JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 9, NO. 16, 2016

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER
http://dx.doi.org/10.1016/j.jcin.2016.05.031

# Phosphate- or Citrate-Buffered Tirofiban Versus Unfractionated Heparin and its Impact on Thrombocytopenia and Clinical Outcomes in Patients With Acute Coronary Syndrome

## A Post Hoc Analysis From the PRISM Trial

Marianna Adamo, MD,[a,b] Sara Ariotti, MD,[a,c] Francesco Costa, MD,[a,d] Salvatore Curello, MD,[b] Aris Moschovitis, MD,[c] Ton de Vries, MA,[e] Harvey D. White, DSc,[f] Stephan Windecker, MD, PhD,[c] Marco Valgimigli, MD, PhD[a,c]

## ABSTRACT

**OBJECTIVES** The aim of this study was to investigate whether the 2 tirofiban formulations tested in the early and late phases of the PRISM (Platelet Receptor Inhibitor in Ischemic Syndrome Management) trial might differ with respect to risk for thrombocytopenia and clinical outcomes compared with unfractionated heparin (UFH).

**BACKGROUND** Citrate-buffered tirofiban is currently marketed as brand-name drug. However, tirofiban has recently been promoted in some countries as a generic drug with different formulations, such as phosphate-buffered product.

**METHODS** In the PRISM trial 3,232 patients were randomly assigned to receive tirofiban or UFH. In the early phase, 879 patients were allocated to phosphate-buffered tirofiban and 874 patients to UFH group. After a protocol amendment due to a study drug instability report, citrate-buffered tirofiban replaced the phosphate-buffered formulation. Therefore, in the late phase, 737 and 742 patients were treated with citrate-buffered tirofiban and UFH, respectively.

**RESULTS** The relative risk for thrombocytopenia (nadir $<$90,000/mm$^3$ or $<$100,000/mm$^3$) was increased in patients treated with phosphate-buffered tirofiban in the early phase (odds ratio [OR]: 3.51; 95% confidence interval [CI]: 1.15 to 10.73; p = 0.027; and OR: 2.83; 95% CI: 1.11 to 7.22; p = 0.029, respectively) but not in patients treated with citrate-buffered tirofiban in the late phase (OR: 1.01; 95% CI: 0.20 to 5.05; p = 0.987; and OR: 0.99; 95% CI: 0.26 to 3.45; p = 0.991, respectively). Using a combined definition of thrombocytopenia (nadir $<$150,000/mm$^3$ or a decrease $\geq$50%), the randomization period significantly modified the effect of the treatment (tirofiban vs. UFH) on platelet decrease (p for interaction = 0.024). Thrombocytopenia was associated with a 5- to 10-fold increased risk for TIMI (Thrombolysis In Myocardial Infarction) bleeding and a 2-fold increased risk for net adverse cardiovascular events.

**CONCLUSIONS** Phosphate-buffered tirofiban, currently marketed as a generic drug, is associated with a higher rate of thrombocytopenia with a potentially increased risk for adverse clinical outcomes compared with citrate-buffered tirofiban. (J Am Coll Cardiol Intv 2016;9:1667–76) © 2016 by the American College of Cardiology Foundation.

From the [a]Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands; [b]Catheterization Laboratory, Spedali Civili, Brescia, Italy; [c]Department of Cardiology, Bern University Hospital, Bern, Switzerland; [d]Department of Clinical and Experimental Medicine, Policlinico "G. Martino," Messina, Italy; [e]Cardialysis BV, Rotterdam, the Netherlands; and the [f]Green Lane Cardiovascular Service, Auckland City Hospital, Auckland, New Zealand. The authors have reported they have no relationships relevant to the contents of this paper to disclose.

Manuscript received January 28, 2016; revised manuscript received May 9, 2016, accepted May 18, 2016.

**ABBREVIATIONS AND ACRONYMS**

**ACS** = acute coronary syndrome

**CI** = confidence interval

**GPI** = glycoprotein IIb/IIIa inhibitor

**HR** = hazard ratio

**MI** = myocardial infarction

**NACE** = net adverse cardiovascular event

**OR** = odds ratio

**RGD** = arginine-glycine-aspartic acid

**UFH** = unfractionated heparin

Patients with acute coronary syndromes (ACS) are frequently treated with intravenous glycoprotein IIb/IIIa inhibitors (GPI) (1,2). Among these agents, tirofiban was first approved by the U.S. Food and Drug Administration in 1998. Since initial approval, the dose has been revised, and tirofiban given as a high-dose bolus is currently the most frequently used GPI (3,4).

PRISM (Platelet Receptor Inhibitor in Ischemic Syndrome Management) was the first randomized clinical study investigating the safety and efficacy of tirofiban, and it demonstrated a clinical benefit of this GPI compared with unfractionated heparin (UFH) with respect to acute ischemic events and 30-day mortality in the absence of an increased risk for bleeding. At variance with all other placebo-controlled studies, PRISM reported a significant increase in the rate of thrombocytopenia in the tirofiban compared with UFH group (5).

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Two different formulations of tirofiban were used in the PRISM trial in a sequential manner. After a protocol amendment due to a drug instability report, the phosphate-buffered product, which was used as the study drug during the early phase of the study, was replaced by the citrate-buffered formulation, which is currently marketed as a brand-name drug (Aggrastat; Correvio Ltd. in the United Kingdom and Medicure Pharma in the United States) (6). However, tirofiban has been recently promoted as a generic drug in several European countries with different formulations, such as phosphate-buffered tirofiban.

In this post hoc analysis of the PRISM trial, we sought to investigate whether the 2 tirofiban formulations used during the early and late phases of the study and currently marketed as generic and brand-name drugs might differ with respect to rates of thrombocytopenia and clinical outcomes compared with UFH.

## METHODS

The design and the main findings of the PRISM trial were previously reported (5).

Briefly, PRISM was a randomized, controlled, multicenter, double-blind trial including patients with non-ST-segment elevation ACS. Patients were randomly assigned to receive tirofiban (bolus of 0.6 μg/kg/min over 30 min followed by 0.15 μg/kg/min infusion for 48 h) or UFH (bolus of 5,000 IU followed by infusion of 1,000 IU/h for 48 h, adjusted for activated partial thromboplastin time at 6 and 24 h).

During the early recruitment phase of the trial, tirofiban was administered as a phosphate-buffered product that ranged in concentration from 0.17 to 0.5 mg/ml; sodium chloride was used to render the product iso-osmotic. During the late recruitment phase, this composition was abandoned and substituted by a citrate-buffered product (10 mmol/l) containing sodium chloride. The change in composition was deemed necessary because of instability report of the phosphate-buffered composition and the finding of precipitates in vials stored for 24 months or more (6). Sodium porcine heparin was provided as 1,000 U/ml (10-ml fill) or as 10,000 U/ml (5-ml fill) without differences through the early and late recruitment phases.

**STUDY ENDPOINTS.** To maintain the randomization scheme, we primarily aimed to compare outcomes in patients treated with phosphate-buffered tirofiban versus UFH during the early phase and those treated with citrate-buffered tirofiban versus UFH during the late phase. As sensitivity analyses, we also compared patients receiving the 2 tirofiban formulations throughout the 2 different time periods.

Thrombocytopenia was defined as platelet nadir $<90{,}000/mm^3$ (used in the PRISM trial [5]), as platelet count $<100{,}000/mm^3$ (the most frequent cutoff used in previous studies [7–9]), and as a combination of nadir value $<150{,}000/mm^3$ and decrease of platelet count $\geq 50\%$ (used in a previous large registry [10]). Severe thrombocytopenia was defined as platelet count $<50{,}000/mm^3$.

We also investigated the 30-day ischemic endpoints reported in the PRISM trial (2): death, myocardial infarction (MI), refractory ischemia; readmission for unstable angina, a composite of major adverse cardiovascular events including all single endpoints previously mentioned and a composite of death and MI.

Bleeding events were defined according to the TIMI (Thrombolysis In Myocardial Infarction) classification (11).

Finally, a composite endpoint of net adverse cardiovascular events (NACEs) including major adverse cardiovascular events and major or minor TIMI bleeding was assessed.

**STATISTICAL ANALYSIS.** Continuous variables were expressed as mean ± SD and were compared using the Student *t* test. Categorical variables were expressed as counts and percentages and were compared using the chi-square or Fisher exact test, as appropriate.

The proportionality assumptions were checked by visual estimation after plotting the log cumulative hazard versus (log) time at follow-up after the index