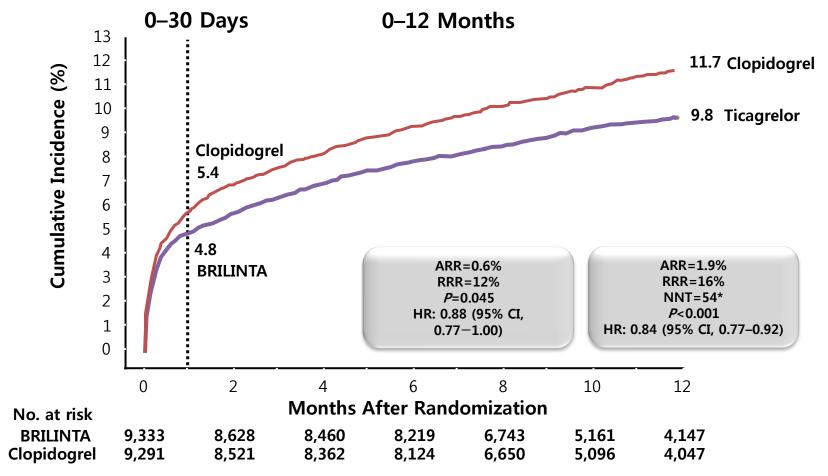
 While prasugrel demonstrated a greater benefit on ischemic end points in the indicated 'Core clinical cohort\*' compared with the total TRITON-TIMI 38 trial population, there was no significant increase in the risk of TIMI major bleeding <sup>2</sup>

Core clinical cohort -no history of stroke/transient ischemic attack, age <75years, and weight ≥60kg</li>

Figure. Main results figure in Core clinical cohort



### **PLATO: Primary Efficacy Endpoint** (CV death, MI, or Stroke)



Both groups included aspirin. \*NNT at one year.

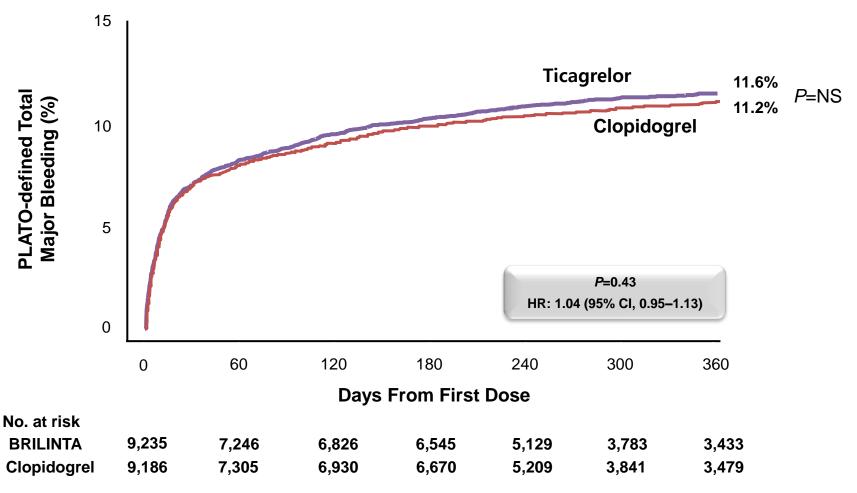
Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

ARR: Absolute risk reduction, RRR: Relative risk reduction

NNT: Number needed to treat, HR: Hazard ration, CI: Confidential interval



## **PLATO: Primary Safety Endpoint** (Total PLATO major bleeding)



Both groups included aspirin.

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.



### Purpose

✓ To evaluate the efficacy and safety of New P2Y12 receptor inhibitors (Prasugrel or Ticagrelor) compared to clopidogrel in Korean patients with AMI underwent successful PCI

## KOREA CENTERS FOR DISEASE CONTROL & PREVENTION

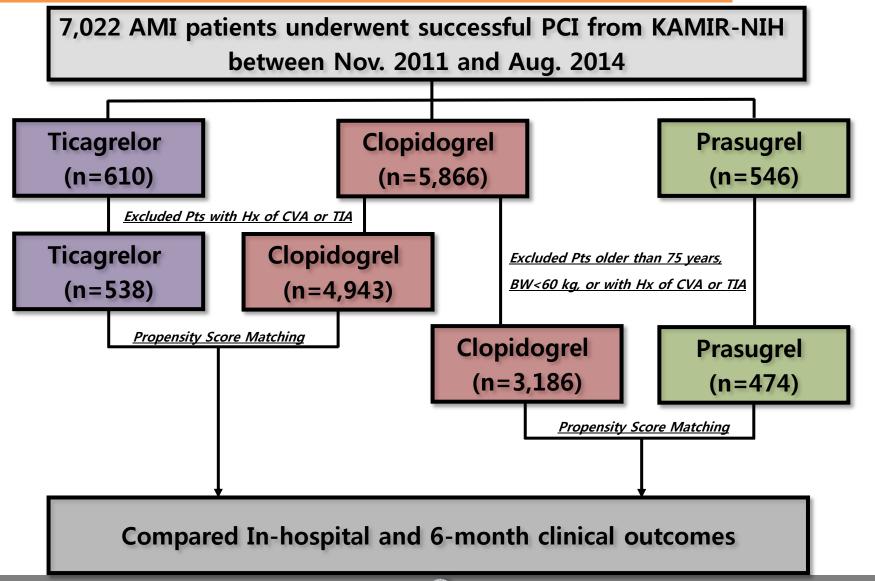
# Prospective Cohort Study for Acute Myocardial Infarction Prognostic and Surveillance Index (KAMIR-NIH registry)



### **Study Flow Chart**

#### **Exclusion criteria**

: the Pts with in-hospital switching among three anti-platelet agents



#### **Definition**

#### ✓ Primary end-point

: a composite of cardiac death, MI, and stroke during hospitalization

#### ✓ Safety end-point

: Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding during hospitalization

### ✓ 2ndary end-points

: the composite of cardiac death, non-fatal MI, stroke, and target vessel revascularization at 6-month follow-up.

### **Baseline Clinical Characteristics**

|   | Ticagrelor (n=538) | Clopidogrel (n=4,943) | p-value |
|---|--------------------|-----------------------|---------|
| Age, years                                      | 61.57±12.16        | 63.88±12.53           | <0.001  |
| Male gender (%)                                 | 402 (74.7)         | 3,630 (73.4)          | 0.521   |
| Hypertension (%)                                | 230 (42.8)         | 2,462 (49.8)          | 0.002   |
| Diabetes (%)                                    | 127 (23.6)         | 1,376 (27.8)          | 0.037   |
| Dyslipidemia (%)                                | 62 (11.3)          | 550 (11.1)            | 0.882   |
| Current smoker (%)                              | 242 (45.0)         | 1,980 (40.1)          | 0.027   |
| Family Hx of CAD (%)                            | 42 (7.8)           | 344 (7.0)             | 0.466   |
| Previous MI (%)                                 | 25 (4.6)           | 365 (7.4)             | 0.019   |
| Previous angina (%)                             | 20 (3.7)           | 505 (10.2)            | <0.001  |
| Killip class (%)                                |                    |                       | <0.001  |
| I   | 458 (85.1)         | 3,829 (77.5)          |         |
| п   | 34 (6.3)           | 498 (10.1)            |         |
| III   | 21 (3.9)           | 384 (7.8)             |         |
| IV  | 25 (9.7)           | 232 (4.7)             |         |
| Final diagnosis                                 |                    |                       | <0.001  |
| Non ST elevation MI                             | 204 (37.9)         | 2,497 (50.5)          |         |
| ST elevation MI                                 | 334 (62.1)         | 2,446 (49.5)          |         |
| LV ejection fraction, %                         | 52.53±10.22        | 51.73±11.15           | 0.088   |
| Creatinine clearance, ml/min/1.73m <sup>2</sup> | 84.08±48.99        | 76.28±36.80           | <0.001  |

### **Baseline Procedural Characteristics**

|                                     | Ticagrelor (n=538) | Clopidogrel (n=4,943) | p-value |
|-------------------------------------|--------------------|-----------------------|---------|
| Vascular access (%)                 |                    |                       | <0.001  |
| Transradial approach                | 211 (39.2)         | 1,396 (28.2)          |         |
| Transfemoral approach               | 323 (60.0)         | 3,513 (71.1)          |         |
| Both approach                       | 4 (0.7)            | 34 (0.7)              |         |
| Infarct-related artery (%)          |                    |                       | 0.774   |
| LAD                                 | 240 (44.6)         | 2,284 (46.2)          |         |
| LCX                                 | 93 (17.3)          | 889 (18.0)            |         |
| RCA                                 | 193 (35.9)         | 1,666 (33.7)          |         |
| LM                                  | 12 (2.2)           | 104 (2.1)             |         |
| Involved vessel number (%)          |                    |                       | 0.006   |
| Single vessel                       | 270 (50.2)         | 2,392 (48.4)          |         |
| Two vessel                          | 154 (28.6)         | 1,516 (30.7)          |         |
| Three vessel                        | 93 (17.3)          | 831 (16.8)            |         |
| LM disease (simple)                 | 8 (1.5)            | 20 (0.4)              |         |
| LM disease (complex)                | 13 (2.4)           | 184 (3.7)             |         |
| ACC/AHA Type B2/C (%)               | 479 (89.0)         | 4,117 (83.3)          | 0.001   |
| Glycoprotein IIb/IIIa inhibitor (%) | 94 (17.5)          | 687 (13.9)            | 0.024   |
| Stent diameter at target lesion     | 3.17±0.46          | 3.12±0.44             | 0.005   |
| Stent length at target lesion       | 25.82±7.07         | 24.79±7.31            | 0.003   |

## **In-hospital Medication**

|                              | Ticagrelor (n=538) | Clopidogrel (n=4,943) | p-value |
|------------------------------|--------------------|-----------------------|---------|
| Aspirin (%)                  | 538 (100)          | 4,943 (100)           | 1.000   |
| Clopiodogrel (%)             | 0 (0.0)            | 4,943 (100)           | <0.001  |
| Ticagrelor (%)               | 538 (100)          | 0 (0.0)               | <0.001  |
| Cilostazol (%)               | 5 (0.9)            | 877 (17.7)            | <0.001  |
| Beta-blocker (%)             | 464 (86.2)         | 4,268 (86.3)          | 0.949   |
| Calcium channel blockers (%) | 15 (2.8)           | 309 (6.3)             | 0.001   |
| ACEi or ARB (%)              | 450 (83.6)         | 4,081 (82.6)          | 0.529   |
| Statin (%)                   | 512 (95.2)         | 4,561 (92.3)          | 0.015   |

### **Baseline Clinical Characteristics (PSM)**

|   | Ticagrelor (n=538) | Clopidogrel (n=538) | p-value |
|---|--------------------|---------------------|---------|
| Age, years                                      | 61.57±12.16        | 62.15±12.51         | 0.438   |
| Male gender (%)                                 | 402 (74.7)         | 411 (76.4)          | 0.523   |
| Hypertension (%)                                | 230 (42.8)         | 234 (43.5)          | 0.806   |
| Diabetes (%)                                    | 127 (23.6)         | 139 (25.8)          | 0.396   |
| Dyslipidemia (%)                                | 61 (11.3)          | 58 (10.8)           | 0.771   |
| Current smoker (%)                              | 242 (45.0)         | 237 (44.1)          | 0.759   |
| Family Hx of CAD (%)                            | 42 (7.8)           | 36 (6.7)            | 0.481   |
| Previous MI (%)                                 | 25 (4.6)           | 27 (5.0)            | 0.887   |
| Previous angina (%)                             | 20 (3.7)           | 21 (3.9)            | 1.000   |
| Killip class (%)                                |                    |                     | 0.294   |
| I   | 458 (85.1)         | 472 (87.7)          |         |
| II  | 34 (6.3)           | 27 (5.0)            |         |
| III   | 21 (3.9)           | 24 (4.5)            |         |
| IV  | 25 (4.6)           | 15 (2.8)            |         |
| Final diagnosis                                 |                    |                     | 0.851   |
| Non ST elevation MI                             | 204 (37.9)         | 207 (38.5)          |         |
| ST elevation MI                                 | 334 (62.1)         | 331 (61.5)          |         |
| LV ejection fraction, %                         | 52.53±10.22        | 52.99±10.56         | 0.475   |
| Creatinine clearance, ml/min/1.73m <sup>2</sup> | 84.08±48.99        | 84.44±39.52         | 0.895   |

### **Baseline Procedural Characteristics (PSM)**

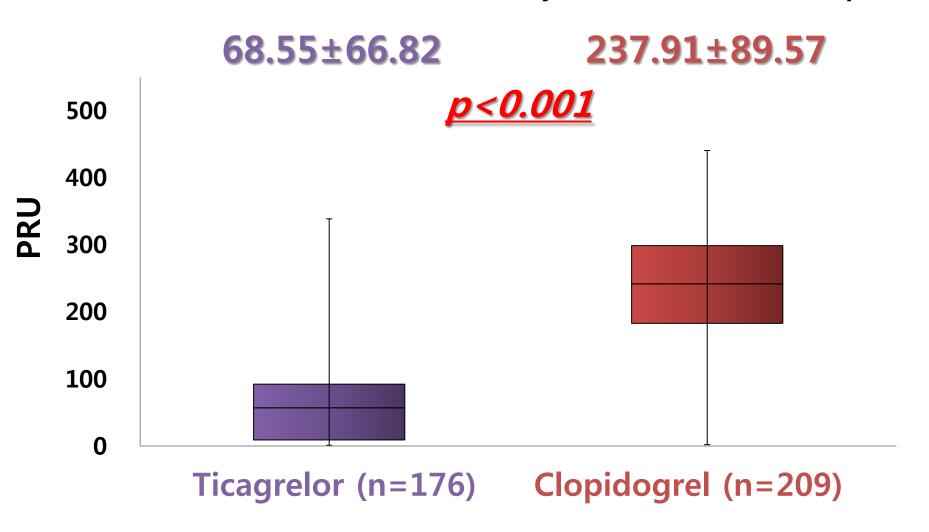
|                                     | Ticagrelor (n=538) | Clopidogrel (n=538) | p-value |
|-------------------------------------|--------------------|---------------------|---------|
| Vascular access (%)                 |                    |                     | 0.580   |
| Transradial approach                | 211 (39.2)         | 218 (40.5)          |         |
| Transfemoral approach               | 323 (60.0)         | 313 (58.2)          |         |
| Both approach                       | 4 (0.7)            | 7 (1.3)             |         |
| Infarct-related artery (%)          |                    |                     | 0.991   |
| LAD                                 | 240 (44.6)         | 239 (44.5)          |         |
| LCX                                 | 93 (17.3)          | 91 (16.9)           |         |
| RCA                                 | 193 (35.9)         | 197 (36.6)          |         |
| LM                                  | 12 (2.2)           | 11 (2.0)            |         |
| Involved vessel number (%)          |                    |                     | 0.762   |
| Single vessel                       | 270 (50.2)         | 264 (49.1)          |         |
| Two vessel                          | 154 (28.6)         | 156 (29.0)          |         |
| Three vessel                        | 93 (18.2)          | 93 (17.3)           |         |
| LM disease (simple)                 | 8 (1.5)            | 4 (0.7)             |         |
| LM disease (complex)                | 13 (2.4)           | 16 (3.0)            |         |
| ACC/AHA Type B2/C (%)               | 479 (89.0)         | 476 (88.5)          | 0.772   |
| Glycoprotein IIb/IIIa inhibitor (%) | 94 (17.5)          | 88 (16.4)           | 0.626   |
| Stent diameter at target lesion     | 3.17±0.46          | 3.14±0.44           | 0.163   |
| Stent length at target lesion       | 25.82±7.07         | 24.73±7.10          | 0.014   |

### **In-hospital Medication (PSM)**

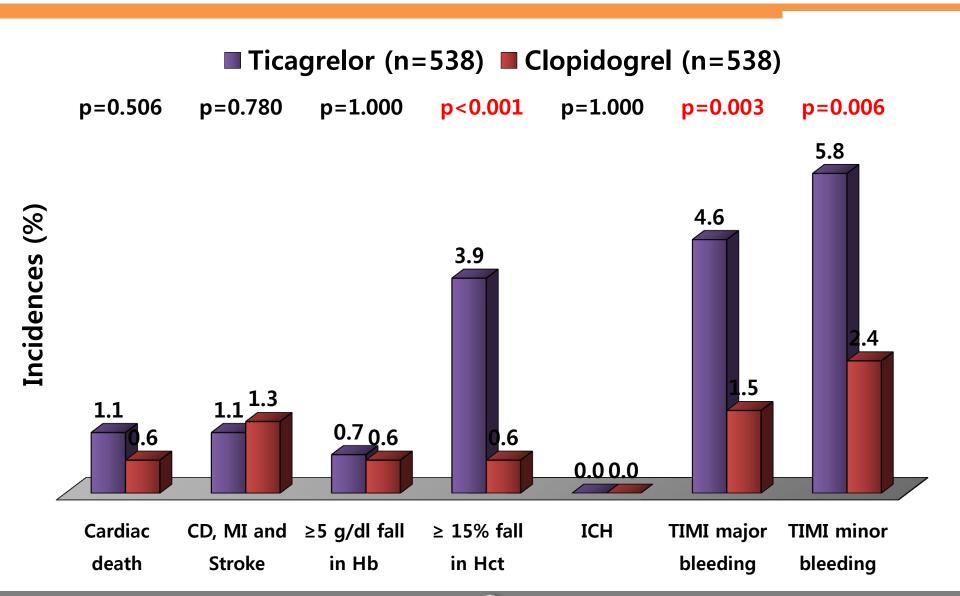
|                              | Ticagrelor (n=538) | Clopidogrel (n=538) | p-value |
|------------------------------|--------------------|---------------------|---------|
| Aspirin (%)                  | 538 (100)          | 538 (100)           | 1.000   |
| Clopiodogrel (%)             | 0 (0.0)            | 538 (100)           | <0.001  |
| Ticagrelor (%)               | 538 (100)          | 0 (0.0)             | <0.001  |
| Cilostazol (%)               | 5 (0.9)            | 99 (18.4)           | <0.001  |
| Beta-blocker (%)             | 464 (86.2)         | 468 (87.0)          | 0.720   |
| Calcium channel blockers (%) | 15 (2.8)           | 13 (2.4)            | 0.708   |
| ACEi or ARB (%)              | 450 (83.6)         | 454 (84.4)          | 0.739   |
| Statin (%)                   | 512 (95.2)         | 509 (94.6)          | 0.678   |

### PRU between Ticagrelor vs. Clopidogrel

Only available 35.8% of all patients



### In-hospital Clinical Outcomes in Ticagrelor

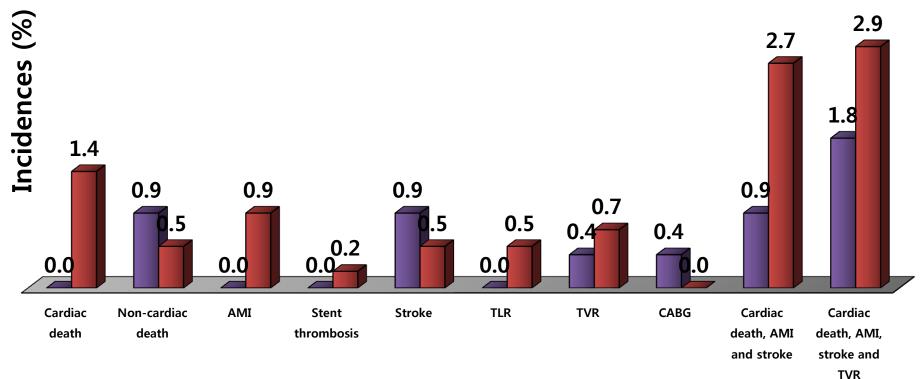


### 6-month Clinical Outcomes in Ticagrelor

Only available 62.4% of Survivors

■ Ticagrelor (n=228) ■ Clopidogrel (n=443)

p = 0.101p = 0.608p = 0.305p=1.000 p=0.608 p=0.551 p=1.000 p=0.340 p=0.156



### **Baseline Clinical Characteristics**

|   | Prasugrel (n=474) | Clopidogrel (n=3,186) | p-value |
|---|-------------------|-----------------------|---------|
| Age, years                                      | 55.13±8.93        | 57.71±9.914           | <0.001  |
| Male gender (%)                                 | 446 (94.1)        | 2,870 (90.1)          | 0.005   |
| Hypertension (%)                                | 179 (37.8)        | 1,409 (44.2)          | 0.008   |
| Diabetes (%)                                    | 100 (21.1)        | 824(25.9)             | 0.026   |
| Dyslipidemia (%)                                | 53 (11.3)         | 414 (13.0)            | 0.270   |
| Current smoker (%)                              | 273 (57.6)        | 1,637 (51.4)          | 0.012   |
| Family Hx of CAD (%)                            | 30 (6.3)          | 294 (9.2)             | 0.038   |
| Previous MI (%)                                 | 22 (4.6)          | 225 (7.1)             | 0.050   |
| Previous angina (%)                             | 21 (4.4)          | 291 (9.1)             | 0.001   |
| Killip class (%)                                |                   |                       | 0.008   |
| I   | 415 (87.6)        | 2,584 (81.1)          |         |
| II  | 25 (5.3)          | 265 (8.3)             |         |
| III   | 16 (3.4)          | 174 (5.5)             |         |
| IV  | 18 (3.8)          | 163 (5.1)             |         |
| Final diagnosis                                 |                   |                       | <0.001  |
| Non ST elevation MI                             | 169 (35.7)        | 1,522 (47.8)          |         |
| ST elevation MI                                 | 305 (64.3)        | 1,664 (52.2)          |         |
| LV ejection fraction, %                         | 52.57±9.80        | 52.64±10.63           | 0.893   |
| Creatinine clearance, ml/min/1.73m <sup>2</sup> | 100.57±33.38      | 89.93±34.40           | <0.001  |

### **Baseline Procedural Characteristics**

|                                     | Prasugrel (n=474) | Clopidogrel (n=3,186) | p-value |
|-------------------------------------|-------------------|-----------------------|---------|
| Vascular access (%)                 |                   |                       | <0.001  |
| Transradial approach                | 196 (41.4)        | 927 (29.1)            |         |
| Transfemoral approach               | 277 (58.4)        | 2,245 (70.5)          |         |
| Both approach                       | 1 (0.2)           | 14 (0.4)              |         |
| Infarct-related artery (%)          |                   |                       | 0.616   |
| LAD                                 | 224 (47.3)        | 1,474 (46.3)          |         |
| LCX                                 | 83 (17.5)         | 603 (18.9)            |         |
| RCA                                 | 160 (33.8)        | 1,038 (32.6)          |         |
| LM                                  | 7 (1.5)           | 71 (2.2)              |         |
| Involved vessel number (%)          |                   |                       | 0.085   |
| Single vessel                       | 275 (58.6)        | 276 (58.8)            |         |
| Two vessel                          | 133 (28.4)        | 111 (23.7)            |         |
| Three vessel                        | 51 (10.9)         | 65 (13.9)             |         |
| LM disease (simple)                 | 4 (0.9)           | 2 (0.4)               |         |
| LM disease (complex)                | 6 (1.3)           | 15 (3.2)              |         |
| ACC/AHA Type B2/C (%)               | 430(90.7)         | 2,649 (83.1)          | <0.001  |
| Glycoprotein IIb/IIIa inhibitor (%) | 104 (21.9)        | 505 (15.9)            | 0.001   |
| Stent diameter at target lesion     | 3.28±0.45         | 3.18±0.46             | <0.001  |
| Stent length at target lesion       | 24.38±7.37        | 24.71±7.32            | 0.374   |

## **In-hospital Medication**

|                              | Prasugrel (n=474)  | Clopidogrel (n=3,189) | p-value |
|------------------------------|--------------------|-----------------------|---------|
| Aspirin (%)                  | 469 (98.9)         | 3,141 (98.6)          | 0.531   |
| Clopiodogrel 75mg MD (%)     | 0 (0.0)            | 3,189 (100.0)         | <0.001  |
| Prasugrel 10mg/5mg MD (%)    | 459 (96.8)/15(3.2) | 0 (0.0)               | <0.001  |
| Cilostazol (%)               | 2 (0.4)            | 527 (16.5)            | <0.001  |
| Beta-blocker (%)             | 433 (91.4)         | 2,797 (87.8)          | 0.025   |
| Calcium channel blockers (%) | 15 (3.2)           | 208 (6.5)             | 0.004   |
| ACEi or ARB (%)              | 400 (84.4)         | 2,662 (83.6)          | 0.646   |
| Statin (%)                   | 450 (94.9)         | 2,950 (92.6)          | 0.064   |

### **Baseline Clinical Characteristics (PSM)**

|   | Prasugrel (n=469) | Clopidogrel (n=469) | p-value |
|---|-------------------|---------------------|---------|
| Age, years                                      | 55.14±8.88        | 55.38±10.11         | 0.693   |
| Male gender (%)                                 | 446 (94.5)        | 446 (95.1)          | 0.660   |
| Hypertension (%)                                | 177 (37.7)        | 167 (35.6)          | 0.498   |
| Diabetes (%)                                    | 99 (21.1)         | 86 (18.3)           | 0.286   |
| Dyslipidemia (%)                                | 53 (11.3)         | 60 (12.8)           | 0.483   |
| Current smoker (%)                              | 269 (57.4)        | 266 (56.7)          | 0.843   |
| Family Hx of CAD (%)                            | 30 (6.4)          | 20 (4.3)            | 0.146   |
| Previous MI (%)                                 | 22 (4.7)          | 29 (6.2)            | 0.313   |
| Previous angina (%)                             | 21 (4.5)          | 12 (2.6)            | 0.111   |
| Killip class (%)                                |                   |                     | 0.922   |
| I   | 411 (87.6)        | 413 (88.1)          |         |
| II  | 24 (5.1)          | 20 (4.3)            |         |
| III   | 16 (3.4)          | 18 (3.8)            |         |
| IV  | 18 (3.8)          | 18 (3.8)            |         |
| Final diagnosis                                 |                   |                     | 1.000   |
| Non ST elevation MI                             | 167 (35.6)        | 167 (35.6)          |         |
| ST elevation MI                                 | 302 (64.4)        | 302 (64.4)          |         |
| LV ejection fraction, %                         | 52.56±9.81        | 52.28±9.87          | 0.675   |
| Creatinine clearance, ml/min/1.73m <sup>2</sup> | 100.57±33.38      | 99.26±38.15         | 0.578   |

### **Baseline Procedural Characteristics (PSM)**

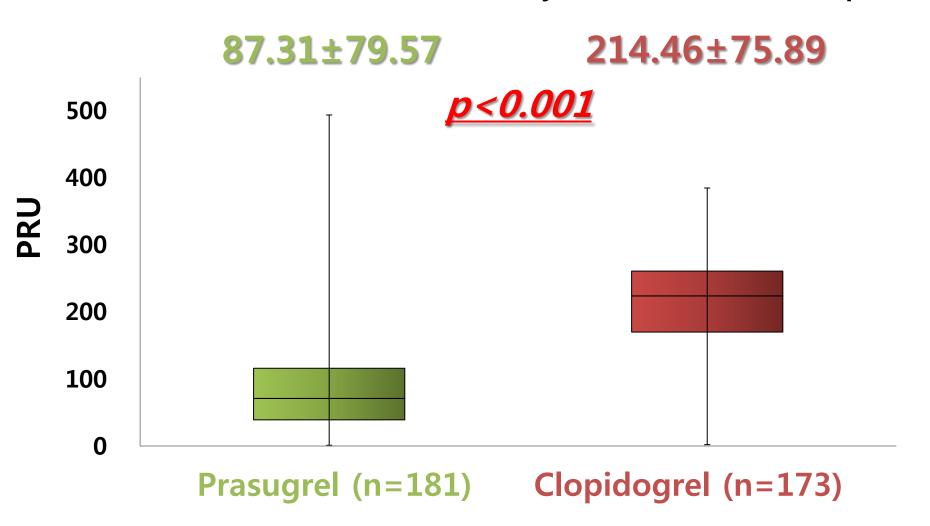
|                                     | Prasugrel (n=469) | Clopidogrel (n=469) | p-value |
|-------------------------------------|-------------------|---------------------|---------|
| Vascular access (%)                 |                   |                     | 0.868   |
| Transradial approach                | 193 (41.2)        | 185 (39.4)          |         |
| Transfemoral approach               | 275 (58.6)        | 283 (60.3)          |         |
| Both approach                       | 1 (0.2)           | 1 (0.2)             |         |
| Infarct-related artery (%)          |                   |                     | 0.945   |
| LAD                                 | 223 (47.5)        | 226 (48.2)          |         |
| LCX                                 | 81 (17.3)         | 86 (18.3)           |         |
| RCA                                 | 158 (33.7)        | 150 (32.0)          |         |
| LM                                  | 7 (1.5)           | 7 (1.5)             |         |
| Involved vessel number (%)          |                   |                     | 0.085   |
| Single vessel                       | 275 (58.6)        | 276 (58.8)          |         |
| Two vessel                          | 133 (28.4)        | 111 (23.7)          |         |
| Three vessel                        | 51 (10.9)         | 65 (13.9)           |         |
| LM disease (simple)                 | 4 (0.9)           | 2 (0.4)             |         |
| LM disease (complex)                | 6 (1.3)           | 15 (3.2)            |         |
| ACC/AHA Type B2/C (%)               | 426 (90.8)        | 419 (89.3)          | 0.444   |
| Glycoprotein IIb/IIIa inhibitor (%) | 103 (22.0)        | 99 (21.1)           | 0.751   |
| Stent diameter at target lesion     | 3.28±0.45         | 3.22±0.46           | 0.054   |
| Stent length at target lesion       | 24.40±7.33        | 25.40±7.20          | 0.041   |

### **In-hospital Medication (PSM)**

|                              | Prasugrel (n=469)  | Clopidogrel (n=469) | p-value |
|------------------------------|--------------------|---------------------|---------|
| Aspirin (%)                  | 469 (100.0)        | 469 (100.0)         | 1.000   |
| Clopiodogrel 75mg MD (%)     | 0 (0.0)            | 469 (100.0)         | <0.001  |
| Prasugrel 10mg/5mg MD (%)    | 454 (96.8)/15(3.2) | 0 (0.0)             | <0.001  |
| Cilostazol (%)               | 2 (0.4)            | 73 (15.6)           | <0.001  |
| Beta-blocker (%)             | 430 (91.7)         | 432 (92.1)          | 0.811   |
| Calcium channel blockers (%) | 15 (3.2)           | 13 (2.8)            | 0.701   |
| ACEi or ARB (%)              | 397 (84.6)         | 414 (88.3)          | 0.105   |
| Statin (%)                   | 447 (95.3)         | 446 (95.1)          | 0.879   |

### PRU between Prasugrel vs. Clopidogrel

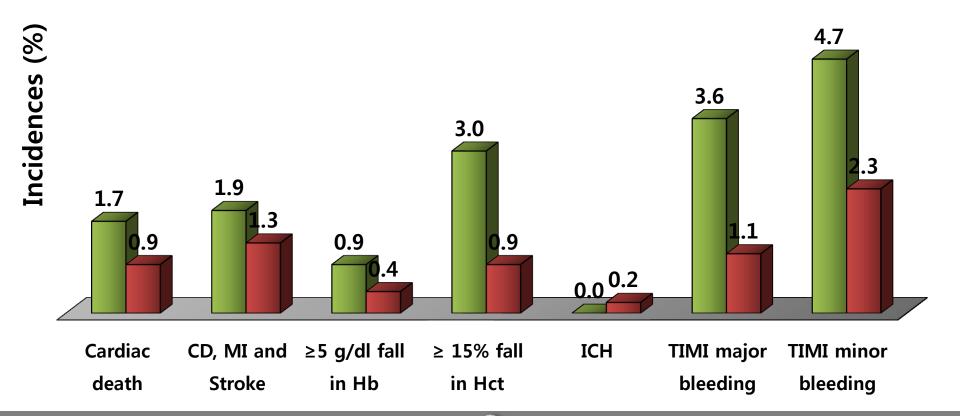
Only available 37.7% of all patients



### In-hospital Clinical Outcomes in Prasugrel

■ Prasugrel (n=496)
■ Clopidogrel (n=496)

p = 0.686p = 0.029p=1.000p = 0.385p = 0.604p = 0.010p = 0.051

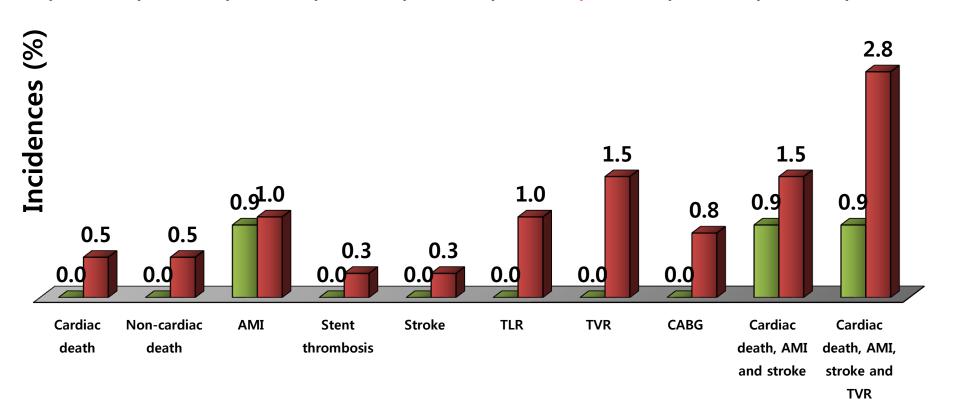


#### 6-month Clinical Outcomes

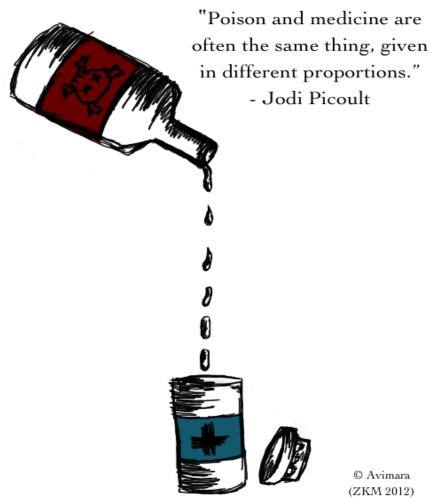
Only available 77.3% of Survivors

■ Prasugrel (n=334)
■ Clopidogrel (n=391)

p=1.000 p=1.000 p=0.129 p=0.034 p=0.254 p=0.517p = 0.502p = 0.502p=1.000p = 0.101



## Are the New P2Y12 RI really harmful to **Korean AMI patients?**



#### What can we do?

✓ Patients selection in Ticagrelor

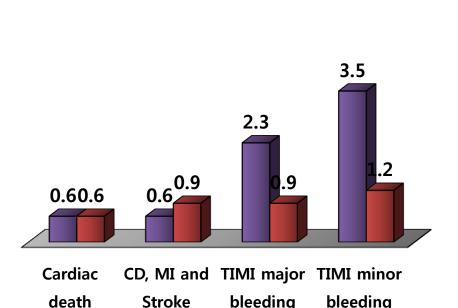
✓ Pretreatment of Prasugrel in NSTE-ACS

✓ Optimal MD of Prasugrel

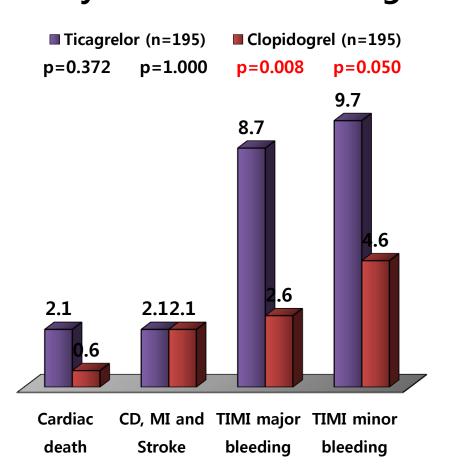
### In-hospital Clinical Outcome in Ticagrelor : Core Cohort

#### <75 yrs old or BW ≥60kg





#### ≥75 yrs old or BW <60kg



## **2014 ESC/EACTS Guidelines for STEMI undergoing Primary PCI**

| Recommendations  | Class <sup>a</sup> | Levelb | Ref <sup>c</sup>    |
|--|--------------------|--------|---------------------|
| Antiplatelet therapy   |                    |        |                     |
| ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.) and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy. | 1                  | A      | 776,794             |
| A $P2Y_{12}$ inhibitor is recommended in addition to ASA and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:   | -                  | A      | -                   |
| <ul> <li>Prasugrel (60 mg loading dose, 10 mg daily dose) if no contraindication</li> </ul>  | Ι                  | В      | 828                 |
| • Ticagrelor (180 mg loading dose, 90 mg twice daily) if no contraindication   | -1                 | В      | 823                 |
| • Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are contraindicated.   | ı                  | В      | 812                 |
| It is recommended to give P2Y <sub>12</sub> inhibitors at the time of first medical contact.   | - 1                | В      | 777,846–848         |
| GP IIb/IIIa inhibitors should be considered for bail-out or evidence of no-reflow or a thrombotic complication.  | lla                | С      | -                   |
| Upstream use of a GP IIb/IIIa inhibitor (vs. in-lab use) may be considered in high-risk patients undergoing transfer for primary PCI.  | IIb                | В      | 271,834,<br>835,849 |

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#### Pretreatment with Prasugrel in Non–ST-Segment Elevation Acute Coronary Syndromes

Gilles Montalescot, M.D., Ph.D., Leonardo Bolognese, M.D., Dariusz Dudek, M.D., Ph.D., Patrick Goldstein, M.D., Christian Hamm, M.D., Jean-Francois Tanguay, M.D., Jurrien M. ten Berg, M.D., Ph.D., Debra L. Miller, R.N., Timothy M. Costigan, Ph.D., Jochen Goedicke, M.D., Johanne Silvain, M.D., Ph.D., Paolo Angioli, M.D., Jacek Legutko, M.D., Ph.D., Margit Niethammer, M.D., Zuzana Motovska, M.D., Ph.D., Joseph A. Jakubowski, Ph.D., Guillaume Cayla, M.D., Ph.D., Luigi Oltrona Visconti, M.D., Eric Vicaut, M.D., Ph.D., and Petr Widimsky, M.D., D.Sc., for the ACCOAST Investigators\*

#### ABSTRACT

#### BACKGROUND

Although  $P2Y_{12}$  antagonists are effective in patients with non–ST-segment elevation (NSTE) acute coronary syndromes, the effect of the timing of administration — before or after coronary angiography — is not known. We evaluated the effect of administering the  $P2Y_{12}$  antagonist prasugrel at the time of diagnosis versus administering it after the coronary angiography if percutaneous coronary intervention (PCI) was indicated.

#### METHODS

We enrolled 4033 patients with NSTE acute coronary syndromes and a positive troponin level who were scheduled to undergo coronary angiography within 2 to 48 hours after randomization. Patients were randomly assigned to receive prasugrel (a 30-mg loading dose) before the angiography (pretreatment group) or placebo (control group). When PCI was indicated, an additional 30 mg of prasugrel was given in the pretreatment group at the time of PCI and 60 mg of prasugrel was given in the control group.

#### RESULTS

The rate of the primary efficacy end point, a composite of death from cardiovascular causes, myocardial infarction, stroke, urgent revascularization, or glycoprotein IIb/IIIa inhibitor rescue therapy (glycoprotein IIb/IIIa bailout) through day 7, did not differ significantly between the two groups (hazard ratio with pretreatment, 1.02; 95% confidence interval [CI], 0.84 to 1.25; P=0.81). The rate of the key safety end point of all Thrombolysis in Myocardial Infarction (TIMI) major bleeding episodes, whether related or not related to coronary-artery bypass grafting (CABG), through day 7 was increased with pretreatment (hazard ratio, 1.90; 95% CI, 1.19 to 3.02; P=0.006). The rates of TIMI major bleeding and life-threatening bleeding not related to CABG were increased by a factor of 3 and 6, respectively. Pretreatment did not reduce the rate of the primary outcome among patients undergoing PCI (69% of the patients) but increased the rate of TIMI major bleeding at 7 days. All the results were confirmed at 30 days and in prespecified subgroups.

#### CONCLUSIONS

Among patients with NSTE acute coronary syndromes who were scheduled to undergo catheterization, pretreatment with prasugrel did not reduce the rate of major ischemic events up to 30 days but increased the rate of major bleeding complications. (Funded by Daiichi Sankyo and Eli Lilly; ACCOAST ClinicalTrials.gov number, NCT01015287.)

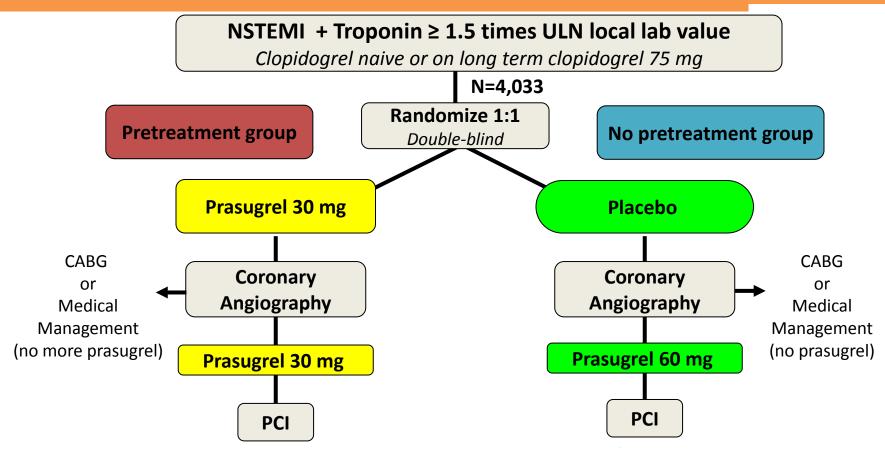
The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Montalescot at the ACTION Study Group, Institut de Cardiologie, Centre Hospitalier Universitaire Pitié—Salpětrière, 47 Blvd. de l'Hôpital, 75013 Paris, France, or at gilles.montalescot@psl.aphp.fr.

\*Investigators in the Comparison of Prasugrel at the Time of Percutaneous Coronary Intervention (PCI) or as Pretreatment at the Time of Diagnosis in Patients with Non-ST Elevation Myocardial Infarction (ACCOAST) are listed in the Supplementary Appendix, available at NEJM.org.

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## Study Design



Prasugrel 10 mg or 5 mg (based on weight and age) for 30 days

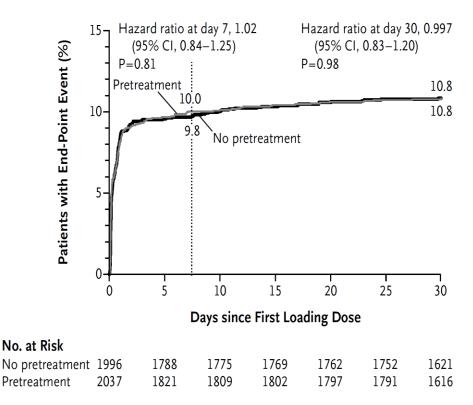
1° Endpoint: CV Death, MI, Stroke, Urg Revasc, GP IIb/IIIa bailout, at 7 days

Montalescot G et al. *Am Heart J* 2011;161:650-656.

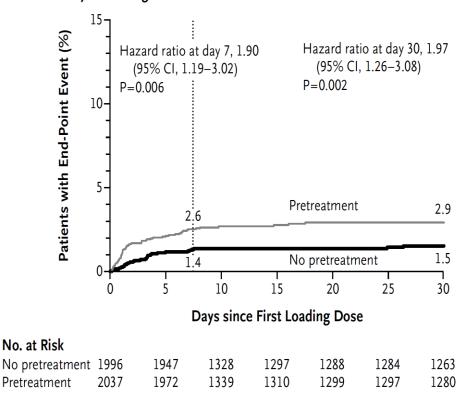


# Primary Efficacy and Safety Endpoints : All patients

#### A Primary Efficacy End Point



#### B All TIMI Major Bleeding



Montalescot G et al. *N Engl J Med* 2013;369:999-1010.

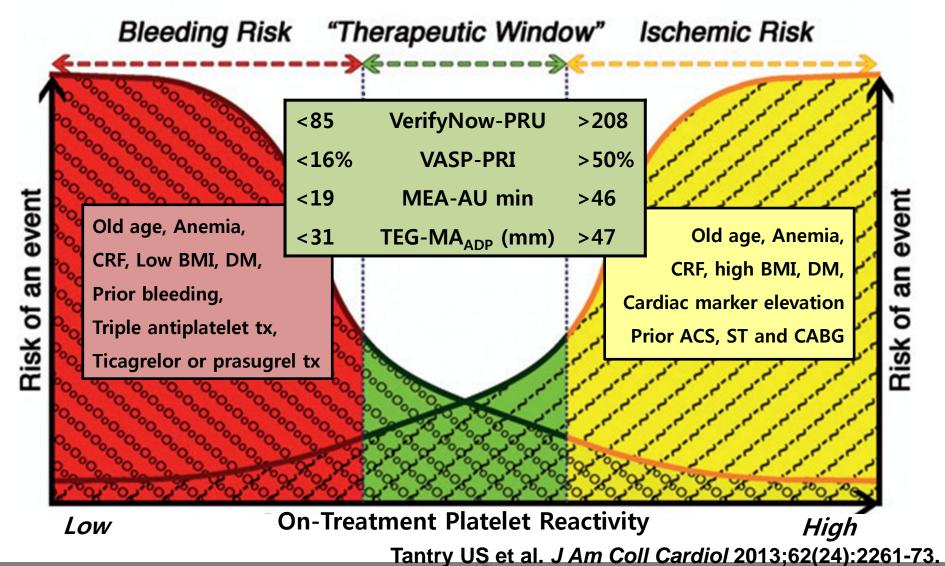


### **2014 ESC/EACTS Guidelines for NSTE-ACS undergoing PCI**

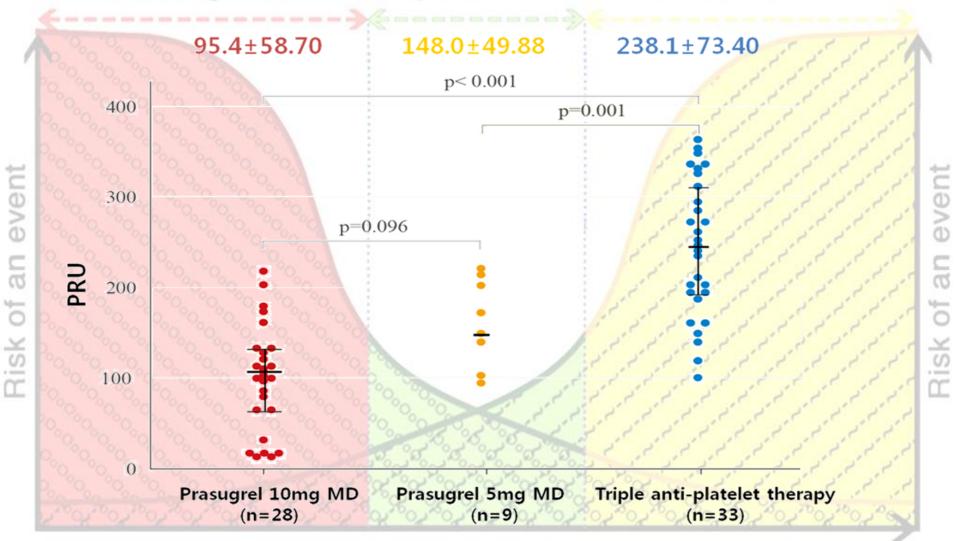
| Recommendations  | Class <sup>a</sup> | Level <sup>b</sup> | <b>R</b> ef <sup>c</sup> |
|--|--------------------|--------------------|--------------------------|
| Antiplatelet therapy   |                    |                    |                          |
| ASA is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 80–150 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.      | 1                  | A                  | 774,776,794              |
| A P2Y <sub>12</sub> inhibitor is recommended in addition to ASA, and maintained over 12 months unless there are contraindications such as excessive risk of bleeding. Options are:   | 1                  | A                  | 337,341,825              |
| <ul> <li>Prasugrel (60 mg loading dose, 10 mg daily dose) in patients in whom coronary anatomy is known and who are<br/>proceeding to PCI if no contraindication.</li> </ul>   | 1                  | В                  | 337                      |
| • Ticagrelor (180 mg loading dose, 90 mg twice daily) for patients at moderate-to-high risk of ischaemic events, regardless of initial treatment strategy including those pre-treated with clopidogrel if no contraindication. | 1                  | В                  | 341                      |
| <ul> <li>Clopidogrel (600 mg loading dose, 75 mg daily dose), only when prasugrel or ticagrelor are not available or are<br/>contraindicated.</li> </ul>   | -1                 | В                  | 812,825                  |
| GP IIb/IIIa antagonists should be considered for bail-out situation or thrombotic complications.   | lla                | С                  |                          |
| Pre-treatment with prasugrel in patients in whom coronary anatomy not known, is not recommended.   | Ш                  | В                  | 826                      |
| Pre-treatment with GP IIb/IIIa antagonists in patients in not known, is not recommended.   | III                | A                  | 357,815                  |

## What is the Optimal Dosage of Prasugrel in Korean AMI Patients?

# Impact of Platelet Reactivity on the Balanace between Safety and Efficacy



## PRU at Pre-discharge according to MD Prasugrel in Korean STEMI Patients Bleeding Risk "Therapeutic Window" Ischemic Risk

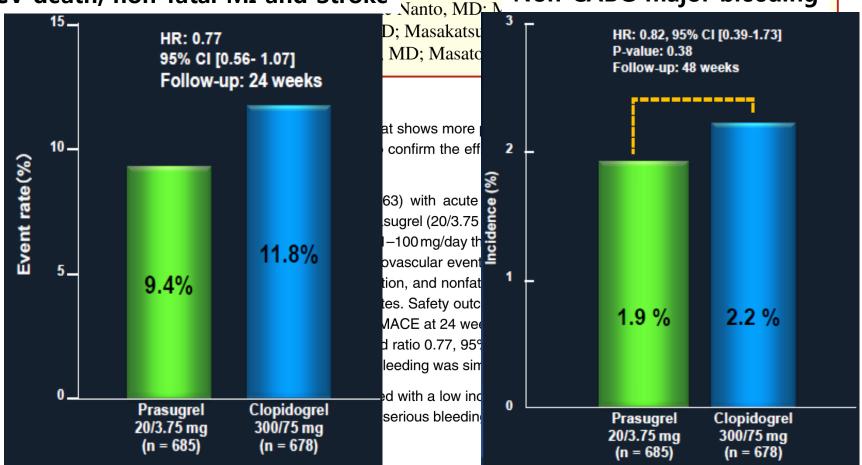




#### Efficacy and Safety of Adjusted-Dose Prasugrel Compared With Clopidogrel in Japanese Patients With Acute Coronary Syndrome

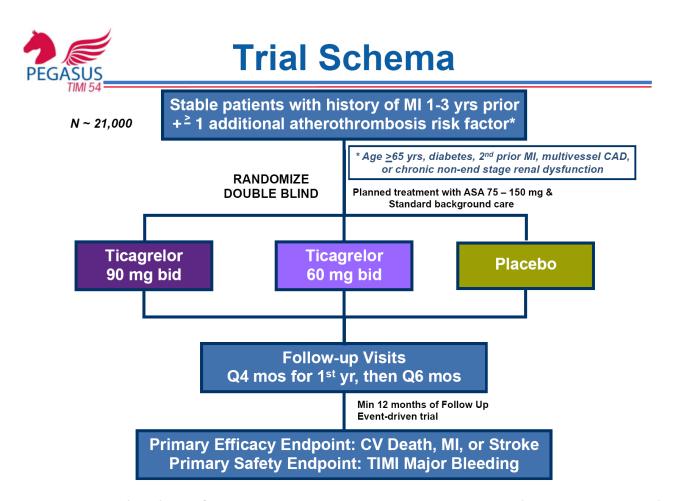
The PRASFIT-ACS Study –

CV death, non-fatal MI and Stroke CV death, non-fatal MI and Stroke CV death, Non-CABG major bleeding



**Key Words:** Acute coronary syndrome; Clopidogrel; Major adverse cardiovascular events; Percutaneous coronary intervention; Prasugrel

### Low Dosage of Ticagrelor



Study Schema for PEGASUS-TIMI 54. CAD, Coronary artery disease; MI, myocardial infarction.

Bonaca MP et al. *Am Heart J* 2014;167:437-444.



### **Study Limitations**

✓ Our study was a large, prospective, observational registry and non-randomized trial.

This might have introduced a significant bias in patient selection, even though it was partially compensated for by propensity score matching analysis to control the baseline biases.

Long-term follow-up data were not available.

#### Conclusion

- ✓ New P2Y12 RI (Ticagrelor or Prasugrel) are superior to clopidogrel for AMI/PCI with statistically significant higher inhibition of platelet aggregation (IPA).
- ✓ In the KAMIR-NIH registry, a significantly higher incidence of in-hospital bleeding complications is observed in New P2Y12 RI compared with clopidogrel, even though it couldn't be affected in short-term mortality.
- ✓ Therefore, further large, long-term, and randomized trial will be needed to evaluate the efficacy and the safety of new P2Y12 RI in Korean AMI patients.

## Thank you for your attention !

