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Prasugrel in Clopidogrel Nonresponders Undergoing Percutaneous Coronary Intervention

The RECLOSE-3 Study (REsponsiveness to CLOpidogrel and StEnt Thrombosis)

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ABSTRACT

OBJECTIVES This study sought to investigate the efficacy of prasugrel compared with clopidogrel in clopidogrel nonresponders.

BACKGROUND Clopidogrel nonresponsiveness is a strong marker of the risk of cardiac death and stent thrombosis after a percutaneous coronary intervention (PCI). It is unknown whether clopidogrel nonresponsiveness is a nonmodifiable risk factor or whether prasugrel with more potent and predictable platelet inhibition as measured by ex vivo techniques is associated with a positive effect on clinical outcome.

METHODS The RECLOSE-3 (REsponsiveness to CLOpidogrel and StEnt thrombosis) study screened clopidogrel nonresponders after a 600-mg loading dose of clopidogrel. Clopidogrel nonresponders switched to prasugrel (10 mg/day) the day of the PCI, and an adenosine diphosphate (ADP) test (10 μmol/l of ADP) was performed 6 days after the PCI. The primary endpoint was 2-year cardiac mortality. Patient outcome was compared with the RECLOSE-2-ACS study.

RESULTS We screened 1,550 patients, of whom 302 were clopidogrel nonresponders. The result of the ADP test was 77.6 ± 6.2%. After switching to prasugrel, the ADP test result decreased to 47.1 ± 16.8%. The 2-year cardiac mortality rate was 4% in the RECLOSE-3 study and 9.7% in nonresponders of the RECLOSE-2-ACS study ($p = 0.007$). The definite and probable stent thrombosis rates were 0.7% and 4.4%, respectively ($p = 0.004$). On multivariable analysis, prasugrel treatment was related to the risk of 2-year cardiac death (hazard ratio: 0.32, $p = 0.036$).

CONCLUSIONS Clopidogrel nonresponsiveness can be overcome by prasugrel (10 mg/day), and optimal platelet aggregation inhibition on prasugrel treatment is associated with a low rate of long-term cardiac mortality and stent thrombosis. (J Am Coll Cardiol Intv 2015;8:1563–70) © 2015 by the American College of Cardiology Foundation.

Several studies have shown that high residual platelet reactivity while on clopidogrel treatment is a strong marker of the risk ischemic events in patients undergoing percutaneous coronary intervention (PCI) (1-16). Prasugrel in clopidogrel nonresponders is effective in providing platelet aggregation inhibition in most patients (17). No evidence exists showing that the achievement of optimal platelet aggregation inhibition in clopidogrel nonresponders by prasugrel modifies the risk profile of these patients. The TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy with Prasugrel) trial is the only randomized trial that compared prasugrel with clopidogrel in clopidogrel nonresponders and was terminated prematurely for futility due to the low event rate (18).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

ADP = adenosine diphosphate

CI = confidence interval

HR = hazard ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

The RECLOSE-3 (REsponsiveness to CLOpidogrel and StEnt thrombosis) study sought to determine the efficacy of prasugrel treatment in clopidogrel nonresponders undergoing a PCI.

METHODS

PATIENT SELECTION AND INTERVENTIONS. From April 2010 to December 2012, consecutive patients undergoing PCI were screened for nonresponsiveness to clopidogrel using a loading dose of 600 mg of clopidogrel and assessing platelet reactivity with light transmittance aggregometry.

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There were no exclusion criteria except current treatment with prasugrel. All patients with high residual platelet reactivity were switched to prasugrel (10 mg/day or 5 mg in patients older than 75 years of age or with a history of stroke if the adenosine diphosphate [ADP] test result was <70%) the same day of the PCI. All patients underwent drug-eluting stent implantation, and the PCI was performed using standard techniques. Dual antiplatelet treatment was prescribed for at least 6 months. Because of the nonrandomized study design, the clinical outcome of clopidogrel nonresponders who switched to prasugrel was compared with that of the historical cohort of clopidogrel nonresponders in the RECLOSE-2-ACS (n = 248) study. Details of this study were previously reported (15). Briefly, the RECLOSE-2-ACS study enrolled 1,789 patients with acute coronary syndromes (ACS) and treated with PCI, of whom 248 were clopidogrel nonresponders. Clopidogrel nonresponders had an increased long-term dose of clopidogrel (150 to 300 mg/day) or switched to ticlopidine (500 to 1,000 mg/day) under ADP test results guidance, with the goal of reaching an ADP test result of <70% platelet aggregation. The primary endpoint was a composite of cardiac death, myocardial infarction, any urgent coronary revascularization, and stroke at 2-year follow-up. Secondary endpoints were stent thrombosis and each component of the primary endpoint. The 2-year cardiac mortality rate was 9.7% in clopidogrel nonresponders and 4.3% in clopidogrel responders, and the clopidogrel nonresponsiveness was independently associated with the risk of 2-year cardiac death (hazard ratio [HR] compared with clopidogrel responders (HR: 1.81; 95% confidence interval [CI]: 1.18 to 2.76; p = 0.006) (15).

PLATELET REACTIVITY ASSESSMENT. Blood samples anticoagulated with 0.129 mol/l sodium citrate (9:1 ratio) for platelet reactivity assessment was obtained at least 12 h after clopidogrel loading and 6 days after the PCI while the patient was on prasugrel treatment. Platelet-rich plasma, obtained by centrifuging whole blood for 10 min at 200*g*, was stimulated with 10 μmol/l of ADP (Mascia Brunelli, Milan, Italy) and residual aggregation was assessed using an APACT 4 light transmittance aggregometer (Helena Laboratories, Milan, Italy). The 100% line was set using platelet-poor plasma and the 0 baseline established with platelet-rich plasma (adjusted from 18×10^9/l up to 30×10^9/l). Platelet aggregation (according to the Born method) was evaluated considering the maximal percentage of platelet aggregation in response to stimulus. High residual platelet reactivity was defined as platelet aggregation by ADP ≥70% (5,10–13).

FOLLOW-UP. All patients had scheduled examinations at 1, 6, 12, and 24 months. All other possible information derived from hospital readmission or by the referring physician, relatives, or municipality live registries was entered into the prospective database.

ENDPOINTS. The primary endpoint of the study was the 2-year cardiac mortality. Secondary endpoints were: 1) myocardial infarction (MI); 2) ischemic stroke; 3) composite of cardiac death and MI, 4) stent thrombosis; 5) major bleeding; and 6) degree of platelet aggregation inhibition as assessed by light transmittance aggregometry. All deaths were considered cardiac unless an unequivocal noncardiac cause could be documented. The diagnosis of non-Q-wave MI was on the basis of an increase in creatine kinase-myocardial band isoenzyme or troponin I >3 times the upper limit of normal or for patients with elevated values on admission, as a re-elevation of creatine kinase-myocardial band or troponin I values. A Q-wave MI was defined as the development of new Q waves in 2 or more electrocardiographic leads, and in addition to creatine kinase-myocardial band or troponin I elevation. Ischemic stroke was defined as an acute neurological defect lasting more than 24 h without computed tomography evidence of bleeding. Stent thrombosis was defined according to the Academic Research Consortium criteria (19). Major bleeding was defined according to the Thrombolysis In Myocardial Infarction-38 criteria (20).

The study was approved by the institutional review committee of Careggi Hospital, and all patients gave written informed consent to participate in the study and undergo PCI.

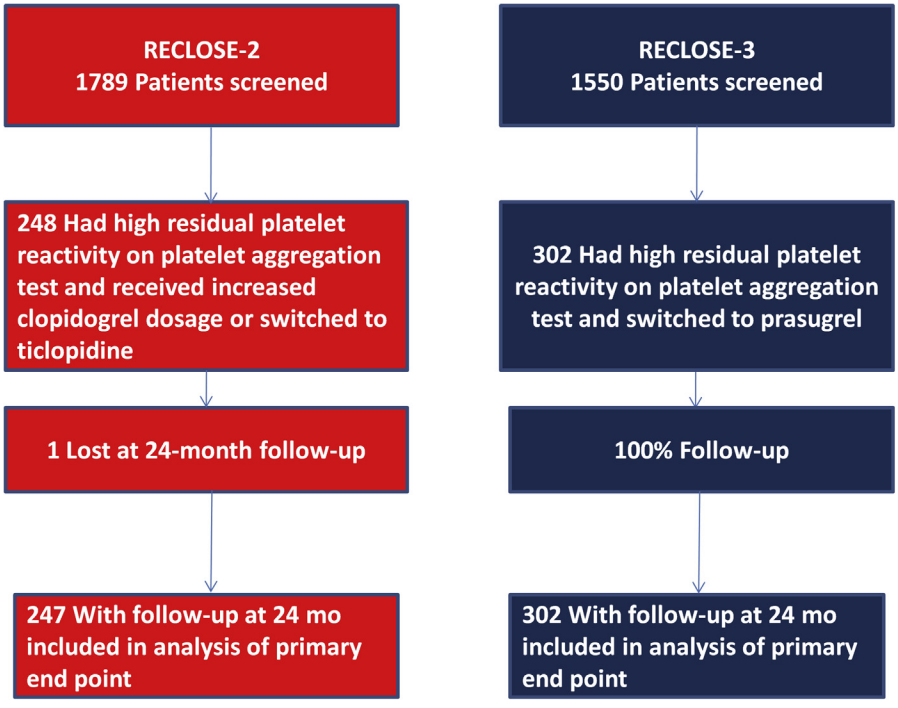
STATISTICAL ANALYSIS. In the RECLOSE-3 study, the statistical hypothesis assumed a decrease of 50% in 2-year cardiac mortality in patients switched to

prasugrel compared with clopidogrel nonresponders of the RECLOSE-2-ACS study. According to this hypothesis, statistical power was >80% on the basis of a maximal sample size of 500 patients for the primary endpoint. Discrete data were summarized as frequencies, and continuous data were expressed as mean ± SD or median and interquartile range, as appropriate. The chi-square test was used for comparison of categorical variables, and the unpaired 2-tailed Student *t* test or Mann-Whitney rank sum test was used to test differences among continuous variables. Survival curves were generated using the Kaplan-Meier method, and the difference between groups was assessed by the log-rank test. A multivariable Cox proportional hazards model was performed to evaluate the independent contribution of clinical, angiographic, and procedural variables to the primary endpoint of cardiac mortality. Variables known to be related to prognostic outcome or variables with a p value <0.05 on Cox univariate analysis were forced into the final multivariate model. The following variables were tested: age 75 years and older, sex, body mass index ≥30 kg/m^2, smoking, diabetes mellitus, hypertension, hypercholesterolemia, history of MI, ACS on admission, serum creatinine level >1.50 mg/dl, left ventricular ejection fraction <40%, 3-vessel coronary disease, implanted drug-eluting stent, and prasugrel treatment. The proportional hazard assumption was assessed and satisfied graphically by plotting log (−log) survival curves against log survival time for each predictor category and verifying whether curves were parallel, and, in addition, using time-dependent covariates. All tests were 2-sided, and a p value <0.05 was considered significant. Analyses were performed using the software package SPSS version 19 (SPSS Inc., Chicago, Illinois).

RESULTS

We screened 1,550 patients after administering a 600-mg loading dose of clopidogrel. Of these, 302 patients had a residual platelet reactivity >70% on the ADP test and were switched to prasugrel treatment. This patient cohort was compared with that of the RECLOSE-2-ACS study that included 248 clopidogrel nonresponders (Figure 1). Table 1 summarizes the baseline clinical characteristics of the 2 groups. Nonresponders in the RECLOSE-3 had a higher incidence of hypertension, a history of MI, a history of

FIGURE 1 Flow Chart of the RECLOSE-2-ACS and RECLOSE-3 Studies



RECLOSE = Responsiveness to CLOpidogrel and StEnt Thrombosis.

TABLE 1 Baseline Clinical Characteristics

	Total (N = 550)	RECLOSE 2-ACS (n = 248)	RECLOSE-3 (n = 302)	p Value
Age, yrs	71.8 ± 11.1	71.7 ± 11.3	71.9 ± 10.9	0.795
Age ≥75 yrs	264 (48)	127 (51)	137 (45)	0.174
Men	421 (76)	191 (77)	230 (76)	0.813
Hypercholestherolemia	313 (57)	134 (54)	179 (59)	0.217
Hypertension	366 (57)	151 (61)	215 (71)	0.011
Smokers	124 (22)	48 (19)	76 (25)	0.105
Body mass index, kg/m^2	26.5 ± 3.7	26.6 ± 3.9	26.4 ± 3.7	0.849
Diabetes mellitus	162 (29)	70 (28)	92 (30)	0.567
History of PCI	188 (34)	47 (19)	141 (48)	<0.001
History of coronary surgery	45 (8.2)	16 (6.5)	29 (9.6)	0.180
History of myocardial infarction	189 (34)	70 (28)	119 (39)	0.006
Creatinine >1.50 mg/dl	77 (14)	28 (11)	49 (16)	0.097
LVEF ≤40%	168 (30)	97 (39)	71 (23)	<0.001
ACS on admission	374 (68)	248 (100)	126 (42)	<0.001
STEMI	98 (18)	82 (33)	16 (5.3)	<0.001
Unstable angina/non-STEMI	276 (50)	166 (67)	110 (36)	<0.001
ADP test after clopidogrel LD				
	77.6 ± 6.5	77.6 ± 6.8	77.6 ± 6.2	0.992
	76 (72–81)	76 (72–81)	76 (73–82)	0.606
ADP test after treatment adjustment or switch to prasugrel				
	53.6 ± 18.1	63.6 ± 15.2	47.1 ± 16.8	<0.001
	56 (40–67)	64 (54–75)	47 (34–62)	<0.001
ADP test in ACS patients	(N = 374)	(n = 248)	(n = 126)	
After clopidogrel LD				
	77.7 ± 6.5	77.6 ± 6.8	78.0 ± 5.8	0.554
	76 (73–81)	76 (72–81)	77 (73–82)	0.173
After treatment adjustment or switch to prasugrel				
	58.3 ± 16.5	63.6 ± 15.2	50.0 ± 15.2	<0.001
	60 (47–71)	64 (54–75)	48 (39–62)	<0.001
ADP test in non-ACS patients			(n = 176)	
After clopidogrel LD				
			77.3 ± 6.4	
			76 (72–82)	
After switch to prasugrel				
			45.1 ± 17.6	
			45 (31–62)	

Values are mean ± SD, n (%), or median (interquartile range).

ACS = acute coronary syndrome; ADP = adenosine diphosphate; LD = loading dose; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

PCI, and better left ventricular function than the RECLOSE-2-ACS nonresponders. The clinical presentation was an ACS in 42% of patients of the RECLOSE-3, whereas all patients in the RECLOSE-2-ACS had an ACS on admission. The ADP test results after 600-mg loading dose of clopidogrel was administered were nearly identical in the 2 groups (77.6 ± 6.2% in the RECLOSE-3, and 77.6 ± 6.8% in the RECLOSE-2-ACS, p = 0.992). Overall, the ADP test result decreased to 47.1 ± 16.8% after switching to prasugrel (p < 0.001), and only 26 patients had a residual platelet reactivity >70% (mean value, 73.9 ± 3.8%).

Table 2 shows the angiographic and procedural characteristics of the 2 groups. The RECLOSE-3 group showed a trend toward more 3-vessel PCIs and unprotected left main PCIs than the RECLOSE-2-ACS group. The number of stents and the total stent length per patient were higher in the RECLOSE-3 cohort and almost all patients (91%) received drug-eluting stents. At discharge, RECLOSE-3 patients were prescribed aspirin and proton pump inhibitors less frequently than the RECLOSE-2-ACS patients.

Table 3 summarizes the 2-year clinical outcome (follow-up rate: 99.8%). The median follow-up length was 961 days (interquartile range [IQR]: 786 to 1,260 days).

At 1 year, 91% and 88% of the patients in the RECLOSE-2-ACS and RECLOSE-3, respectively, were receiving thienopyridine treatment, and the number of patients had decreased to 68% and 21%, respectively, at 2-year follow-up.

The 2-year cardiac mortality rate was 4.0% in the RECLOSE-3 group and 9.7% in the RECLOSE-2-ACS group (p = 0.007). The difference in 2-year cardiac mortality remained considering exclusively patients with ACS on admission who accounted for the major difference in baseline characteristics between groups: 3.2% and 9.7%, respectively (p = 0.023) (Table 3). The rates of composite of cardiac death and MI and of definite and probable stent thrombosis were lower in the RECLOSE-3 group than in the RECLOSE-2-ACS cohort: 6.6% and 13.0% (p = 0.012), and 0.7% and 4.4% (p = 0.004), respectively. The cardiac survival rate was 96 ± 1% in the RECLOSE-3 group and 90 ± 2% in the RECLOSE-2-ACS group (p = 0.011) (Figure 2A). Similarly, the survival rate of freedom from cardiac death and MI was 93 ± 1% in the RECLOSE-3 group and 87 ± 2% in the RECLOSE-2-ACS group (p = 0.025) (Figure 2B). On the final model of multivariable analysis, prasugrel treatment was inversely related to the risk of 2-year cardiac death (HR: 0.32, 95% CI: 0.11 to 0.92, p = 0.036); the other variables significantly related to the risk of cardiac death were age 75 years and older (HR: 2.89, 95% CI: 1.34 to 6.23, p = 0.007) and renal insufficiency (HR: 2.35, 95% CI: 1.12 to 4.95, p = 0.024), whereas left ventricular ejection fraction <40% (HR: 1.63, 95% CI: 0.83 to 3.21, p = 0.155) and ACS (HR: 0.56, 95% CI: 0.17 to 1.88, p = 0.345) were not related to the primary endpoint.

There were no differences in major bleeding rates, whereas the minor bleeding rate was higher in the RECLOSE-3 group (Table 3).

DISCUSSION

The main finding of the RECLOSE-3 study is that nonresponsiveness to clopidogrel is a modifiable risk factor for cardiac death after PCI. The RECLOSE-3 shows that clopidogrel nonresponders switching to prasugrel treatment is associated with a 2-year cardiac mortality rate nearly identical to the population of clopidogrel responders in the RECLOSE-2-ACS: 4% and 4.3%, respectively. Moreover, the rates of definite or probable stent thrombosis were lower in the RECLOSE-3 group than in the RECLOSE-2-ACS group (0.7% and 4.4%, respectively, p = 0.004).

TABLE 2 Angiographic and Intervention Characteristics

	RECLOSE-2-ACS (N = 248)	RECLOSE-3 (N = 302)	p Value
Multivessel CAD	162 (65)	213 (70)	0.192
3-vessel CAD	82 (33)	115 (38)	0.222
3-vessel PCI	25 (10)	45 (15)	0.091
Treated vessel			
LAD	145 (58)	181 (60)	0.728
RCA	96 (39)	124 (41)	0.576
Circumflex artery	94 (38)	105 (35)	0.446
Left main artery	22 (8.9)	43 (14)	0.052
Ramus	9 (3.6)	5 (1.7)	0.144
No. of stents per patient	1.9 ± 1.1	2.4 ± 1.4	<0.001
Total stent length, mm	36.0 ± 26.5	50.5 ± 36.0	<0.001
Drug-eluting stent	133 (54)	275 (91)	<0.001
Aspirin at discharge	239 (96)	260 (86)	<0.001
Warfarin at discharge	5 (2.0)	12 (4.0)	0.187
Proton pump inhibitor at discharge	169 (68)	178 (59)	0.026

Values are n (%) or mean ± SD.

CAD = coronary artery disease; LAD = left anterior descending artery; PCI = percutaneous coronary intervention; RCA = right coronary artery.

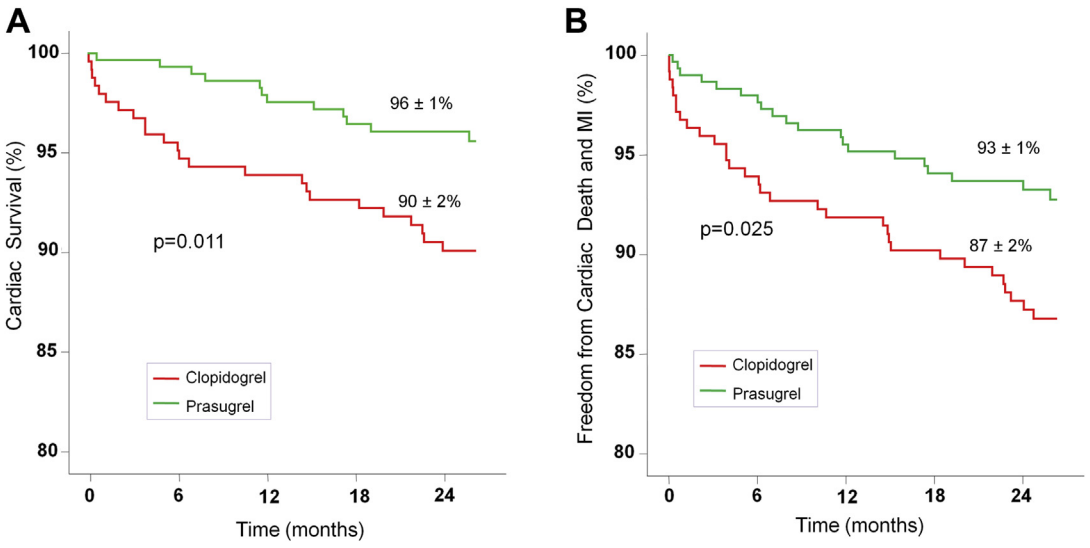
TABLE 3 2-Year Clinical Outcome

	RECLOSE-2-ACS (n = 247)	RECLOSE-3 (n = 302)	p Value
Cardiac death	24 (9.7)	12 (4.0)	0.007
Myocardial infarction	8 (3.2)	8 (2.6)	0.683
Stroke	3 (1.2)	2 (0.7)	0.498
Cardiac death and myocardial infarction	32 (13)	20 (6.6)	0.012
Stent thrombosis	15 (6.1)	8 (2.6)	0.046
Definite	7 (2.8)	2 (0.7)	0.046
Probable	4 (1.6)	0	0.026
Possible	4 (1.6)	6 (2.0)	0.749
Major bleeding	0	3 (1.0)	0.116
Minor bleeding	3 (1.2)	16 (5.3)	0.009
ACS patients	(n = 247)	(n = 126)	
Cardiac death	24 (9.7)	4 (3.2)	0.023
Myocardial infarction	8 (3.2)	6 (4.8)	0.464
Cardiac death and myocardial infarction	32 (13)	10 (7.9)	0.147
Stent thrombosis	15 (6.1)	2 (1.6)	0.049
Definite/probable	11 (4.4)	1 (0.8)	0.058
Non-ACS patients		(n = 176)	
Cardiac death		8 (4.5)	
Myocardial infarction		2 (1.1)	
Cardiac death and myocardial infarction		10 (5.7)	
Stent thrombosis		6 (3.4)	
Definite/probable		1 (0.6)	

Values are n (%).

ACS = acute coronary syndrome.

FIGURE 2 Survival Analyses of Clopidogrel Nonresponders in RECLOSE-2-ACS and RECLOSE-3 Studies



(A) Two-year cardiac survival analysis of clopidogrel nonresponders in the RECLOSE-2-ACS and RECLOSE-3 studies. **(B)** Two-year survival analysis of freedom from cardiac death and myocardial infarction (MI) in clopidogrel nonresponders in the RECLOSE-2-ACS and RECLOSE-3 studies.

Two previous studies, the GRAVITAS (Gauging Responsiveness With A VerifyNow Assay-Impact on Thrombosis And Safety) (21) and the RECLOSE-2-ACS (15), tried to overcome clopidogrel resistance with an increased dose of clopidogrel, which had some effect on the platelet reactivity tests but without any significant impact on clinical outcome.

As shown by previous studies, prasugrel may afford effective platelet aggregation inhibition in most patients with high residual platelet reactivity on clopidogrel treatment (17,18). In the RECLOSE-3, the ADP test result decreased <50% in the majority of patients, and all 26 patients with high residual platelet reactivity on prasugrel treatment had an ADP test result very close to the pre-specified cutoff of 70%. Similar effects on in vitro testing were revealed in the TRIGGER-PCI trial, which is the only randomized trial that compared prasugrel with clopidogrel in clopidogrel nonresponders (18). This TRIGGER-PCI study could not demonstrate the efficacy of the strategy of switching to prasugrel in clopidogrel nonresponders. The lack of demonstration of the clinical efficacy of switching to prasugrel in clopidogrel nonresponders may be explained by the fact that patients enrolled in the TRIGGER-PCI trial had a short-term follow-up (6 months), very low risk of events (stable coronary artery disease, single stent implantation in the majority of patients, patients with periprocedural complications were excluded), and the sample size was too small to demonstrate any significant impact of prasugrel (of 212 patients randomized to prasugrel, only 136 completed the study) on clinical outcome (18).

STUDY LIMITATIONS. The RECLOSE-3 study has a nonrandomized design and as such has the inherent limitations of this type of study. However, several strengths of the study should be outlined. In the RECLOSE-3 study, consecutive patients were screened without any restriction on the basis of 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 by PCI. Second, all patients recruited in the study received the same loading dose of clopidogrel, and platelet reactivity assessment was made using light transmittance aggregometry and a cutoff of the ADP test that have been validated in thousands of patients. The comparison with the historical cohort of the patients of the RECLOSE-2-ACS study was made with appropriate statistical adjustment to correct for differences between groups, including in the model of multivariable analysis the variables ACS and left ventricular ejection fraction <40% that accounted for the major differences between the RECLOSE-2-ACS and RECLOSE-3 patient

cohorts. The short time lag between the enrollment of patients in the RECLOSE-2-ACS and RECLOSE-3 avoided the potential confounding effects of possible advances in PCI and adjunctive pharmacological treatment. However, despite the appropriate statistical methods, we cannot exclude the effect of untested confounding variables. Finally, the aim of the study was to test the hypothesis that nonresponsiveness to clopidogrel is a modifiable risk factor and not the comparison of prasugrel with clopidogrel or other antiplatelet drugs in clopidogrel nonresponders, and ethical issues make the possibility of performing a randomized study using clopidogrel in the control arm in clopidogrel nonresponders unlikely.

CONCLUSIONS

Clopidogrel nonresponsiveness can be overcome by prasugrel treatment. In clopidogrel nonresponders, prasugrel therapy is associated with a high rate of long-term cardiac survival.

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PERSPECTIVES

WHAT IS KNOWN? Dual antiplatelet treatment is the standard of care in patients undergoing PCI, and clopidogrel is still the more used thienopyridine in current practice. Nonresponsiveness to clopidogrel is a major pitfall of this adjunctive therapy and is associated with a very high risk of death and other thrombotic events.

WHAT IS NEW? Prasugrel treatment overcomes nonresponsiveness to clopidogrel and results in a thrombotic risk similar to that in clopidogrel responders.

WHAT IS NEXT? The results of this study should be considered for further studies of tailored therapy using new antithrombotic agents.

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