# Prasugrel in Clopidogrel Nonresponders:
## Results of the REsponsiveness to CLOpidogrel and Stent-related Events (RECLOSE)-3 Study

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- **Conflict of interest: none**

# Background

➤ The RECLOSE-2 trial showed that high residual platelet reactivity after a clopidogrel loading dose of 600 mg is a strong predictor of major adverse cardiovascular events in patients with acute coronary syndrome (JAMA 2011; 306:1215-23).

➤ It is unknown if non-responsiveness to clopidogrel loading is a risk factor modifiable by prasugrel treatment.

# Objectives

Assessment of **2-year clinical outcome** after PCI of clopidogrel nonresponders switched to prasugrel.

**Clinical outcome comparison** between:

RECLOSE-2 **clopidogrel** nonresponder patients

Clopidogrel nonresponders switched to **prasugrel**

# Methods

- ➤ **Residual platelet reactivity** was assessed by light transmittance aggregometry using 10 µmol/L of ADP as agonist.

- ➤ **Non-responders to clopidogrel** were identified by residual platelet reactivity ≥ 70%.

- ➤ Light transmittance aggregometry was repeated after the switch to prasugrel treatment.

- ➤ The **primary end point** of the study was 2-year cardiac mortality .

- ➤ The **secondary end points** were the composite of cardiac death and myocardial infarction, and, stent thrombosis.

- ➤ The statistical hypothesis assuming a decrease of 50% in 2-year cardiac mortality in patients switched to prasugrel compared to clopidogrel non-responders of the RECLOSE-2 study required a sample size of 250 patients for each group. Screened patients in the RECLOSE-3 1,550 patients

- ➤ *Sponsor: Italian Department of Health*.

# Baseline Characteristics

| | Overall n=550 | RECLOSE-2 n=248 | RECLOSE-3 n=302 | p value |
|---|---|---|---|---|
| ➢ Age (yrs) | 71.8 ± 11.1 | 71.7 ± 11.3 | 71.9 ± 10.9 | 0.795 |
| ➢ Male gender | 421 (76) | 191 (77) | 230 (76) | .813 |
| ➢ Hypercholesterolemia | 313 (57) | 134 (54) | 179 (59) | .217 |
| ➢ Hypertension | 366 (57) | 151 (61) | 215 (71) | 0.011 |
| ➢ Diabetes | 162 (29) | 70 (28) | 92 (30) | .567 |
| ➢ Pre PCI | 188 (34) | 47 (19) | 141 (48) | <.001 |
| ➢ Pre CABG | 45 (8) | 16 (6) | 29 (10) | .180 |
| ➢ Pre MI | 189 (34) | 70 (28) | 119 (39) | .006 |
| ➢ Creatinine > 1.50 mg/dL | 77 (14) | 28 (11) | 49 (16) | .097 |
| ➢ LVEF ≤ 40% | 168 (30) | 97 (39) | 71 (23) | <.001 |
| ➢ STEMI at presentation | 98 (18) | 82 (33) | 16 (5.3) | <.001 |
| ➢ Mean platelet reactivity, % | 77.6 ± 6.5 | 77.6 ± 6.8 | 77.6 ± 6.2 | .992 |
| ➢ After switch to prasugrel | | | 46.6 ± 16.6 | <.001 |

# Angiographic and Procedural Characteristics

| | Overall n=550 | RECLOSE-2 n=248 | RECLOSE-3 n=302 | p value |
|---|---|---|---|---|
| ➤ **Multivessel coronary disease** | 375 (68) | 162 (65) | 213 (70) | .192 |
| ➤ **Three-vessel coronary disease** | 197 (36) | 82 (33) | 115 (38) | .222 |
| ➤ **Multivessel PCI** | 233 (42) | 96 (39) | 137 (45) | .116 |
| ➤ **Three-vessel PCI** | 73 (13) | 25 (10) | 45 (15) | .091 |
| ➤ **Treated vessel** | | | | |
|   ➤ **Left anterior descending artery** | 326 (59) | 145 (58) | 181 (60) | .728 |
|   ➤ **Right coronary artery** | 220 (40) | 96 (39) | 124 (41) | .576 |
|   ➤ **Circumflex coronary artery** | 199 (36) | 94 (38) | 105 (35) | .446 |
|   ➤ **Left main** | 65 (12) | 22 (8.9) | 43 (14) | .052 |
|   ➤ **Ramus** | 14 (2.5) | 9 (3.6) | 5 (1.7) | .144 |
| ➤ **N° of stents per patient** | $2.2 \pm 1.3$ | $1.9 \pm 1.2$ | $2.4 \pm 1.4$ | <.001 |
| ➤ **Total stent lenght** | $44.0 \pm 32.8$ | $36.0 \pm 26.5$ | $50.5 \pm 36.0$ | <.001 |
| ➤ **DES** | 408 (74) | 133 (54) | 275 (91) | <.001 |

# Two-year Clinical Outcome

| | Overall n=549 | RECLOSE-2 n=247 | RECLOSE-3 n=302 | p value |
|---|---|---|---|---|
| ➤ Major Acute Cardiovascular Events | 62 (11.3) | 36 (14.6) | 26 (8.6) | .028 |
| • Cardiac Death | 36 (6.6) | 24 (9.7) | 12 (4.0) | .007 |
| • Myocardial Infarction | 16 (2.9) | 8 (3.2) | 8 (2.6) | .683 |
| ➤ Stent thrombosis | | | | |
| • Definite | 9 (1.6) | 7 (2.8) | 2 (0.7) | .046 |
| • Probable | 4 (0.7) | 4 (1.6) | 0 | .026 |

| | | RECLOSE-2 | RECLOSE-3 | |
|---|---|---|---|---|
| ACS patients | | N = 247 | N = 126 | |
| Cardiac death | | 24 (9.7) | 4 (3.2) | 0.023 |

# Predictors of 2-year Cardiac Mortality

| | HR | 95%CI | p value |
|---|---|---|---|
| ➤ Prasugrel | 0.50 | 0.29-0.88 | .017 |
| ➤ Age (yrs) | 1.03 | 1.00-1.06 | .035 |
| ➤ Creatinine > 1.5 mg/dL | 2.17 | 1.16-4.06 | .016 |

*Median Follow Up 790 days [IQR 728-790]*          *Follow Up rate 99%*

# Long-term Outcomes



**Cardiac survival**

- %
- p=0.011
- 96 ± 1%
- 90 ± 2%

**Cumulative event-free survival**
(cardiac death + myocardial infarction)

- p=0.021
- 93 ± 1%
- 87 ± 2%

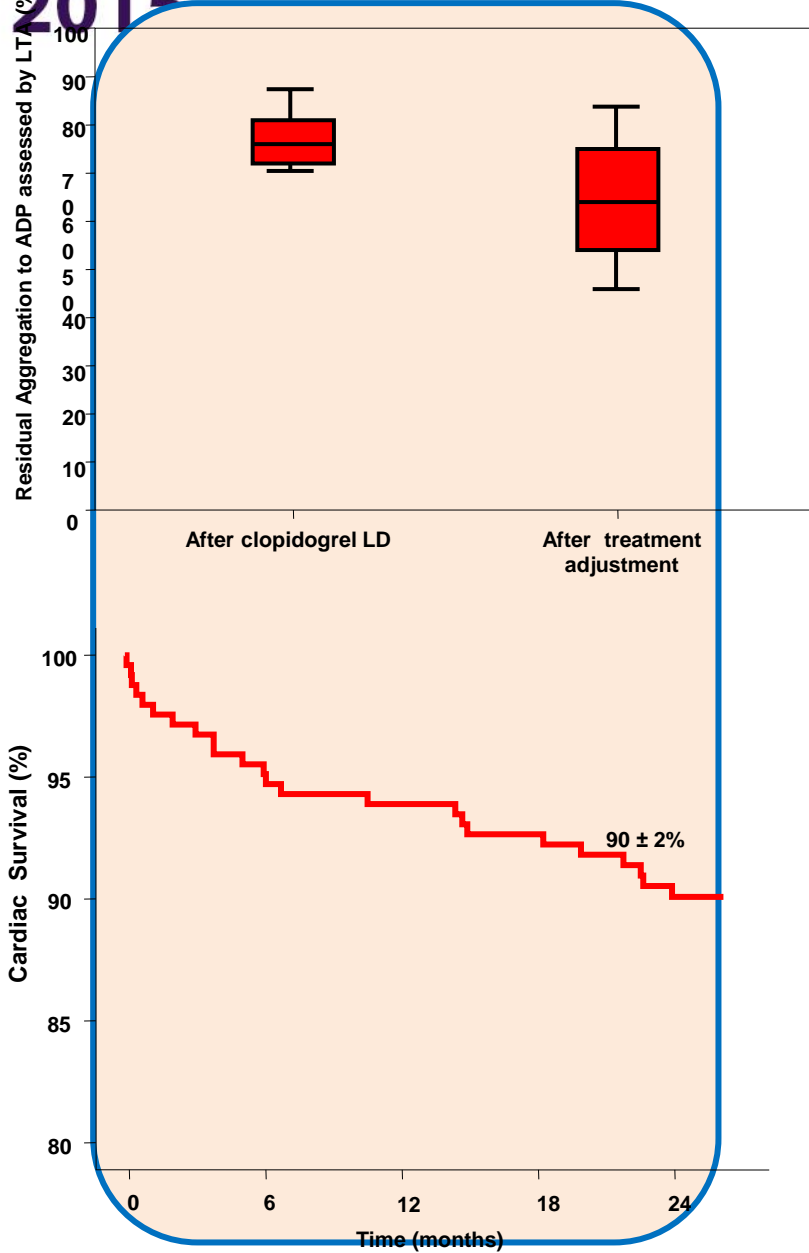— Clopidogrel
— Prasugrel

Time (months)
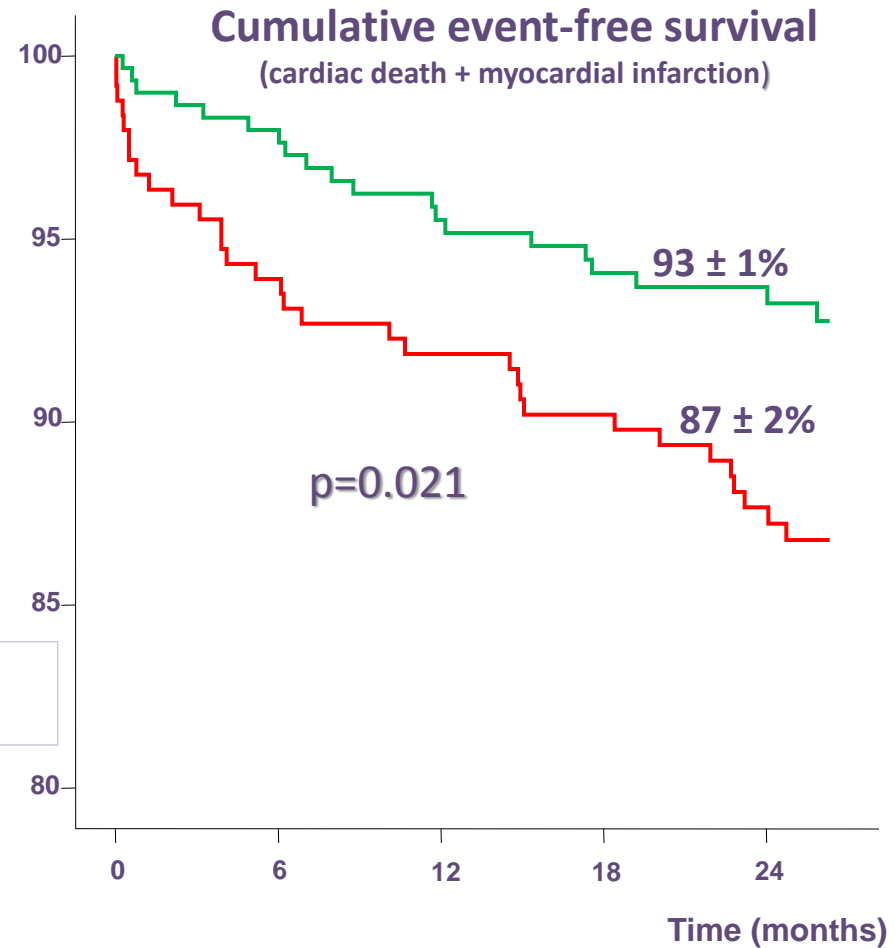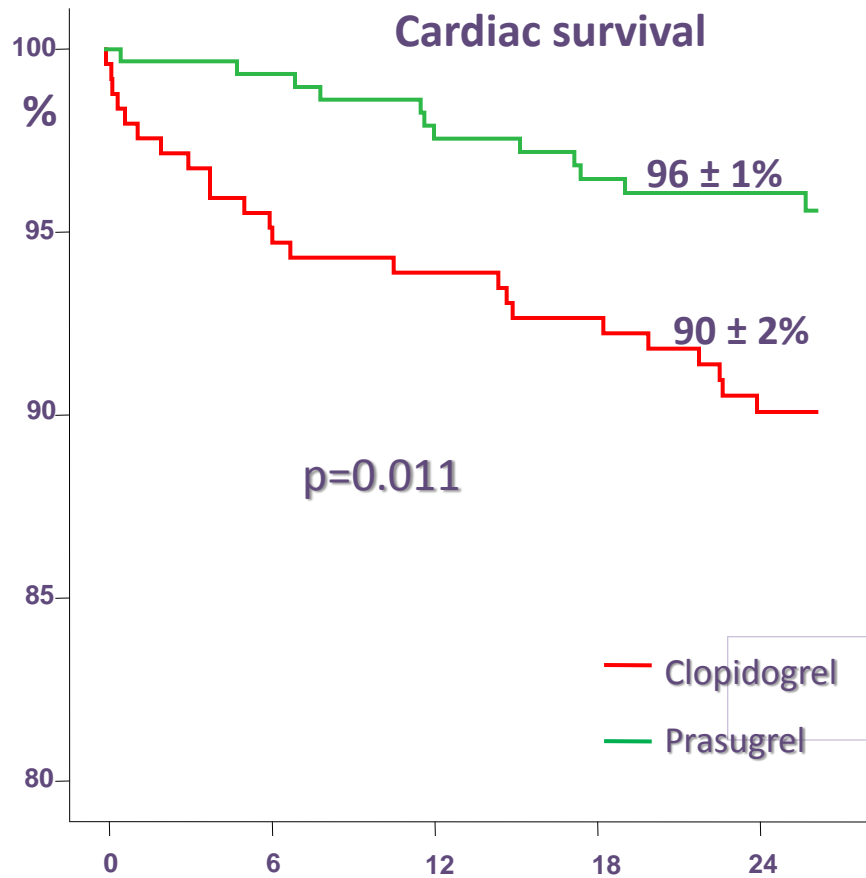
# Study Limitations

➢ **The RECLOSE-3 study has a nonrandomized design. However, ethical issues make unlikely the possibility to perform a randomized study using clopidogrel in the control arm in clopidogrel nonresponders.**

➢ **In the RECLOSE-3 study consecutive patients were screened without any restriction based on age, clinical presentation,  or coronary anatomy complexity, and this patient cohort may be considered representative of the broad spectrum of patients with coronary artery disease who are treated with PCI.**

➢ **The comparison with the historical cohort of the patients of the RECLOSE-2 study was made with appropriate statistical adjustment to correct for differences between groups, including in the model of multivariable analysis  the variables ACS and LVEF < 0.40 that accounted for the major differences between the RECLOSE-2 and RECLOSE-3 patient cohorts.**

# Conclusions

**In nonresponders to clopidogrel undergoing PCI, prasugrel treatment provided:**

➤ **A deep platelet aggregation inhibition in nearly all patients.**

➤ **A better clinical outcome at 2-year follow-up as compared to the RECLOSE-2 nonresponders, including cardiac mortality and stent thrombosis.**

➤ **Clopidogrel nonresponsiveness is a risk factor that can be modified by prasugrel.**

**RECLOSE-2**

**RECLOSE-3**