Comparison of Prasugrel and Ticagrelor Loading Doses in ST-Segment Elevation Myocardial Infarction Patients

RAPID (Rapid Activity of Platelet Inhibitor Drugs) Primary PCI Study

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Objectives
This study sought to compare the action of prasugrel and ticagrelor in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary percutaneous coronary intervention (PPCI).

Background
It has been documented that prasugrel and ticagrelor are able to provide effective platelet inhibition 2 h after a loading dose (LD). However, the pharmacodynamic measurements after prasugrel and ticagrelor LD have been provided by assessing only healthy volunteers or subjects with stable coronary artery disease.

Methods
Fifty patients with STEMI undergoing PPCI with bivalirudin monotherapy were randomized to receive 60 mg prasugrel LD (n = 25) or 180 mg ticagrelor LD (n = 25). Residual platelet reactivity was assessed by VerifyNow at baseline and 2, 4, 8, and 12 h after LD.

Results
Platelet reactivity units (PRU) 2 h after the LD (study primary endpoint) were 217 (12 to 279) and 275 (88 to 305) in the prasugrel and ticagrelor groups, respectively (p = NS), satisfying pre-specified noninferiority criteria. High residual platelet reactivity (HRPR) (PRU ≥240) was found in 44% and 60% of patients (p = 0.258) at 2 h. The mean time to achieve a PRU <240 was 3 ± 2 h and 5 ± 4 h in the prasugrel and ticagrelor groups, respectively. The independent predictors of HRPR at 2 h were morphine use (odds ratio: 5.29; 95% confidence interval: 1.44 to 19.49; p = 0.012) and baseline PRU value (odds ratio: 1.014; 95% confidence interval: 1.00 to 1.03; p = 0.046).

Conclusions
In patients with STEMI, prasugrel showed to be noninferior as compared with ticagrelor in terms of residual platelet reactivity 2 h after the LD. The 2 drugs provide an effective platelet inhibition 2 h after the LD in only a half of patients, and at least 4 h are required to achieve an effective platelet inhibition in the majority of patients. Morphine use is associated with a delayed activity of these agents. (Rapid Activity of Platelet Inhibitor Drugs Study, NCT01510171) (J Am Coll Cardiol 2013;61:1601–6) © 2013 by the American College of Cardiology Foundation

Current guidelines recommend prasugrel and ticagrelor in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI) (1,2). The rapid onset of actions of prasugrel or ticagrelor may maximize the benefit of bivalirudin therapy in STEMI patients undergoing PPCI, and potentially decrease the risk of acute stent thrombosis. In fact, it has documented that prasugrel and ticagrelor are able to provide effective platelet inhibition after very few hours (2 h) from loading dose (LD) administration. However, the pharmacodynamic measurements after prasugrel and ticagrelor LD have been provided by assessing only healthy volunteers or subjects with stable coronary artery disease (3–7). On the contrary, PPCI for STEMI is the clinical arena in which rapid onset of antplatelets effect is pivotal, especially when a strategy without intravenous antplatelets agents is adopted.

Thus, the aim of the RAPID (Rapid Activity of Platelet Inhibitor Drugs) study was to compare the action of prasugrel...
and ticagrelor in patients with STEMI undergoing PPCI with bivalirudin monotherapy.

**Methods**

**Study design.** The RAPID study was a randomized, 2-arm, prospective study. The study was approved by the local ethical committee. All patients gave informed written consent. The study flow-chart is reported in Figure 1.

**Patient population.** Fifty patients with STEMI were randomized to receive 60 mg prasugrel LD (n = 25) or 180 mg ticagrelor LD (n = 25) before PPCI. The LD were performed as soon as possible in the Emergency Room or in the Cath Lab. Dual antiplatelet therapy (100 mg aspirin associated with 5 or 10 mg prasugrel or 180 mg ticagrelor) was recommended for 12 months. Study inclusion criteria were diagnosis of STEMI within 12 h of symptoms onset and informed written consent. Exclusion criteria were the following: 1) age <18 years; 2) active bleeding or bleeding diathesis; 3) any previous transient ischemic attack/stroke; 4) administration in the week before the index event of clopidogrel, ticlopidine, prasugrel, ticagrelor; 5) known relevant hematological deviations; 6) life expectancy <1 year; or 7) known severe liver or renal disease.

**Concomitant medications:** The following were concomitant medications: 1) aspirin: 500 mg LD followed by 100 mg daily dose; 2) bivalirudin: bolus 0.75 mg/kg followed by 1.75 mg/kg/h infusion during PCI, after PPCI a bivalirudin infusion of 0.25 mg/kg/h for 4 h was allowed; 3) unfractionated heparin use was discouraged; and 4) glycoprotein IIb/IIIa inhibitors were not allowed.

**Platelet function tests.** Residual platelet reactivity was assessed at baseline (time of LD), and after 2, 4, 8, and 12 h by VerifyNow. High residual platelet reactivity (HRPR) was defined as a platelet reactivity units (PRU) ≥240. Inhibition of platelet aggregation was defined as the percentage decrease in aggregation values obtained at baseline and after treatment: 100 × (PRU baseline – PRU after drug)/PRU baseline. Moreover, platelet reactivity was also assessed by light transmittance aggregometry (LTA) (APACT4, Helena Laboratories, Milan, Italy), using 10 μM ADP as agonist, 12 to 24 h after drug LD as previously reported (8).

**Endpoints.** The primary study endpoint was residual platelet reactivity by PRU VerifyNow 2 h after LD. Secondary endpoints were the following: 1) percentage of patients with an HRPR 2 h after LD; 2) acute stent thrombosis; and 3) in-hospital Thrombolysis In Myocardial Infarction major, minor, or minimal bleedings.

**Sample size calculation.** The study was designed on the basis of the noninferiority principle. As compared with

![Figure 1 Patient Flow and Study Design](image-url)
ticagrelor, prasugrel may carry some little advantages including 1 daily dose, reduced cost, and a limited number of patients having dyspnoea. Thus, we hypothesized that prasugrel would be noninferior as compared with ticagrelor. We assumed that the primary endpoint (PRU at 2 h) would be 55 ± 40 in the ticagrelor group, and 72 ± 40 in the prasugrel group. We admitted a noninferiority limit of 35. The planned enrollment of 50 patients provides 90% power for detecting this PRU difference at an alpha level of 0.05.

Statistical analysis. Continuous data are expressed as mean ± SD or medians (quartiles) as appropriate, and categorical data as proportions (%). Data were compared by means of the chi-square test for categorical variables and unpaired Student t test or Mann-Whitney U test for continuous variables. To control for type I error in multiple comparisons, the Bonferroni-adjusted significance level was used for the 5 time points of PRU assessment. We performed the analysis of variance for repeated measures of PRU at different times to test equality of means. The multivariable analysis used to evaluate the independent contribution of clinical characteristics to HRPR at 2 h was performed by the forward stepwise binary logistic regression analysis. The variables entered into the model were age (years), body mass index, diabetes mellitus, left ventricular ejection fraction, cardiogenic shock, morphine use, randomization arm, and baseline PRU value. A significance of 0.05 was required for a variable to be included in the multivariate model, whereas 0.10 was the cutoff value for exclusion. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. A p value <0.05 was considered statistically significant. All tests were 2-sided, except the noninferiority test. Analyses were performed with SPSS version 19 (IBM Corporation, Somers, New York).

Results

Baseline and procedural characteristics. The 2 groups were well matched in all baseline characteristics (Table 1). The study drug LD was performed in 18 (36%) patients in the Emergency Room, and in 32 (64%) patients in the Cath Lab, without differences between the 2 groups. Seven patients received 5,000 UI of unfractionated heparin in the Emergency Room, with subsequent switching to bivalirudin.

Residual platelet reactivity. After 2 h, PRU values ranged from 2 to 398 (median: 242 [54 to 293]). There was no difference in PRU value at 2 h between prasugrel and ticagrelor group: 217 (12 to 279) and 275 (88 to 305),
respectively (p = 0.207). Prasugrel showed to be noninferior as compared with ticagrelor in inhibiting platelet activity 2 h after the LD (Δ: -41; 95% CI: -115 to +31; which was behind the predefined +35 noninferiority margin) (Fig. 2). At 8 h, PRU value was significantly lower in the prasugrel group as compared with the ticagrelor group (Fig. 3). However, the analysis of variance showed not significant between-subjects treatment effect (p = 0.338), and treatment by time interaction effect (p = 0.744). We also calculated inhibition of platelet aggregation values that are able to correct for potential differences in baseline PRU (Fig. 4). The percentage of HRPR patients at different time points in the prasugrel and ticagrelor groups are reported in Figure 5. Residual platelet reactivity evaluated by LTA was $34 \pm 14$ and $39 \pm 14$ (p = 0.215) in prasugrel and ticagrelor groups, respectively. The mean time to achieve a PRU <240 was 3 ± 2 h and 5 ± 4 h in the prasugrel and ticagrelor groups, respectively. The independent predictors of HRPR 2 h after LD were morphine use (OR: 5.29; 95% CI: 1.44 to 19.49; p = 0.012) and baseline PRU value (OR: 1.014; 95% CI: 1.00 to 1.03; p = 0.046).

In-hospital outcome. The clinical events observed are reported in Table 2. There was no difference in event rates between the 2 study drugs, but a higher rate of dyspnoea and contrast-induced nephropathy in the ticagrelor group. There were 2 deaths in the ticagrelor group due to refractory heart failure. One patient with HRPR after prasugrel LD had a stent thrombosis 3 h after PPCI.

Discussion

The study results can be summarized as follows: 1) prasugrel showed to be noninferior as compared with ticagrelor in terms of residual platelet reactivity 2 h after the LD; 2) 2 h
after a LD of the new P2Y_{12} receptor inhibitors a wide variability in drug response must be expected in STEMI patients, and the PRU values are higher than those reported for healthy volunteers or subjects with stable coronary artery disease; 3) one-half of STEMI patients treated with a LD of prasugrel or ticagrelor show HRPR after 2 h, and at least 4 h are required to achieve a sufficient drug effect; and 4) morphine use is associated with a delayed activity of the new oral antiplatelet agents.

Platelet function test results in STEMI patients treated by prasugrel or ticagrelor LD are scarce; in fact, the pharmacodynamic substudies of the TRITON–TIMI-38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction–38) (5) and PLATO (Platelet Inhibition and Patient Outcomes) trials (9) included only 4 and 5 patients with STEMI, respectively. Our data revealed a wide variability of drug response suggesting that the gastrointestinal absorption of orally administered drugs may be limited or delayed in STEMI patients because of multiple reasons including reduced or delayed drug adsorption in patients with hemodynamic disarrangement, systemic vasoconstriction, adrenergic activation, and at high risk of vomit. Moreover, advanced age, high body weight, and polypharmaco therapy may be additional parameters potentially able to influence the time of drug effect onset (10,11). The PRU findings obtained in the present study were clearly higher than that observed in previous studies, which analyzed prasugrel or ticagrelor pharmacokinetic data in healthy volunteers or subjects with stable coronary artery disease (3–7). Of note, more than a half of patients treated with the new antiplatelet agents still show HRPR 2 h after the LD. This means that the majority of the procedures of stenting of the infarct-related artery were performed without functional evidence of a significant antiplatelet effect. In a previous study, it has been demonstrated that a nontrivial number of acute coronary syndrome patients do not achieve optimal platelet inhibition despite the use of prasugrel LD and that such patients have a higher risk of major adverse cardiac events (12). Moreover, given the fact that HRPR is an important determinant of the risk of stent thrombosis, and that the majority of STEMI patients require at least 4 h to achieve a sufficient drug effect after a prasugrel or ticagrelor LD, we can imagine a significant time window after PPCI, in which many patients are at high risk of stent thrombosis. Thus, all these findings raise the question for the need of different pharmacological strategies in the first hour after STEMI onset. Regarding the comparison of the 2 drugs, prasugrel, despite being adsorbed as a prodrug, was noninferior as compared with ticagrelor in reducing the primary endpoint of the study of residual platelet reactivity 2 h after the LD. We do not know if the differences obtained in PRU values between the 2 study drugs may be related to not statistically significant (e.g., cardiogenic shock) or unmeasured differences in the baseline characteristics of the 2 groups, or may be associated to the fact that ticagrelor LD is just the daily dose, while prasugrel LD is 6-fold the chronic daily dose. As expected, baseline PRU value resulted as a predictor of HRPR 2 h after drug LD. Thus, higher is the activation of the platelet in STEMI patients before treatment and more time the new antiplatelet drugs take to achieve a sufficient platelet inhibition. Finally, morphine use resulted to be associated with a delayed activity of the new oral antiplatelet agents. We do not know if it is only a play of chance or if it has biological basis likely related to the inhibition of the normal muscular activity of the stomach and the intestines, which may lead to vomit or delayed drug adsorption. However, if these findings will be confirmed by further studies, more caution should be used regarding morphine administration in STEMI patients.

**Study limitations.** First, the small sample size is certainly its most important limitation. However, we were able to enroll a prospective homogenous populations of patients with STEMI that mirrors other similar studies, and clinical outcome data were reported only as indicative. Second, we evaluated residual platelet reactivity by only 1 test (VerifyNow) that was available in our Hospital 7/7 days and 24/24 h allowing the enrollment of consecutive patients. LTA data were available only 12 to 24 h after drug LD and confirmed similar and optimal platelet inhibition of prasugrel and ticagrelor at that time point. Third, the PRU values were measured in STEMI patients treated with bivalirudin monotherapy and it is unknown if they can be extrapolated to patients treated with different pharmacological strategies. Finally, overfitting risk cannot be excluded in our multivariable model.

**Conclusions**

These limitations notwithstanding, the present study provides several unique and potentially important insights in the treatment of STEMI patients by PPCI.

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