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Effect of Early, Pre-Hospital Initiation of High Bolus Dose Tirofiban in Patients With ST-Segment Elevation Myocardial Infarction on Short- and Long-Term Clinical Outcome

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Objectives The purpose of this trial was to study the effect of a high bolus dose (HBD) of tirofiban on clinical outcome in patients undergoing primary percutaneous coronary intervention for ST-segment elevation myocardial infarction (STEMI).

Background The On-TIME 2 (Ongoing Tirofiban In Myocardial infarction Evaluation 2) placebo-controlled, double-blind, randomized trial showed that early administration of HBD tirofiban in the ambulance improves ST-segment resolution in patients with STEMI undergoing primary percutaneous coronary intervention. The effect of early tirofiban treatment on clinical outcome is unclear.

Methods The On-TIME 2 trial consisted of 2 phases: an open-label phase, followed by a double-blind, placebo-controlled phase. STEMI patients were randomized to either HBD tirofiban or no tirofiban (phase 1) or placebo (phase 2) in addition to aspirin, heparin, and high-dose clopidogrel. The protocol pre-specified a pooled analysis of the 2 study phases to assess the incidence of major adverse cardiac events at the 30-day follow-up and on total mortality at the 1-year follow-up.

Results During a 3-year period, 1,398 patients were randomized, 414 in phase 1 and 984 in phase 2. Major adverse cardiac events at 30 days were significantly reduced (5.8% vs. 8.6%, $p = 0.043$). There was a strong trend toward a decrease in mortality (2.2% vs. 4.1%, $p = 0.051$) in patients who were randomized to tirofiban pre-treatment, which was maintained during the 1-year follow-up (3.7% vs. 5.8%, $p = 0.08$). No clinically relevant difference in bleeding was observed.

Conclusions Early, pre-hospital initiation of HBD tirofiban, in addition to high-dose clopidogrel, improves the clinical outcome after primary percutaneous coronary intervention in patients with STEMI. (Ongoing 2b/3a inhibition In Myocardial infarction Evaluation; ISRCTN06195297) (J Am Coll Cardiol 2010;55:2446–55) © 2010 by the American College of Cardiology Foundation

Early and complete restoration of blood flow in the infarct-related vessel in patients with ST-segment elevation myocardial infarction (STEMI) is of utmost importance to improve the chance of survival and the clinical outcome (1–3). Primary percutaneous coronary intervention (pPCI) has been shown to be the most effective treatment modality for restoring

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the blood flow in the infarct-related vessel (4,5). Transporting patients to an intervention center, however, inevitably leads to a delay in initiation of the pPCI and thus prolongs ischemic time. The early initiation of antithrombotic treatment for STEMI patients before pPCI potentially opens the occluded vessel during transportation and reduces periprocedural thrombotic complications (6). Glycoprotein (GP) IIb/IIIa receptor blockers are very effective inhibitors of platelet aggregation, even when administered in addition to aspirin and clopidogrel (7) and have been shown to reduce thrombotic complications in patients undergoing percutaneous coronary intervention (PCI) (8). In our randomized, double-blind, placebo-controlled On-TIME 2 (Ongoing Tirofiban In Myocardial

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infarction Evaluation 2) trial, we recently demonstrated that the GP IIb/IIIa receptor blocker tirofiban, when given in the ambulance, resulted in an improvement in ST-segment resolution as a marker for myocardial perfusion in patients with STEMI undergoing pPCI (9). However, this trial did not have sufficient power to study the effect of a high bolus dose (HBD) of tirofiban on clinical outcome. In this article, we present a pre-specified pooled analysis of the placebo-controlled study phase and the open-label study phase to investigate the effect of early administration of HBD tirofiban on clinical outcome. This larger sample size also enabled us to study subgroups of patients who would most likely benefit from early administration of HBD tirofiban.

Methods

The On-TIME 2 trial was a multicenter, prospective, randomized clinical trial. The study consisted of 2 phases: a randomized, open-label phase (phase 1) and a placebo-controlled, randomized, double-blind phase (phase 2). The rationale and design of the study were described previously (10). In brief, the study population consisted of patients with STEMI who were candidates for pPCI treatment. Eligible patients were men and women 21 to 85 years of age with symptoms of acute myocardial infarction (MI) for >30 min but <24 h, and an ST-segment elevation of >1 mV in 2 adjacent electrocardiogram leads. Exclusion criteria were known severe renal dysfunction, therapy-resistant cardiogenic shock, persistent severe hypertension, and an increased risk of bleeding. Also excluded were patients with a left bundle branch block and patients with a life expectancy of <1 year.

Written informed consent was obtained by an intensive care nurse in the ambulance or, in a minority of the patients, by a physician in the referral center. The study protocol was approved by all local ethics committees involved.

Patients were randomly assigned to pre-hospital treatment with tirofiban (25-μg/kg bolus and 0.15-μg/kg/min maintenance infusion) or no tirofiban (phase 1), or placebo (phase 2). Each participating ambulance or referral center was supplied with sealed study kits in blocks of 4, containing either open-label tirofiban or saline solution vials (phase 1) or blinded study medication (phase 2). The study flowchart is presented in Figure 1. In the ambulance or referral center, all patients also received a bolus of unfractionated heparin (5,000 IU) intravenously, together with aspirin 500 mg (Aspegic) intravenously and an oral 600-mg loading dose of clopidogrel. Before pPCI, an additional 2,500 IE unfractionated heparin was only administered if the activated clotting time was <200 s.

Coronary angiography and PCI were performed according to each institution's guidelines and standards. During or after pPCI, bail-out tirofiban could be administered for the following indications: decrement in Thrombolysis In Myocardial Infarction (TIMI) flow grade (TIMI flow grades of 0 to 2 or slow reflow), dissection with decreased flow, distal embolization, side branch closure, abrupt closure of the culprit vessel, clinical instability, and prolonged ischemia. Bail-out tirofiban was administered in a HBD (25-μg/kg bolus). In the double-blind phase of the trial, blinded bail-out vials were included in the medication box to maintain blinding of the initial treatment assignment to avoid double-dosing. When a bailout vial was administered, the study infusion was replaced by open-label tirofiban. In the open-label phase, the doses of bail-out tirofiban and the indications for administration were similar to those in the double-blind phase.

The key primary end point of this pooled analysis was the incidence of major adverse cardiac events (MACE), as defined by the composite of death, recurrent MI, or urgent target vessel revascularization at the 30-day follow-up. The secondary end point was total mortality at the 1-year follow-up. A blinded independent Clinical Endpoint Committee adjudicated all clinical end points. Death was defined as all-cause mortality. Recurrent MI was defined as a new increase of creatine kinase, myocardial bound ≥3 times the upper limit of normal present in 2 separate blood samples and accompanied by chest pain and/or changes on the electrocardiogram. Early recurrent MI was defined as a decrease in creatine kinase, myocardial bound of at least 50% of the upper limit of normal from a previous peak concentration to a valley, followed by a new increase with a value above the sum of the preceding valley and 3 times the upper limit of normal. Urgent target vessel revascularization during the hospitalization period was defined as a new episode of ischemic signs or symptoms at rest, with docu-

Abbreviations and Acronyms

CI = confidence interval
GP = glycoprotein
HBD = high bolus dose
IQR = interquartile range
MACE = major adverse cardiac events
MI = myocardial infarction
OR = odds ratio
PCI = percutaneous coronary intervention
pPCI = primary percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction