

Role of tirofiban with dual antiplatelet therapy in patients with STEMI undergoing primary PCI

To the Editor,

I read with great interest the manuscript written by Kaymaz et al. (1) entitled "The effects of tirofiban infusion on clinical and angiographic outcomes of patients with STEMI undergoing primary PCI" published in the *Anatolian Journal of Cardiology* on December 25, 2014 (Epub ahead of print). The article showed that tirofiban in addition to aspirin, high-dose clopidogrel, and unfractionated heparin administered prior to primary PCI significantly improves myocardial reperfusion, ST segment resolution, in-hospital mortality, and total mortality rates in patients with STEMI without an increased risk of major bleeding. Several trials performed before the routine use of dual antiplatelet therapy (DAPT), mostly using abciximab, documented clinical benefits of GP IIb/IIIa inhibitors as adjuncts to primary PCI performed with UFH (2). The FINESSE trial found that the routine upstream use of abciximab before primary PCI did not yield clinical benefit but led to an increased risk of bleeding compared with routine use in the catheterization laboratory (3). The FINESSE trial showed that for patients progressing to primary PCI, there does not appear to be any appreciable benefit, but only harm, in starting GP IIb/IIIa inhibitors in the pre-hospital setting. Similarly, Jeremias et al. (4) showed that the routine use of abciximab in patients with STEMI treated with primary stenting may reduce short-term rates of death or reinfarction in patients not administered pre-procedural thienopyridine therapy, but the use of abciximab does not appear to be beneficial in those who receive pre-procedural thienopyridines in a meta-analysis of five randomized trials (4). According to these studies, the 2012 ESC guideline defined that there is no definitive answer regarding the current role of the routine use of GP IIb/IIIa inhibitors in primary PCI in the era of potent DAPT, particularly when prasugrel or ticagrelor is used (5). On the other hand, recent studies (6, 7) of tirofiban with DAPT in STEMI support the findings of Kaymaz et al. (1) Tirofiban administered with primary PCI following the administration of 600 mg clopidogrel improved the primary efficacy outcome at 30-day and 1-year follow-up without an increase in major bleeding. Zhu et al. (7) demonstrated that the upstream use of tirofiban is significantly associated with an increased incidence of spontaneous reperfusion and a decreased incidence of MACE at 30-day as well as 90-day follow-up in patients treated with primary PCI for STEMI. I appreciate the authors for highlighting the use of tirofiban with DAPT in STEMI patients. There are some issues that need to be clarified to obtain more data from the study. The intracoronary use of GP IIb/IIIa inhibitors has been tested in several small studies, and it is associated with some benefits (7). Did you apply intracoronary tirofiban in the peri-Tiro group in any patients? Was thrombus aspiration performed with a manual aspiration catheter in any study patient? If not, why? Why did you prefer "pain-to-balloon time" instead of "first medical contact (FMC) to balloon time"? Can you provide additional information about the effect of tirofiban on the no-reflow phenomenon in your study? Did patients with a high thrombus burden or no-reflow undergo repeat angiography after tirofiban infusion? Was the tirofiban infusion dose reduced in patients with renal insufficiency? Finally, do patients visiting non-PCI hospitals within 4 h of symptom onset and requiring transfer have a survival benefit from the

use of abciximab in post-hoc subset analysis of the FINESSE trial (8)? Is there a correlation between the benefits of tirofiban and pain-to-balloon time in your study?

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DOI:10.5152/AnatolJCardiol.2015.6654



Author's Reply

To the Editor,

I read with great interest the letter related to our manuscript entitled "The effects of tirofiban infusion on clinical and angiographic outcomes of patients with STEMI undergoing primary PCI" published

in the Anatolian Journal of Cardiology on December 25, 2014 (Epub ahead of print) by Kaymaz et al. (1). Here, I am going to answer of the abovementioned questions.

As summarized in this letter, our article showed that tirofiban treatment in addition to aspirin, high-dose clopidogrel, and unfractionated heparin prior to primary PCI significantly improves myocardial reperfusion, ST segment resolution, in-hospital sudden cardiac death, and in-hospital all-cause mortality rates in patients with STEMI without an increased risk of major bleeding. The major limitation of our study was the absence of a prospective randomized clinical trial design because of the critical difficulties in the reimbursement of the treatment cost in our country. Despite this important limitation, comparison of the baseline characteristics of the treatment groups permitted us to assess the efficacy and safety issues of tirofiban treatment among the groups. Despite the higher TIMI risk score in the pre-PCI or upstream tirofiban group than those in the other three groups, the benefits in TIMI flow grade, corrected TIMI frame count, ST segment resolution, in-hospital sudden cardiac death, and in-hospital all-cause mortality were also significantly higher in the upstream tirofiban subset than those in the other groups. Our results represent the potential benefit of tirofiban added to aspirin, high-dose clopidogrel, and unfractionated heparin treatment combinations, and should be considered to provide important data concerning the use of tirofiban treatment in the dual antiplatelet therapy (DAPT) era. However, the results of our study are limited to DAPT including aspirin and high-dose clopidogrel, but cannot be generalized to combinations with the novel antiplatelet agents prasugrel and ticagrelor (2). Our rationale for bridging treatment with tirofiban in this setting was targeted to minimize the risk of intracoronary rethrombosis within the first hours of primary PCI, in which the level of platelet inhibition still remains sub-therapeutic because of the kinetics of clopidogrel, even with a 600-mg loading dose and well-known procoagulant state of STEMI. Currently, this risk of early rethrombosis and the need for GP IIb/IIIa inhibitors seem to be eliminated with the novel fast-acting and the more potent platelet inhibitors, prasugrel and ticagrelor.

It may not be appropriate to, compare a study based on non-randomized retrospective data with the FINESSE trial that showed no appreciable benefit, but only harm, in starting GP IIb/IIIa inhibitors in the pre-hospital setting for patients progressing to primary PCI (3). The comments of Jeremias et al. (4) were based on formal searches of electronic databases (Medline, Cochrane) from January 1990 to April 2009 and included five trials randomizing 2,937 patients (1,475 in the abciximab group and 1,462 in the placebo group). They concluded that the routine use of abciximab in patients with STEMI treated with primary PCI does not appear to be beneficial in those who receive pre-PCI thienopyridines (4). However, their comments are limited to a meta-analysis from five abciximab series and cannot be compared with the main results of our retrospective study including a total of 994 out of the 1,242 patients with STEMI in whom tirofiban was used prior to, during, or after primary PCI. Indeed, recent studies have confirmed our positive results with upstream tirofiban treatment (5, 6). The first study showed that tirofiban administered with primary PCI following 600 mg clopidogrel improved the primary efficacy outcome at 30-day and 1-year follow-up without an increase in major bleeding (5). In the other study, the upstream use of tirofiban was significantly associated with an increased incidence of spontaneous reperfusion and a decreased incidence of MACE at 30-day as well as 90-day follow-up in patients treated with primary PCI for STEMI (6).

Intracoronary tirofiban injection was the treatment of choice in all patients in the peri-PCI tirofiban group, whereas only the intravenous

route was used in the upstream or post-PCI tirofiban treatment groups. Although the median difference in pain-to-balloon time was only 25 min between the upstream and peri-PCI tirofiban groups, the more positive results with upstream treatment can be considered as consistent with the potential benefit of earlier intravenous tirofiban treatment over intracoronary injection of this drug at cath lab.

At the time of enrollment, a manual aspiration catheter was not available in our center. In our opinion, "pain-to-balloon time" instead of "first medical contact-to-balloon time" seems to be a more appropriate measure for the estimation of total ischemic time. Despite the risk of its subjectivity, this definition also includes the time delay from occurrence of the pain to first medical contact. Data from TIMI flow, corrected TIMI frame count, and ST segment resolution in pre-PCI, peri-PCI, and post-PCI subsets can answer question concerning the effect of tirofiban on the no-reflow phenomenon in our study. All patients with no-reflow or a high thrombus burden without satisfactory ST segment resolution underwent repeat angiography after tirofiban infusion. In patients with renal insufficiency, bolus treatment with tirofiban was not followed by infusion. In our study, median pain-to-balloon time (185–210 min) and in-hospital door-to-balloon time (30 min) were included into the analysis. In our study, pain-to-balloon time was not related to the angiographic, electrocardiographic, and clinical benefits of tirofiban.

Finally, I would like to thank the author of this comprehensive letter, which leads to a seminal discussion concerning the use of upstream GP IIb/IIIa inhibitors as an adjunct treatment to DAPT in patients who underwent primary PCI.

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Tirofiban usage and prognosis after myocardial infarction

To the Editor,

I read the article by Kaymaz et al. (1), entitled "The effects of tirofiban infusion on clinical and angiographic outcomes of patients with STEMI undergoing primary PCI." which was recently published online in your journal, with great interest. In their study, the authors reported that additional tirofiban usage significantly improves myocardial reperfusion, ST-segment resolution, in-hospital mortality rate, and in-hospital sudden cardiac death in patients with ST-segment elevation myocardial infarction (STEMI). I would like to make a critique on the methodology and results of the present study.

Tirofiban usage may be beneficial in patients with STEMI, but its effect on mortality is unclear. In the present study by Kaymaz et al. (1), there are no data about medications that are known to significantly reduce mortality and cardiovascular events in patients with STEMI. It is well known that statins, angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin-receptor blockers (ARBs), and beta-blockers significantly reduce in-hospital and long-term mortalities and cardiovascular events in patients with STEMI (2). Also, Kaymaz et al. (1) did not report any data on the left ventricular ejection fraction for the patient groups. A low left ventricular ejection fraction is a strong predictor of mortality after myocardial infarction, and it is a predictor of in-hospital mortality in patients with STEMI who underwent primary percutaneous coronary intervention (3, 4). Additionally, aldosterone receptor antagonists significantly reduce mortality in post-myocardial infarction patients with left ventricle dysfunction (5). Therefore, lower medication rates with statins, ACEIs/ARBs, aldosterone antagonists, and beta-blockers and a lower ejection fraction in the non-tirofiban group may be another reason for higher mortality rates and cardiac events. The authors should state the mean ejection fraction and medications for each group and should compare the groups based on their medications and ejection fraction.

In conclusion, tirofiban usage may have beneficial effects in addition to standard therapy in patients with STEMI. However, to define its exact role on mortality, ejection fraction and medications that are known to reduce mortality should be taken into consideration.

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DOI:10.5152/AnatolJCardiol.2015.6685

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As summarized in this letter, we showed that tirofiban treatment (TRT) in addition to aspirin, high-dose clopidogrel, and unfractionated heparin prior to primary PCI significantly improves myocardial reperfusion, ST-segment resolution, in-hospital sudden cardiac death, and in-hospital all-cause mortality rates in patients with STEMI without an increased risk of major bleeding. The major limitation was the absence of prospective and randomized clinical trial designs because of the critical difficulties in the reimbursement of treatment cost. Despite this limitation, the comparison of baseline characteristics permitted us to assess the efficacy and safety issues of TRT among groups. Despite the higher TIMI risk score in the pre-PCI or upstream TRT group than in the other groups, the benefit in TIMI flow grade, corrected TIMI frame count, ST-segment resolution, in-hospital sudden cardiac death, and in-hospital all-cause mortality were also significantly higher in the upstream TRT subset than in the other subset. As I said before in my reply to first letter; our results should be considered to provide important data concerning the use of TRT combined with dual antiplatelet therapy (DAPT) including aspirin and high-dose clopidogrel, but it cannot be generalized to DAPT combinations with prasugrel or ticagrelor. Our bridging TRT was targeted to minimize the risk of intracoronary rethrombosis within the first hours of primary PCI in which the level of platelet inhibition still remains subtherapeutic because of the kinetics of clopidogrel, even with a 600-mg loading dose, and the well-known procoagulant state of STEMI.

It may not be appropriate to compare a study based on non-randomized and retrospective data with the FINESSE trial showing no appreciable benefit and only harm in starting GP IIb/IIIa inhibitors in the prehospital setting for patients treated with primary PCI (2). The comments of Jeremias et al. (3) were based on the meta-analysis of five randomized trials. They concluded that the routine use of abcix-