Prasugrel Versus Tirofiban Bolus With or Without Short Post-Bolus Infusion With or Without Concomitant Prasugrel Administration in Patients With Myocardial Infarction Undergoing Coronary Stenting

The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) Trial

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Objectives The authors sought to compare the effect on inhibition of platelet aggregation (IPA) of prasugrel therapy versus tirofiban bolus with or without a post-bolus short drug infusion in ST-segment elevation myocardial infarction (STEMI) patients.

Background The degree and rapidity of IPA after prasugrel alone with or without concomitant glycoprotein IIb/IIIa inhibition in STEMI patients is unknown.

Methods A total of 100 STEMI patients randomly received prasugrel 60 mg versus 25 μg/kg tirofiban bolus with or without post-bolus 2-h infusion of tirofiban, with or without concomitant prasugrel. IPA at light transmission aggregometry was performed throughout 24 h. The primary endpoint was IPA stimulated with 20 μmol/l adenosine diphosphate (ADP) at 30 min.

Results At 30 min, patients in the prasugrel group showed a significantly lower IPA to 20 μmol/l ADP stimulation as compared with tirofiban-treated patients (36 ± 35 vs. 87 ± 31, p < 0.0001). Similarly, patients taking prasugrel showed a suboptimal degree of platelet inhibition for at least 2 h compared with tirofiban patients. Post-bolus tirofiban infusion was necessary to maintain a high level of IPA beyond 1 h after bolus administration if concomitant clopidogrel was given, whereas the bolus-only tirofiban and concomitant prasugrel led to the higher and more consistent IPA levels after both ADP and thrombin receptor-activating peptide stimuli than either therapy alone.

Conclusions Our study shows that prasugrel administration leads to a suboptimal IPA for at least 2 h in STEMI patients. Yet, prasugrel, given in association with a bolus only of glycoprotein IIb/IIIa inhibitor, obviates the need of post-bolus infusion and almost completely abolishes residual variability of IPA after treatment. (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse [The FABOLUS PRO trial]; NCT01336348) (J Am Coll Cardiol Intv 2012;5:268–77) © 2012 by the American College of Cardiology Foundation.
Given the pivotal role of the platelet in acute coronary syndromes (ACS), measures to inhibit platelet activity are paramount to its management (1). Over time, a growing recognition of the various pathways driving platelet activity has given rise to the need for multiple agents, which impart complimentary mechanisms of action.

Blocking simultaneous platelet upstream activation via aspirin and clopidogrel, a rather weak P2Y_{12} receptor blocker, and downstream aggregation pathway with glycoprotein IIb/IIIa inhibitors (GPI) has been shown to be beneficial in preventing ischemic periprocedural complications in patients with ACS undergoing coronary intervention (2–5).

Yet, the recent advent of potent and fast-acting oral P2Y_{12} inhibitors, such as prasugrel or ticagrelor, which are able to almost completely suppress adenosine diphosphate (ADP)-induced platelet aggregation (PA) (6–8), is questioning the additional value of GPI in contemporary practice.

Pharmacokinetic data on the effect of prasugrel administration in ACS patients are limited, however (9,10), and there is no randomized comparison of GPI versus prasugrel measuring potency and rapidity of PA inhibition. This evaluation appears particularly critical for ST-segment elevation myocardial infarction (STEMI) patients, in whom the capability of clopidogrel to suppress ADP-induced platelet activation is largely inferior to what would be predicted based on assessments in stable patients (11).

We compared the degree of platelet inhibition after administration of prasugrel only versus a treatment strategy based on tirofiban bolus with or without a post-bolus short drug infusion, with or without concomitant prasugrel, in STEMI patients undergoing primary percutaneous coronary intervention (PCI).

Methods

Study design and patient population. The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading DoSe) study is a single-center, open-label, prospective randomized pharmacodynamic investigation of 2 main antiplatelet treatment strategies in patients undergoing coronary intervention for STEMI: oral administration of prasugrel alone at a loading dose of 60 mg or the administration of tirofiban 25 μg/kg bolus with or without a 0.15 μg/kg/min 2-h post-bolus infusion of tirofiban with concomitant or post-infusion administration of either 60 mg of prasugrel or 600 mg of clopidogrel (Fig. 1).

The study protocol was approved by the ethics committee and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Eligible subjects were those older than 18 years old, undergoing coronary intervention for symptoms of ischemia that were lasting at least 30 min with an electrocardiographic ST-segment elevation ≥1 mm in 2 or more contiguous electrocardiogram leads, or with a new left bundle-branch block, and admission either within 12 h of symptom onset or between 12 and 24 h after onset with evidence of continuing ischemia. The exclusion criteria included administration of fibrinolytics in the previous 30 days, major surgery within 15 days, current bleeding, or previous stroke in the last 6 months. All patients underwent primary angioplasty immediately after the start of the oral and/or intravenous treatment.

Randomization. An independent study nurse performed assignments of study treatments via a procedure employing sealed envelopes. A 3:1:1:1 computer-generated random sequence in blocks of 6, without stratification and supplied by an academic statistician was used to treat patients with the following 4 different treatment strategies: 1) prasugrel 60 mg only; 2) tirofiban 25 μg/kg bolus only and concomitant clopidogrel 600 mg; 3) tirofiban 25 μg/kg bolus only and concomitant prasugrel 60 mg; and 4) tirofiban 25 μg/kg bolus followed by 0.15 μg/kg/min 2-h tirofiban post-bolus infusion without any concomitant oral P2Y_{12} inhibitors. At the time of discontinuation of the tirofiban infusion, this group of patients was subsequently randomly allocated to receive either prasugrel 60 mg or clopidogrel 600 mg according to a 1:1 computer-generated random sequence in blocks of 4.

Study medications and interventions. Upon presentation, patients received aspirin at 160 to 325 mg orally or 250 mg intravenously, followed by 100 mg orally indefinitely. Prasugrel was given at a 60-mg loading dose followed by 10 mg/day for at least 30 days, whereas clopidogrel was administered at a loading dose of 600 mg followed by 75 mg daily. Tirofiban was given as a bolus of 25 μg/kg with or without post-bolus infusion of 0.15 μg/kg/min for 2 h. In all patients, anticoagulation during the procedure was achieved via administration of unfractionated heparin given as a bolus of 100 U/kg, targeting an activated clotting time of at least 300 s.

Platelet function testing. PA was performed as previously reported (1,12) immediately before the administration of
tirofiban and/or oral P2Y12 receptor blockers (baseline sample), at 15 ± 5 min, 30 ± 5 min, 60 ± 5 min, 120 ± 5 min, and 360 ± 5 min, and 18 to 24 h after start of the treatment (i.e., intravenous tirofiban bolus and/or oral prasugrel administration). Blood samples that were anticoagulated with 0.129 mol/l sodium citrate were collected for platelet reactivity. Platelet-rich plasma, obtained by centrifuging whole blood for 10 min at 70 g, was stimulated with 5 and 20 μmol/l ADP and 5 and 15 μmol/l thrombin receptor agonist peptide (TRAP) (Alfa Wasserman, Bologna, Italy), and aggregation was assessed using an AggRAM Advanced Modular System light transmittance aggregometer (Helena Laboratories, Beaumont, Texas). 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). PA (according to Born’s method) was evaluated considering the maximal percentage of PA in response to stimulus (Aggmax). Inhibition of PA (IPA) was defined as the percentage decrease in aggregation values (Aggmax) obtained at baseline and after treatment: (IPA Tbaseline — IPA Tafter drug)/IPA Tbaseline.

**Study endpoints and statistical analysis.** The primary endpoint was the IPA at light transmission aggregometry, stimulated with 20 μmol/l ADP 30 min after start of the treatment on a superiority basis. Key secondary endpoints in all recruited patients included IPA after both ADP and TRAP stimuli at any measured time point. The primary hypothesis of the study is that the IPA after 20 μmol/l ADP at 30 min will be superior in the tirofiban arm, analyzed as an aggregate, versus the prasugrel-alone group.

The sample size of 100 patients was based on an anticipated %IPA of 90% in the tirofiban group versus 80% in the prasugrel arm, with a sigma of 0.15, an estimated power of 90% at a 2-sided alpha level of 0.05. Continuous variables are shown as mean ± SD and were compared by using the Student unpaired t test. Categorical variables are presented as counts and percentages and

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Figure 1. Patient Flow and Study Design

(A) The number of patients screened and finally recruited in each study arm. (B) Shows the study design and sampling schedule.
compared with the Fisher exact test. The kinetics of platelet inhibition and possible differences between the 2 treatments in the whole model or at specific time points were studied by using a linear mixed model with linear contrast, adjusted for the value of baseline IPA. The model selection was performed using the Akaike Information Criterion, and we assumed treatments as a fixed effect and the intercept as a random one. To reduce the type I error probability, the p values were adjusted according to Holm’s step-down procedure (13). To define whether significant interindividual variability was present in response to antiplatelet treatment, the coefficient of variability was used (coefficient of variability = SD/mean). All analyses, carried out based on the intention-to-treat principle, were performed using Stata, version 9.2 (Stata Corp., College Station, Texas).

**Results**

**Baseline and procedural characteristics.** Patients were recruited from April 2010 to June 2011. The 2 main study groups (i.e., the prasugrel monotherapy group and the tirofiban arm) were well matched for all baseline and angiographic characteristics (Table 1). Patients were predominantly male, roughly 20% had diabetes, with an average ejection fraction at transthoracic echocardiogram below 50% and a relatively stable hemodynamic profile.

No patient received treatment with an oral P2Y12 receptor blocker before the index event, whereas overall, 12 (12%) patients were regularly taking aspirin before hospital admission. The procedural success was achieved in all but 1 in each group in whom less than Thrombolysis In Myocardial Infarction flow grade 3 persisted despite intervention. Clinical outcomes at 30 days, both in terms of ischemic and bleeding endpoints, are shown in Table 2.

**Platelet inhibition during and after PCI.** Figure 2A shows the study primary endpoint result. At 30 min, patients in the prasugrel group showed an IPA to 20 μmol/l ADP that was significantly lower than the value observed in overall tirofiban-treated patients (36 ± 35 vs. 87 ± 31, p < 0.001). Similarly, the proportion of patients showing 80% or more IPA to 20 μmol/l ADP was 20% in the prasugrel group versus 87% in the tirofiban arm (p < 0.001).

### Table 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Prasugrel 60 mg (n = 52)</th>
<th>All Patients (n = 48)</th>
<th>And Prasugrel 60 mg (n = 16)</th>
<th>And Clopidogrel 600 mg (n = 14)</th>
<th>And 2-h Infusion (n = 18)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>68 ± 11</td>
<td>68 ± 12</td>
<td>66 ± 11</td>
<td>67 ± 10</td>
<td>70 ± 12</td>
<td>0.89</td>
</tr>
<tr>
<td>Male</td>
<td>37 (71)</td>
<td>32 (67)</td>
<td>11 (69)</td>
<td>11 (78)</td>
<td>10 (63)</td>
<td>0.68</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>26 ± 4</td>
<td>27 ± 4</td>
<td>27 ± 5</td>
<td>26 ± 4</td>
<td>28 ± 4</td>
<td>0.61</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 (21)</td>
<td>9 (19)</td>
<td>3 (19)</td>
<td>3 (21)</td>
<td>3 (19)</td>
<td>0.56</td>
</tr>
<tr>
<td>Non-insulin-dependent</td>
<td>11 (21)</td>
<td>8 (17)</td>
<td>3 (19)</td>
<td>2 (14)</td>
<td>3 (19)</td>
<td>0.49</td>
</tr>
<tr>
<td>Insulin-dependent</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (7)</td>
<td>0 (0)</td>
<td>0.79</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33 (63)</td>
<td>30 (62)</td>
<td>10 (63)</td>
<td>11 (79)</td>
<td>9 (56)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>25 (48)</td>
<td>24 (50)</td>
<td>8 (50)</td>
<td>9 (64)</td>
<td>7 (44)</td>
<td>0.29</td>
</tr>
<tr>
<td>Current smokers</td>
<td>31 (60)</td>
<td>28 (58)</td>
<td>10 (63)</td>
<td>10 (71)</td>
<td>8 (50)</td>
<td>0.30</td>
</tr>
<tr>
<td>Creatinine, mg/dl</td>
<td>1.2 ± 0.41</td>
<td>1.3 ± 0.43</td>
<td>1.2 ± 0.33</td>
<td>1.3 ± 0.47</td>
<td>1.2 ± 0.44</td>
<td>0.69</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>48 ± 10</td>
<td>47 ± 12</td>
<td>47 ± 11</td>
<td>48 ± 12</td>
<td>49 ± 13</td>
<td>0.68</td>
</tr>
</tbody>
</table>

| Medical history     |                         |                      |                             |                            |                        |         |
| PCI                 | 4 (8)                   | 3 (6)                | 2 (12)                      | 1 (7)                      | 0 (0)                  | 0.36    |
| Myocardial infarction | 7 (13)                | 9 (19)               | 4 (25)                      | 2 (14)                     | 3 (19)                 | 0.47    |
| TIA/stroke          | 0 (0)                   | 0 (0)                | 0 (0)                       | 0 (0)                      | 0 (0)                  | >0.99   |
| Heart failure       | 0 (0)                   | 0 (0)                | 0 (0)                       | 0 (0)                      | 0 (0)                  | >0.99   |
| Severe COPD*        | 4 (8)                   | 3 (6)                | 1 (6)                       | 1 (7)                      | 1 (6)                  | 0.28    |
| Peripheral arterial disease | 11 (21)           | 8 (17)               | 4 (25)                      | 1 (7)                      | 3 (19)                 | 0.78    |
| Carotid artery disease | 2 (4)                | 1 (2)                | 1 (6)                       | 0 (0)                      | 0 (0)                  | 0.45    |

| Clinical presentation |                         |                      |                             |                            |                        |         |
| Killip class >1      | 2 (4)                   | 3 (6)                | 1 (6)                       | 1 (7)                      | 1 (6)                  | 0.78    |
| Systolic blood pressure | 118 ± 23              | 115 ± 28             | 114 ± 26                    | 117 ± 19                   | 116 ± 21              | 0.87    |
| Heart rate, beats/min | 79 ± 22                | 81 ± 24              | 76 ± 18                     | 77 ± 21                    | 82 ± 17               | 0.45    |
| Door to balloon time, min | 69 ± 34               | 62 ± 31              | 67 ± 22                     | 73 ± 34                    | 58 ± 28               | 0.79    |

Values are mean ± SD or n (%). The p values refer to the comparison of prasugrel-alone group versus the tirofiban group analyzed as an aggregate. *Resulting in functional disability, hospitalization, requiring chronic bronchodilator therapy, or forced expiratory volume in 1 s <75% of predicted.

COPD = chronic obstructive pulmonary disease; LV = left ventricular; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.
The overall kinetics of 20 μmol/l ADP–induced platelet inhibition in the 2 main study groups confirms that the IPA remains consistently higher in the tirofiban group, which was analyzed as an aggregate, as compared with the prasugrel-alone arm, through the first 2 h of treatment (p < 0.001 for the trend). It then does not differ at 6 h due to an increase in PA inhibition by prasugrel and a slight IPA decline in the tirofiban group, whereas at the 18–24 h time point, due to a further IPA decline in the tirofiban group, the degree of platelet inhibition was in turn significantly higher in the prasugrel-only group (Fig. 2B). Interestingly, patients treated with both tirofiban and prasugrel, either concomitantly or at the time of infusion discontinuation, display a similar IPA at the 18–24 h time point as compared with previous time points in all tirofiban groups apart from the 18–24 h time point, within 30 min after tirofiban bolus–only administration and divided into the tirofiban-alone group if no PA inhibition, IPA obtained at various time points never reached statistical significance.

Consistent overall kinetics of platelet inhibition was observed after 5 μmol/l TRAP (Fig. 3).

Table 2. Clinical Outcomes at 30 Days

<table>
<thead>
<tr>
<th>event</th>
<th>Prasugrel 60 mg (n = 52)</th>
<th>All Patients (n = 48)</th>
<th>And Prasugrel 60 mg (n = 16)</th>
<th>And Clopidogrel 600 mg (n = 14)</th>
<th>And 2-h Infusion (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>4 (7.7)</td>
<td>4 (7.7)</td>
<td>2 (12.5)</td>
<td>2 (14.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Infarction</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Urgent TVR</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Death, reinfarction, or urgent TVR</td>
<td>5 (9.6)</td>
<td>4 (7.7)</td>
<td>2 (12.5)</td>
<td>2 (14.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Definite stent thrombosis</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Definite or probable stent thrombosis</td>
<td>2 (3.8)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TIMI major bleed</td>
<td>2 (3.8)*</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TIMI minor bleed</td>
<td>0 (0)</td>
<td>1 (2.1)</td>
<td>1 (6.2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TIMI minimal bleed</td>
<td>0 (0)</td>
<td>1 (2.1)</td>
<td>0 (0)</td>
<td>1 (7.1)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are n (%). *Given by an intracranial bleeding and 1 gastrointestinal bleed that required 2 U of red blood cell transfusion.

TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization.

The overall kinetics of 15 μmol/l TRAP-induced platelet inhibition in the 2 main study groups shows that the IPA was constantly higher in the tirofiban group, when analyzed as an aggregate, as compared with the prasugrel-alone arm, through the first 6 h of treatment (p < 0.001 for the trend), whereas it significantly dropped in the tirofiban group at 18 to 24 h, and at this time point, it did not differ anymore as compared with the prasugrel-alone–treated patients. In patients receiving prasugrel-alone therapy, the IPA did not change over time (Fig. 4A). The effect of tirofiban, either administered as a bolus-only regimen or followed by 2-h infusion on top of prasugrel as compared with prasugrel alone is shown in Figure 4B.

As previously noted for ADP–induced IPA, patients receiving tirofiban tended to have a higher degree of TRAP-induced platelet inhibition if concomitantly treated with prasugrel as compared with those with clopidogrel throughout the first 6 h (Fig. 4C) even if the difference in IPA at various time points never reached statistical significance. At 18 to 24 h, IPA dropped significantly as compared with previous time points in all tirofiban groups apart from those receiving the tirofiban bolus and 2-h drug infusion followed by prasugrel administration (Fig. 4C).

Consistent overall kinetics of platelet inhibition was observed after 5 μmol/l TRAP (Fig. 4D).

Effect of simultaneous administration of tirofiban and prasugrel versus either treatment alone. To explore the additive value of a near-total inhibition of upstream platelet activation and downstream PA as compared with either strategy alone on the degree of ADP- and TRAP-induced ex vivo platelet inhibition, IPA obtained at various time points within 30 min after tirofiban bolus–only administration and within 2 h after bolus and 2-h infusion was analyzed as an aggregate and divided into the tirofiban-alone group if no P2Y12 oral receptor blocker or clopidogrel was administered versus tirofiban plus prasugrel if prasugrel was administered concomitantly. IPA obtained at various time points after prasugrel-alone therapy was also cumulatively analyzed and contrasted with the 2 tirofiban groups. As shown in Figure 5A, cumulative IPA obtained after 20 μmol/l ADP
or 15 μmol/l TRAP was significantly higher after concomitant tirofiban and prasugrel (96.1 ± 3.1% [95% confidence interval (CI): 95.0% to 97.2%]; 93.0 ± 7.1% [95% CI: 91.1% to 94.2%], respectively) administration than after prasugrel (50.2 ± 34.0% [95% CI: 46.1% to 54.2%]; 31.2 ± 29.1% [95% CI: 27.0% to 34.2%], respectively) or tirofiban alone (82.4 ± 33.1% [95% CI: 74.1% to 90.4%]; 76.1 ± 35.0% [95% CI: 67.0% to 84.1%], respectively). Interestingly, combined upstream and downstream blockade of both platelet activation and aggregation led to a very consistent level of platelet inhibition after both ADP or TRAP stimuli, with coefficients of variability after tirofiban and prasugrel being at least 10 times lower (0.03 and 0.07, respectively) than those observed after tirofiban (0.40 and 0.46, respectively) or prasugrel alone (0.68 and 1.07, respectively) therapy (Fig. 5B).

Discussion

Our study is the first to our knowledge to assess the differential degree of platelet inhibition obtained after either ADP and TRAP stimulation following prasugrel therapy, tirofiban therapy administered as bolus only or bolus followed by 2-h infusion, or both treatments given simultaneously. Importantly, at variance with previous studies assessing the pharmacokinetics and pharmacodynamics of prasugrel (6,14,15), we focused on STEMI patients undergoing primary PCI.

The results of our study can be summarized as follows:

1. The degree of early platelet inhibition achieved after a 60-mg loading dose of prasugrel is suboptimal at least for the first 2 h in STEMI patients undergoing primary PCI.
2. The administration of tirofiban, given as a high-dose bolus only, leads to a high degree of platelet inhibition for at least 1 h on top of either a clopidogrel or prasugrel loading dose. A 2-h post-bolus tirofiban infusion achieves a sustained degree of platelet inhibition for up to 6 h post-bolus.
3. The administration of high-dose bolus tirofiban and concomitant prasugrel bridges the first hours in which...
prasugrel alone fails to provide complete platelet inhibition. Moreover, concomitant administration of tirofiban bolus only and prasugrel allows immediate, sustained, and consistent platelet inhibition throughout 24 h.

4. The capability of prasugrel to inhibit thrombin-induced platelet activation, mimicked in our study by the use of TRAP, was shown to be limited. By contrast, tirofiban, by blocking the common final pathway mediating aggregation, that is, glycoprotein IIb/IIIa receptor, is a strong TRAP-induced platelet inhibitor.

5. Simultaneous near-total inhibition of upstream platelet activation via prasugrel and downstream PA with tirofiban led to a significantly higher degree of both ADP- and TRAP-induced PA than tirofiban alone. Importantly, the blocking of glycoprotein IIb/IIIa receptor, with simultaneous potent P2Y$_{12}$ receptor inhibition, led to an extraordinary low interindividual variability in response to both ADP and TRAP platelet activation stimuli.

A number of studies have shown that prasugrel, when given at a loading dose of 60 mg in either healthy volunteers or patients with stable coronary artery disease, provides a very high and consistent level of platelet inhibition after ADP within 30 min after ingestion (6,14,15). Yet, prasugrel is currently approved for ACS patients only, in whom the degree of platelet reactivity is known to be higher and in whom, especially in STEMI patients, the pharmacokinetics of another oral P2Y$_{12}$ blocker, clopidogrel, has been shown to be unfavorable compared with stable patients (11). Our study shows for the first time that prasugrel 60 mg provides limited inhibition of ADP- or TRAP-induced PA within the first 2 h after drug administration in our patient population. Importantly, this is the time frame in which STEMI patients are expected to receive PCI. This finding carries relevant clinical and pathophysiological implications and emphasizes the importance of the intravenous route to deliver effective inhibition of platelet activity in critically ill patients, such as those presenting with STEMI.

Previous comparative or placebo-controlled studies on GPIs (16,17) or oral P2Y$_{12}$ blockers (18) have consistently shown the value of intensified platelet inhibition at the time of PCI to minimize ischemic complications. Whether and for how long nearly complete platelet inhibition after coronary stenting is truly needed is far less clear. This is the rationale for testing in our study 2 different tirofiban regimens, i.e., bolus-only administration or bolus followed by 2-h infusion, which could fully inhibit PA during the course of the procedure.

GPI given as bolus only or bolus and short post-bolus infusion immediately before PCI, by fully blocking platelet activity at the time of stenting while allowing thereafter a gradual bridging to oral P2Y$_{12}$ receptor blocker, may represent an appealing strategy to retain the well-established ischemic protection from GPIs and improve their safety profile. Our study shows that tirofiban, administered as a 25 μg/kg bolus only on top of 600-mg clopidogrel and followed by a short 2-h infusion provides near-complete ADP- or TRAP-induced platelet inhibition for at least 6 h. Interestingly, on top of 60-mg prasugrel, a tirofiban bolus–only regimen, irrespective of post-bolus infusion, achieves immediate and sustained near-total platelet inhibition throughout 24 h. The advent of potent oral P2Y$_{12}$ receptor blockers, such as prasugrel, may therefore justify from a mechanistic standpoint the use of GPI given as bolus only. In contemporary practice, on-label prolonged GPI post-bolus infusion of 12 to 24 h and up to 48 h may end up increasing the risk of adverse events, including bleeding and thrombocytopenia without providing additional ischemic benefit. Studies further investigating this topic are warranted and are under way.

A growing recognition of the various pathways driving platelet activity has given rise to the development of multiple agents able to inhibit PA. Currently, cyclooxygenase (COX)-1–mediated and ADP-mediated platelet activation are the only upstream pathways that can be modulated via specific antiplatelet therapy.

Thrombin is the most potent known platelet activator, which may easily displace platelet inhibition carried out via alternative mechanisms, such as COX-1 or ADP P2Y$_{12}$ inhibition (19).

Although protease-activated receptor-1 oral antagonists are being developed in phase II and phase III studies (20), the administration of a GPI, by acting downstream on the final common pathway for aggregation, is the only currently available antiplatelet agent able to modulate thrombin-
induced platelet activation. Indeed, our study confirms that even a potent P2Y\textsubscript{12} receptor inhibitor, such as prasugrel, when given alone, has limited activity on this pathway.

An intriguing observation we made is that the simultaneous inhibition of the P2Y\textsubscript{12} receptor via prasugrel and the glycoprotein IIb/IIIa receptor via tirofiban provides complementary benefit in terms of both magnitude and consistency of ADP- or TRAP-induced PA. This finding is new and deserves attention. In the Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets (CLEAR-PLATELETS) study (21), no discernible effect of clopidogrel at either a 300- or 600-mg loading dose was observed in patients receiving an Food and Drug Administration–approved eptifibatide regimen 3 or 8 h after drug infusion. This may be explained by taking into account the different degree of platelet inhibition exerted by clopidogrel, a relatively weak P2Y\textsubscript{12} receptor blocker, and by a properly dosed GPI in this study, which almost completely suppresses PA.

Contrary to clopidogrel, prasugrel is converted to an active metabolite in a much more efficient manner and provides a much more potent P2Y\textsubscript{12} receptor inhibition. Despite tirofiban being much quicker and potent, as clearly shown in our head-to-head comparison, prasugrel 60 mg was shown to slightly, but significantly, improve the performance in terms of inhibition of ADP-induced platelet activation as compared with tirofiban bolus or tirofiban bolus and post-bolus infusion. Of particular interest is the observation that the addition of prasugrel to tirofiban led to an impressively low interindividual variability as captured by the coefficient of variability of the degree of platelet inhibition. This may be due to the synergistic effect of near-total blocking of platelet activating pathways both upstream via a potent oral P2Y\textsubscript{12} inhibitor, such as prasugrel, and downstream, via tirofiban, a potent glycoprotein IIb/IIIa inhibitor. This “2-hit hypothesis” is new and potentially of great relevance because variability in response to both P2Y\textsubscript{12} and glyco-
protein IIb/IIIa receptors has been previously documented to be associated with differential clinical outcomes (22,23). The hypothesis that local infusion of abciximab-bolus only will decrease infarct size compared with no treatment on top of P2Y12 inhibition is also being tested in the INFUSE–Anterior Myocardial Infarction (AMI) study (NCT00976521).

Study limitations. Our study was not powered to assess the efficacy or safety profile of combining prasugrel with tirofiban with respect to either drug alone. Additional studies are also warranted to investigate the role of concomitant bivalirudin in both ADP- and TRAP-induced PA after prasugrel or clopidogrel administration. Due to the very tight schedule for blood sampling in our study, only the patients who presented during on-hours were recruited.

Conclusions

Our study shows for the first time that prasugrel given as a loading dose of 60 mg leads to a suboptimal degree of platelet inhibition after both ADP- and TRAP-induced platelet activation for at least 2 h after drug administration in STEMI patients. Tirofiban, given as bolus only or bolus followed by 2-h infusion either on top of clopidogrel or prasugrel, leads to a significantly higher degree of platelet inhibition as compared with prasugrel alone. The concomitant administration of a GPI bolus-only regimen and prasugrel is a promising treatment strategy, which allows immediate and sustained inhibition of platelet activation and is associated with a remarkably low interindividual variability in responsiveness to both ADP and TRAP stimuli.

This treatment combination warrants further testing in prospective randomized clinical trials.

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