Differential Effect of Ticagrelor Versus Prasugrel on Coronary Blood Flow Velocity in Patients With Non–ST-Elevation Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention: An Exploratory Study

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Background—Prasugrel and ticagrelor provide a superior anti-ischemic action than clopidogrel, with some of ticagrelor’s benefits possibly attributed to adenosine-mediated mechanisms. We aimed to compare the effect of maintenance dose of ticagrelor versus prasugrel on coronary blood flow velocity (CBFV) during increasing doses of intravenously administered adenosine.

Methods and Results—In a prospective, single-center, single-blind, crossover study, 56 patients with non–ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention were randomized to receive either ticagrelor 90 mg BID or prasugrel 10 mg OD with a 15-day treatment period. At the end of each treatment period, CBFV by transthoracic Doppler echocardiography was assessed at baseline and under incremental doses (50 μg/kg per minute, 80 μg/kg per minute, 110 μg/kg per minute, and 140 μg/kg per minute) of adenosine infusion. Maximal CBFV area under the curve was higher for ticagrelor-treated than for prasugrel-treated patients, with a least squares mean difference of 7.16 (95% confidence interval, 2.61–11.7; P=0.003). Maximal CBFV/baseline CBFV ratio was higher with ticagrelor than prasugrel at 50, 80, and 110 μg/kg per minute but not at 140 μg/kg per minute adenosine infusion rate, with mean difference (95% confidence interval) of 0.17 (0.08–0.26; P<0.001), 0.21 (0.02–0.41; P=0.03), 0.24 (0.01–0.47; P=0.04), and 0.14 (−0.12 to 0.4; P=0.3), respectively.

Conclusions—In patients with non–ST-elevation acute coronary syndrome undergoing percutaneous coronary intervention, ticagrelor augments CBFV to a greater extent than prasugrel when incremental doses of adenosine are administered. Although exploratory, these results may represent a pleiotropic action of ticagrelor, possibly contributing to its beneficial effects in such patients.


Key Words: acute coronary syndrome ■ adenosine ■ P2Y12 receptor ■ prasugrel ■ ticagrelor
WHAT IS KNOWN

- Compared with clopidogrel, prasugrel and ticagrelor have been shown to decrease ischemic events.
- Some of ticagrelor’s benefits have been possibly attributed to adenosine-mediated mechanisms.
- In healthy male volunteers, ticagrelor loading augments the adenosine-induced increase in coronary blood flow velocity.

WHAT THE STUDY ADDS

- In non-ST-segment-elevation acute coronary syndrome patients treated with percutaneous coronary intervention and receiving a maintenance dose of ticagrelor, coronary blood flow velocity augments to a greater degree compared with patients on a prasugrel maintenance dose in response to increasing adenosine concentrations.
- Although exploratory, these findings may represent a pleiotropic action of ticagrelor potentially associated with some of the clinical benefits provided by this agent.

coronary intervention (PCI), we aimed to compare the effect of maintenance dose of ticagrelor versus prasugrel on CBFV as assessed by transthoracic Doppler echocardiography under incremental doses of adenosine infusion.

Methods

Study Protocol

We performed a prospective, single-center, single-blind, investigator-initiated, randomized, crossover study to compare the effect of ticagrelor versus prasugrel on adenosine-induced CBFV responses. Consecutive patients aged 18 to 75 years with NSTE-ACS undergoing PCI with drug-eluting stent implantation were included. Patients admitted with ST-elevation myocardial infarction were excluded to avoid possible influence of the infarcted myocardium and left ventricular remodeling to CBFV. Other exclusion criteria were prior myocardial infarction, prior PCI, coronary artery bypass grafting, nonsinus rhythm, requiring hemodialysis, major periprocedural complications or suboptimal PCI result (residual stenosis >20% by visual assessment), contraindication for ticagrelor or prasugrel administration, weight <60 kg, age ≥75 years, risk for bleeding or bradycardic events, severe chronic obstructive pulmonary disease, requirement for oral anticoagulant, left ventricular ejection fraction <45%, left ventricular hypertrophy, diastolic dysfunction, severe valvular disease, any residual LAD stenosis >40% by visual assessment, and diffuse coronary atherosclerosis.

Between February 2012 and September 2012, 65 eligible patients were screened 24 to 36 hours after PCI for participation in the study. In 4 (6.2%) patients, baseline LAD CBFV assessment could not be adequately obtained, whereas 5 patients refused to participate in the study. The remaining 56 patients were randomized (day 0) in a 1:1 ratio, using computerized random-number generation by an independent investigator, to receive either ticagrelor 90 mg BID (N=28) or prasugrel 10 mg OD (N=28) for 15 days after randomization, as shown in the study flow chart (Figure 1). A day 15 visit (visit 1) was performed to evaluate the adenosine-induced CBFV response (see below). Patient compliance with antplatelet treatment was assessed by interview and tablet counting. Any adverse reactions related to the antplatelet therapy or the adenosine infusions were documented by an independent observer. A crossover directly to the alternate treatment without washout period was performed, and at day 30 (visit 2) the same evaluation was applied. Patients were instructed to receive their treatment of ticagrelor/prasugrel on the predefined time daily (10:00 am for prasugrel and 10:00 am/10:00 pm for ticagrelor) and to avoid coffee or alcohol consumption, smoking, and exercise for 24 hours before each visit. Discharge medication was kept constant across both study periods.

Adenosine-Induced CBFV Changes

Noninvasive assessment of CBFV by transthoracic Doppler echocardiography was performed by 1 experienced echocardiographer (N.K.) who was blind to treatment allocation. All echocardiographic studies were performed between 1:00 and 3:00 pm after a 3-hour fasting period. Resting pulse and blood pressure were measured, with the patient remaining in a quiet, air-conditioned room (temperature between 20°C and 23°C). After 10 minutes of resting, echocardiography was performed with the patient in the left lateral decubitus position. After the completion of the standard echocardiographic examination, LAD flow was detected using a 4 to 6.7 MHz or a 1.7 to 3.4 MHz multifrequency transducer (GE-Vingmed VIVID 7, Norway). A modified apical 2-chamber view was used, and the flow signal was located by color flow mapping as flow toward the transducer containing a dominant diastolic signal. Care was taken to monitor the end-diastolic frame and to avoid poor signal-to-noise ratios. Before the start of each adenosine infusion, a baseline LAD bolus flow velocity was obtained. Adenosine was then infused in increasing doses of 100 μg/kg over 3 minutes, with each dose being administered for 2 minutes. Each dose produced a hyperemic response in the LAD, and the peak velocity of LAD flow during each dose was measured. The data were analyzed by the same investigator who was blind to treatment allocation and who had been previously trained in the technique. An intraobserver variability of 10% was observed. The percentage change in peak CBFV was calculated as:

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\text{Percentage change} = \frac{\text{Peak CBFV after adenosine infusion} - \text{Baseline CBFV}}{\text{Baseline CBFV}} \times 100
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\]
avoid interference of myocardial velocity or pericardial motion. The sample volume size was set at 3 mm. The sampling of the flow by pulsed wave Doppler was obtained as parallel to LAD flow (≤20°) to avoid underestimation of the peak velocities, and the theta angle was not corrected. Recordings were made at baseline and under 2-minute adenosine intravenous administration at incremental doses of 50, 80, 110, and 140 μg/kg per minute, with 5-minute interval between infusions. For the accurate calculation of the adenosine infusion rate, the patients were weighed before each visit. Blood pressure and heart rate were monitored during the whole examination.

CBFV in the LAD was measured at baseline (bCBFV) and at peak hyperemic conditions (maxCBFV) from spectral Doppler signals using the software incorporated in the ultrasound system. The average of 3 cycles for bCBFV and the maximal (out of ≥25 cardiac cycles) CBFV observed during each 2-minute adenosine infusion were used for calculation of maxCBFV. To evaluate operator’s reproducibility, a subgroup of 20 randomly selected patients underwent bCBFV assessment twice on the same day (day 15) by the same examiner (N.K.), 5 minutes apart. Reproducibility was assessed with offline data analysis by an independent physician.

End Points
End points were prespecified in the study protocol and statistical analysis plan. The primary end point was the area under the curve of the LAD maxCBFV at gradually increasing doses of adenosine at the end of the 2 treatment periods. Secondary end points were the ratio of LAD maxCBFV/bCBFV at the end of the 2 treatment periods separately for 50, 80, 110, and 140 μg/kg per minute adenosine infusion rate. A non-prespecified analysis of LAD maxCBFV at the end of the 2 treatment periods separately for 50, 80, 110, and 140 μg/kg per minute adenosine infusion rate was also performed.

Sample Size Calculation
Based on pilot data analysis, we hypothesized that ticagrelor would result in an area under the curve difference of 7.0 with prasugrel (with the assumption that the within-patient SD of the response variable would be 11.2). Choosing a power of 85% and a 2-sided α-level of 0.05, ≥11.2 patients in total were required to reach statistical significance based on the above assumptions.

Statistical Analysis
Categorical data are presented as frequencies and group percentages and continuous data as means±SD. Two-sample t test and the Fisher exact test were used for comparison of continuous and categorical data, respectively. Only patients who successfully completed 21 period of the study were considered for analysis. Individual area under the curves at the end of each treatment period were calculated with the trapezoidal rule and then a mixed linear model was fitted, adjusting for period, treatment sequence (carry-over), and treatment effect (fixed factors), with patient indicator as random intercept. Least squares estimates of the mean difference are presented, with 95% confidence interval (CI) and a 2-sided P value for the treatment effect. Secondary end points and the double product (heart rate×systolic blood pressure) were analyzed with mixed effects model was fitted, adjusting for period, treatment sequence (carry-over), and random intercept and period, sequence, and treatment as fixed effects. Operator’s reproducibility was evaluated by using both a linear regression analysis and the Bland–Altman method for assessing the limits of agreement between the repeated measurements.10 All tests were 2-tailed, and statistical significance was considered for P<0.05. Analyses were performed using SPSS for Windows (version 16.0 SPSS Inc, Chicago, IL) and GraphPad Prism v.5 (GraphPad Software, Inc). The study conforms to the Declaration of Helsinki and was approved by the ethics committee of the University Hospital of Patras, Greece. All patients gave written informed consent for participation.

Results
There were no differences in demographic and clinical characteristics of randomized patients between the 2 groups

| Table 1. Demographic and Clinical Characteristics of Randomized Patients |
|-----------------------------------|-------|-------|
|                                    | Prasugrel | Ticagrelor |
|                                    | (N=28) | (N=28) |
| Male                               | 26 (92.9) | 23 (82.1) | 0.4 |
| Age, y                             | 55.8±10.0 | 57.4±9.8 | 0.5 |
| Body mass index, kg/m²             | 28.8±4.7 | 27.9±3.4 | 0.5 |
| Dyslipidemia                       | 19 (67.9) | 12 (42.9) | 0.1 |
| Hypertension                       | 16 (57.1) | 15 (53.6) | 1.0 |
| Diabetes mellitus                  | 6 (21.4) | 4 (14.3) | 0.7 |
| Smoking                            | 18 (64.3) | 12 (42.9) | 0.2 |
| Family history of CAD             | 11 (39.3) | 9 (32.1) | 0.8 |
| Admission                          | 1.0 |
| Non-ST-elevation myocardal infarction | 15 (53.6) | 14 (50.0) |
| Unstable angina                    | 13 (46.4) | 14 (50.0) |
| Coronary artery disease extent     | 0.7 |
| 1-vessel disease                   | 15 (53.6) | 17 (60.7) |
| 2-vessel disease                   | 12 (42.9) | 9 (32.1) |
| 3-vessel disease                   | 1 (3.6) | 2 (7.1) |
| PCI                                | 0.1 |
| In LAD                             | 20 (71.4) | 13 (46.4) |
| In LCX                             | 7 (25.0) | 14 (50.0) |
| In RCA                             | 8 (28.6) | 3 (10.7) | 0.2 |
| Laboratory evaluation              | 0.6 |
| Hematocrit, %                      | 41.9±3.5 | 41.3±5.0 | 0.6 |
| Creatinine clearance, mL/min       | 106.7±32.3 | 107.7±33.9 | 0.9 |
| LVEF, %                            | 57.5±5.4 | 57.3±3.8 | 0.9 |
| P2Y12 inhibitor prerandomization   | 0.6 |
| Clopidogrel (600 mg/75 mg)         | 12 (42.9) | 16 (57.1) |
| Prasugrel (60 mg/10 mg)            | 9 (32.1) | 7 (25.0) |
| Ticagrelor (180 mg/90 mg)          | 7 (25.0) | 5 (17.9) |
| Discharge medication               | 1.0 |
| Aspirin (100 mg)                   | 28 (100) | 28 (100) |
| Statin                             | 27 (96.4) | 27 (96.4) |
| β-Blocker                          | 25 (89.3) | 28 (100) |
| Nitrate                            | 5 (17.9) | 2 (7.1) | 0.4 |
| Calcium channel blocker            | 1 (3.6) | 1 (3.6) | 1.0 |
| Angiotensin-converting enzyme       | 21 (75.0) | 22 (78.6) |
| Inhibitor                          | 1.0 |
| Angiotensin II blocker             | 6 (21.4) | 3 (10.7) | 0.5 |

Data are expressed as means±SD or n (%). CAD indicates coronary artery disease; LAD, left anterior descending artery; LCX, left circumflex artery; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; and RCA, right coronary artery.
Operator’s reproducibility was high ($r=0.87; P<0.001$). The mean difference between the 2 measurements was $-0.0025$ (95% CI, $-0.013$ to $0.0081$), and the upper and lower limits of agreement between the 2 measurements were $+0.042$ (95% CI, 0.024–0.06) and $-0.047$ (95% CI, $-0.065$ to $-0.029$), respectively.

The primary end point of the LAD maxCBFV area under the curve at gradually increasing doses of adenosine at the end of the 2 treatment periods was higher for ticagrelor-treated than for prasugrel-treated patients, with a least squares mean difference of $7.16$ (95% CI, 2.61–11.7; $P=0.003$; Figure 3). The ratio of LAD maxCBFV/bCBFV combined at the end of the 2 treatment periods separately for 50, 80, 110, and 140 $\mu$g/kg per minute adenosine infusion rate is depicted in Table 2. A significantly higher ratio of LAD maxCBFV/bCBFV was found for ticagrelor compared with prasugrel at 50, 80, and 110 $\mu$g/kg per minute adenosine infusion rate. The difference in LAD maxCBFV between the 2 agents was not significant at 140 $\mu$g/kg per minute adenosine infusion rate.

At rest, mean arterial pressure (mm Hg) and heart rate (bpm) did not differ between ticagrelor- and prasugrel-treated patients: least squares estimate of the mean difference (95% CI) 95.4 (91.2–99.5), 66.0 (63.5–68.5) and 95.5 (91.3–99.6), 66.0 (63.5–68.5), with $P=0.96$ and $P=0.2$, respectively. At peak hyperemia, mean arterial pressure and heart rate did not differ between ticagrelor- and prasugrel-treated patients:

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**Figure 2.** An example of transthoracic Doppler echocardiography images in a single patient. Left anterior descending artery baseline (A) and maximal at 110 $\mu$g/kg per minute adenosine infusion rate (B) coronary blood flow velocity (CBFV) recorded at day 15, while under prasugrel, are shown. The same patient’s images of baseline (C) and maximal at 110 $\mu$g/kg per minute adenosine infusion rate CBFV (D) on day 30, while under ticagrelor, are depicted. The respective ratios of maximal CBFV/baseline CBFV are shown (B and D).

**Figure 3.** Area under the curve (AUC) of left anterior descending artery (LAD) maximal coronary blood flow velocity (maxCBFV) at gradually increasing doses of adenosine. Dotted area indicates the AUC mean difference. For the graphical representation of AUCs, data from Table 3 are used.
Table 2. Ratio of LAD maxCBFV/Baseline CBFV Combined at the End of Treatment Periods

<table>
<thead>
<tr>
<th>Adenosine Infusion, µg/kg per Minute</th>
<th>Ticagrelor LS Estimates (95% CI)</th>
<th>Prasugrel LS Estimates (95% CI)</th>
<th>Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>1.50 (1.38 to 1.62)</td>
<td>1.33 (1.21 to 1.45)</td>
<td>0.17 (0.08 to 0.26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>80</td>
<td>2.29 (2.05 to 2.54)</td>
<td>2.08 (1.83 to 2.32)</td>
<td>0.21 (0.02 to 0.41)</td>
<td>0.03</td>
</tr>
<tr>
<td>110</td>
<td>3.11 (2.89 to 3.32)</td>
<td>2.86 (2.65 to 3.07)</td>
<td>0.24 (0.01 to 0.47)</td>
<td>0.04</td>
</tr>
<tr>
<td>140</td>
<td>3.41 (3.19 to 3.62)</td>
<td>3.27 (3.05 to 3.48)</td>
<td>0.14 (−0.12 to 0.4)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Baseline CBFV indicates baseline coronary blood flow velocity; CI, confidence interval; LAD, left anterior descending artery; LS, least squares; and maxCBFV, maximal coronary blood flow velocity.

Table 3. LAD maxCBFV (cm/s) Combined at the End of Treatment Periods

<table>
<thead>
<tr>
<th>Adenosine Infusion</th>
<th>Ticagrelor LS Estimates (95% CI)</th>
<th>Prasugrel LS Estimates (95% CI)</th>
<th>Mean Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.289 (0.27 to 0.31)</td>
<td>0.286 (0.26 to 0.31)</td>
<td>0.003 (−0.17 to 0.02)</td>
<td>0.7</td>
</tr>
<tr>
<td>50 µg/kg per minute</td>
<td>0.44 (0.39 to 0.49)</td>
<td>0.38 (0.33 to 0.43)</td>
<td>0.06 (0.02 to 0.1)</td>
<td>0.002</td>
</tr>
<tr>
<td>80 µg/kg per minute</td>
<td>0.65 (0.58 to 0.73)</td>
<td>0.57 (0.50 to 0.65)</td>
<td>0.08 (0.03 to 0.13)</td>
<td>0.003</td>
</tr>
<tr>
<td>110 µg/kg per minute</td>
<td>0.87 (0.80 to 0.94)</td>
<td>0.80 (0.73 to 0.86)</td>
<td>0.07 (0.02 to 0.12)</td>
<td>0.009</td>
</tr>
<tr>
<td>140 µg/kg per minute</td>
<td>0.95 (0.88 to 1.02)</td>
<td>0.91 (0.84 to 1.0)</td>
<td>0.05 (−0.006 to 0.09)</td>
<td>0.08</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; LAD, left anterior descending artery; LS, least squares; and maxCBFV indicates maximal coronary blood flow velocity.
Baseline resting period 8929 (8352 to 9506) 8715 (8135 to 9293) 215 (−226 to 655) 0.3
110 μg/kg per minute 9361 (8691 to 10 μg) 8514 (7926 to 9102) 246 (−170 to 663) 0.2
80 μg/kg per minute 9361 (8691 to 10030) 8754 (8090 to 9418) 607 (150 to 1063) 0.01
110 μg/kg per minute 10076 (9360 to 10792) 9581 (8876 to 10286) 495 (0.02 to 990) 0.05
140 μg/kg per minute 10560 (9275 to 11196) 9896 (9275 to 10516) 665 (−144 to 1474) 0.1

CI indicates confidence intervals; and LS, least squares.

Table 4. Double Product (Heart Rate×Systolic Blood Pressure) Combined at the End of Treatment Periods

Before adenosine infusion, there were no differences in CBFV between ticagrelor- and prasugrel-treated patients. It seems, therefore, that it is only during the exposure to the potent vasodilatory action of adenosine infusion when their differences become apparent. Similarly, compared with placebo, neither ticagrelor nor placebo affected basal CBFV before adenosine infusion. The differences in maxCBFV/bCBFV in favor of ticagrelor were apparent at all, but not the highest adenosine infusion rate. This most likely reflects the fact that at the highest used adenosine infusion rate, a maximal coronary vasodilation is expected to occur in the majority of the patients, irrespective of the presence or absence of an adjunctive or auxiliary vasodilatory action. These have been attributed to increased extracellular adenosine levels caused by ticagrelor, although adenosine hypothesis as the cause of dyspnea has been recently disputed.

Ticagrelor Versus Prasugrel Comparison: Possible Clinical Relevance

The previously published head-to-head comparisons of ticagrelor versus prasugrel have been only pharmacodynamic ones comparing their antiplatelet action, without the power to assess any differences in outcome. So far, no direct clinical comparison of ticagrelor versus prasugrel has been performed.

In the PLATO trial, hypotheses were raised that the mechanisms of the beneficial effect observed with ticagrelor might be beyond its antiplatelet action. The reason of lowering total and cardiovascular mortality with ticagrelor remains unclear. It was hypothesized that modulation of adenosine receptors might play an important role. Although there is no direct clinical relevance, the enhancement of adenosine-induced increase in CBFV demonstrated in the present study may represent an off-target cardiovascular effect of ticagrelor, possibly contributing to its beneficial effects seen in the PLATO trial. Other features observed in patients with ST-elevation ACS in the PLATO trial, such as the accruing reduction in secondary efficacy end points over time and the continuing separation of event curves beyond the first month and during long-term treatment, have been attributed to possible adenosine-like actions of ticagrelor. Apart from the beneficiary effects, adverse events, such as bradycardia and dyspnea, have also been associated with ticagrelor but not prasugrel treatment. These have been attributed to increased extracellular adenosine levels caused by ticagrelor, although adenosine hypothesis as the cause of dyspnea has been recently disputed.

Limitations

The main limitation of our study is that adenosine levels were not measured, and therefore the observed differences cannot be considered causative. The reversibility of the adenosine-mediated CBFV response by theophylline was not assessed. However, this has been previously demonstrated to occur in healthy volunteers. Because of the lack of a placebo group, a pleiotropic action for prasugrel cannot be excluded with absolute certainty. However, no possibility that such action may exist has been raised so far. Our results apply to a short-term interval after PCI. Similar possible actions of long-term administration of ticagrelor or prasugrel have not been studied. We did not use low dose of an intravenous contrast for improved color Doppler signal and spectral Doppler signals in the LAD. However, ultrasonographic assessment of the CBFV seems very feasible, reproducible, and accurate in experienced hands, even without contrast agent injection, and is favorably compared with that obtained with invasive Doppler flow wire.

Conclusions

In NSTE-ACS patients treated with PCI and receiving maintenance dose of ticagrelor, CBFV augments to a greater degree compared with those on prasugrel maintenance dose, in response to incremental doses of adenosine. Although these results are exploratory, they may represent a pleiotropic action of ticagrelor potentially associated with some of the clinical benefits provided by this agent.

Sources of Funding

This study was supported by the Research Committee of the Patras University Medical School and by the Hellenic Cardiological Society. Dr Moulas has received scholarship support from the Onassis Foundation.

Disclosures

Dr Alexopoulos reports receipt of speaker fees from AstraZeneca. The other authors have no conflicts to report.

References


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