

Comparison on the Effects of Clopidogrel Versus Tirofiban in Treating High-Risk Non-ST-Segment-Elevation Acute Coronary Syndromes: Risk-Adjusted Prospective Data Analysis

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Received: February 28, 2014

Revised: April 10, 2014

Accepted: April 16, 2014

Published online: May 10, 2014

ABSTRACT

AIM: To compare the outcomes of clopidogrel versus tirofiban in treating non-ST-segment elevation acute coronary syndromes among patients before percutaneous coronary intervention.

METHODS: This was a prospective data bank analysis study with 342 patients (216 in the clopidogrel group and 126 in the tirofiban group) with high risk unstable angina (Braunwald/TIMI risk stratification) and/or non-ST acute myocardial infarction included between May 2010 and November 2012 who were receiving clopidogrel or tirofiban within the first 24 hours of admission and before percutaneous coronary intervention. The following data were obtained: age, sex, diabetes, systemic arterial hypertension, smoke, dyslipidemia, previous coronary artery disease (percutaneous coronary intervention or coronary artery bypass graft), hemoglobin, creatinine, higher troponin, left ventricle ejection fraction and medication used at hospital. The primary endpoint was all cause of in hospital death and major adverse cardiac events (MACE) (death, non-fatal unstable angina or myocardial infarction/ targeted vessel revascularization, Killip III/IV, bleeding and stroke). Comparison between groups was made by Anova and Q-square. Multivariate analysis were determined by logistic regression and was considered significant when $p < 0.05$.

RESULTS: The median age was 64 years and 60.5% were male. In the tirofiban group were observed higher troponin levels ($p=0.02$), higher prevalence in previous coronary artery disease ($p=0.02$)

and differences between use of enoxaparin (92% in the tirofiban group \times 85% in the clopidogrel group, $p=0.02$). No significant difference was observed between the tirofiban versus clopidogrel groups in deaths (15.8% \times 8.3%, $p=0.14$) and MACE (29.4% \times 20.4%, $p=0.72$).

CONCLUSIONS: In patients with high risk non-ST acute coronary syndromes, the use of clopidogrel or tirofiban in the first 24 hours of admission were similar and the result did not show statistical significance difference between groups regarding mortality and MACE, despite higher tendency of that in tirofiban group.

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Key words: Acute coronary syndromes; Tirofiban; Clopidogrel

Soeiro AdeM, Almeida Soeiro MCF, Serrano Jr. CV, Oliveira Jr. MT. Comparison on the Effects of Clopidogrel Versus Tirofiban in Treating High-Risk Non-ST-Segment-Elevation Acute Coronary Syndromes: Risk-Adjusted Prospective Data Analysis. *Journal of Cardiology and Therapy* 2014; 1(4): 84-87 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/674>

INTRODUCTION

The knowledge of the mechanisms of platelet-mediated thrombosis has increased dramatically over the last 40 years. This increased understanding has identified treatment strategies for acute coronary syndromes (ACS) by targeting key mediators of platelet activation and aggregation processes^[1].

Several randomized trials have convincingly demonstrated the usefulness of glycoprotein IIb/IIIa receptor antagonists and clopidogrel. The most recent guidelines for the management of patients presenting with a non-ST-segment-elevation (NSTEMI-ACS) strongly recommend the use of glycoprotein IIb/IIIa receptor antagonists and clopidogrel for high-risk patients when percutaneous coronary intervention (PCI) is planned^[2-5].

The thienopyridine clopidogrel has been the standard of care, but is limited by variable response and treatment failure. Glycoprotein IIb/IIIa targeted agents (tirofiban and abciximab) are also used in ACS patients undergoing PCI. These inhibitors utilize a different

mechanism of action by preventing fibrinogen-mediated platelet aggregation, with short initial time of action^[1]. So, a large number of studies have been discussed which agent should be used and the most appropriate timing for that^[2].

There isn't any study comparing clinical events in patients with ACS that received clopidogrel versus tirofiban. In this context, we developed a prospective study comparing clinical events related to use of clopidogrel or tirofiban within the first 24 hours of admission and before PCI in patients with high-risk NSTEMI-ACS.

METHODS

Study population

This was an observational prospective data bank analysis study performed in a tertiary health center with 342 patients (216 in the clopidogrel group and 126 in the tirofiban group) with high-risk unstable angina (Braunwald/TIMI risk stratification)^[6,7] and/or non-ST acute myocardial infarction (AMI) included between May 2010 and November 2012 who were receiving clopidogrel or tirofiban within the first 24 hours of admission and before PCI. Exclusion criteria included contraindications against clopidogrel or tirofiban, ST-ACS, active bleeding, a history of a major operation/external injury within three months, history of a stroke within six months and low/moderate-risk unstable angina.

The study was approved by the ethics and research committee and in all cases was obtained informed consent by patient or a family member.

Study protocol and medication

All 342 patients were treated according by AHA/ESC Task Force Myocardial Infarction Guidelines^[4,5]. The decision regarding the administration of clopidogrel or tirofiban was made by clinical cardiologist in the admission, according by individual experience. All patients were included in a data bank and followed prospectively until discharge.

Patients in clopidogrel group received an oral loading dose of 300 mg immediately after admission. Clopidogrel were continued with daily maintenance dose of 75 mg. In the tirofiban group, patients received after admission bolus of 0.4 mg/kg/min about 30 minutos, followed by 0.1 mg/kg/min for 48 hours. All coronary angioplasty used bare-metal stent. The number of stents used were left at the discretion of the operator. The patients were submitted to PCI within 24 and 48 hours of admission.

Analytical methods

Blood was sampled immediately after admission prior to administration of medications (baseline) and daily according by institution protocol. Cardiac markers like troponin-T was measured using standard clinical chemistry. Laboratory upper limits of normal were 0.03 ng/mL for troponin-T measured by 4th generation immunoassay for the Elecsys 2010 automated analyzer (Roche Diagnostics GmbH, Germany).

In addition, the following data were obtained: age, sex, diabetes, systemic arterial hypertension, smoke, dyslipidemia, previous coronary artery disease (percutaneous coronary intervention or coronary artery bypass graft), hemoglobin, creatinine, higher troponin, left ventricle ejection fraction and medication used at hospital.

Definitive treatment (coronary artery bypass graft surgery (CABG), coronary angioplasty or clinical treatment) and the number of stents used in each group was compared too.

Patients were followed during internation after the index event.

Long term follow-up was not acquired. Major adverse cardiac events (MACE) included all causes of death, non-fatal unstable angina or AMI/targeted vessel revascularization, Killip III/IV, bleeding (major and minor) and stroke. New electrocardiographic signs and/or the typical rise and fall in troponin were required to document a new unstable angina/AMI during follow-up. Major bleeding events were scored if haemoglobin dropped by ≥ 50 g/L or intracranial bleeding was noted. Minor bleeding complications included macrohaematuria, haematemesis, or a drop in haemoglobin ranging from 30 to 50 g/L.

Statistical Analysis

Descriptive analysis of data collected included median, minimum and maximum values. Comparison between groups was made by Anova and Q-square. If Komolgorov-Smirnov tests confirmed normal distribution, continuous variables were summarized using mean+standard deviation and were compared using the student t-test for independent samples. The Mann-Whitney U test was used to compare continuous variables if they were not normally distributed.

In multivariate analysis, the primary endpoint was all cause of in hospital death and MACE. Multivariate analysis were determined by logistic regression and was considered significative when $p < 0.05$. The variables included all baseline characteristics as showed in table 1. All statistical procedures were performed using the Statistical software SPSS v10.0.

RESULTS

Characteristics of treatment groups

The median age was 64 years and 60.5% were male. In the tirofiban group were observed higher troponin levels ($p=0.02$), higher prevalence in previous coronary artery disease ($p=0.02$) and differences between use of enoxaparin (92% in the tirofiban group \times 85% in the clopidogrel group, $p=0.02$). All baseline characteristics of both groups was showed in table 1.

Significative difference was obtained in number of CABG between groups, with higher prevalence in tirofiban group (18.3% \times 10.6%, $p=0.04$). Treatment data was showed in table 2. All MACE were described in table 3.

Table 1 Baseline characteristics.

	Tirofiban group	Clopidogrel group	P
Age	63.58+11.72	64.25+12.05	0.68
Male (%)	60.5%	61.1%	0.89
Diabetes Mellitus (%)	61.4%	64.3%	0.51
Hypertension (%)	77.7%	77.00%	0.87
Tabagism (%)	58.6%	60.7%	0.14
FH of CAD (%)	12.1%	13.1%	0.74
Dyslipidemia (%)	48.4%	48.4%	0.99
Stable Angina (%)	13.6%	17.3%	0.38
Heart failure(%)	7,00%	4,5%	0.25
Previous AMI (%)	42.3%	31.6%	0.02
CABG (%)	20.5%	17.6%	0.43
PCI (%)	28.4%	32.00%	0.4
SAP (mmHg)	138.61+28.27	138.32+31.30	0.46
Hb (g/dL)	13.88+1.80	13.77+2.0	0.39
Cr (mg/dL)	1.21+1.16	1.21+1.08	0.86
Troponin (higher) (ng/L)	24.41+26.21	20.29+22.13	0.002
EF (%)	51.73+12.41	51.44+11.85	0.36
AAS (%)	99.4%	97.9%	0.38
B-blocker(%)	83.7%	79%	0.07
Enoxaparin (%)	92.1%	84.8%	0.02
ACE inhibitor (%)	74.4%	66.4%	0.12
Statin (%)	90.2%	87.3%	0.32

FH: family history; CAD: coronary artery disease; AMI: acute myocardial infarction; CABG: coronary artery bypass bypass graft surgery; PCI: percutaneous coronary intervention; SAP: systolic arterial pressure; Hb: haemoglobin; Cr: creatinine; EF: ejection fraction; ACE: angiotensin-converting-enzyme.

Table 2 Treatment data.

	Tirofiban group	Clopidogrel group	P
PCI (%)	70 (55.6%)	100 (46.3%)	0.52
Stents/patient	1.28	1.19	0.37
CABG (%)	61.4% (18.3%)	23 (10.6%)	0.04
Clinical (%)	33 (26.1%)	93 (43.1%)	0.03

PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft surgery.

Table 3 Multivariate analysis of death and MACE in tirofiban and clopidogrel groups.

	Tirofiban group	Clopidogrel group	P
Death (%)	20 (15.8%)	18 (8.3%)	0.14
MACE (%)	37 (29.4%)	44 (20.4%)	0.72
Stroke (%)	1 (0.8%)	0	0.98
AMI/TVR (%)	1 (0.8%)	5 (2.3%)	0.76
Killip III/IV (%)	13 (10.3%)	12 (5.6%)	0.10
Bleeding (%)	2 (1.6%)	9 (4.2%)	0.48

MACE: major adverse cardiac events; AMI: acute myocardial infarction; TVR: targeted vessel revascularization.

Multivariate analysis and clinical outcomes

No significant difference was observed between the tirofiban versus clopidogrel groups in deaths (15.8%×8.3%, $p=0.14$) and MACE (29.4%×20.4%, $p=0.72$) as observed in table 3.

DISCUSSION

We didn't find any similar study comparing clopidogrel versus tirofiban and evaluating clinical outcomes. Besides the molecular differences between clopidogrel and tirofiban, in our study no significant difference was observed between the tirofiban versus clopidogrel groups in deaths and MACE. However, this study was made at the major tertiary center of cardiology in Latin America and all patients considered were high-risk, so the patients are more severe than usual, justifying the great mortality and prevalence of diabetes. How PCI's were conducted after 24 hours, we considered that was total action of clopidogrel at the time of catheterization. There were a tendency of higher death and MACE rates in patients that used tirofiban. However, this group showed higher number of patients submitted to CABG and PCI, higher troponin levels and higher prevalence of previous coronary artery disease than clopidogrel group, attributing more complexity in coronary lesions. We have a limited number of patients in tirofiban group and maybe this fact could explain the non-significance difference.

The safety about use of tirofiban or clopidogrel were similar too between groups with bleeding rate of 1.6%×4.2% ($p=0.48$), respectively.

The pathophysiology of AMI damage during PCI can be related to the development of no-reflow and side branch occlusion caused by platelet aggregation and platelet embolization. Administration of clopidogrel or tirofiban is associated with early reinforced anti-platelet treatment, attenuated myocardial damage and reducing the incidences of the composite endpoint of death, AMI or revascularization for the treatment of patients with high-risk NSTEMI-ACS undergoing PCI^[8,9]. In this context, the correct use or association of anti-platelet treatment is questionable because of different times and ways of action and safe related to each medication.

Tirofiban was proved to attenuated minor myocardial damage and the incidence of MACE after long-term follow-up in patients undergoing PCI. The timing of administrating the tirofiban plays an extensive role in the incidence of MACE. The real effect of tirofiban is instantaneous due to intravenous therapy^[10,11]. When the patient receive upstream (within 4-6 hours before PCI) the occurrence of

myocardial damage is lower, comparing with downstream (the guidewire crossing the lesion) administration^[1,2,9,12]. The EVEREST trial demonstrated among high-risk NSTEMI-ACS patients treated with an early invasive strategy and upstream tirofiban, association with improved tissue-level perfusion and attenuated myocardial damage^[2]. AUCITY Timing trial showed that among patients with moderate to high-risk ACS undergoing an invasive treatment strategy, upstream use of tirofiban was associated with fewer ischemic events on the 30th day than downstream use of that (7.1%×7.9%, $p>0.05$)^[13]. In all studies, tirofiban demonstrated safety with major bleeding complications in about 5% of patients, and there were no significant differences between the tirofiban groups and the placebo^[10,13-16].

Clopidogrel is a prodrug that bind adenosine diphosphate, further enhance platelet inhibition and patient outcomes. The inhibition of platelet function may require at least two hours even after administration of a loading dose of 600 mg of clopidogrel, and this time could be until fifteen hours, depending of the initial dose^[1,10]. Besides, important number of patients are clopidogrel non-responders because of multifactorial reasons^[1]. CURE trial was the first and more important study with clopidogrel and showed lower incidence of MACE in patients in use of clopidogrel plus aspirin at short and long-term follow-up^[17]. Such as tirofiban, clopidogrel demonstrated safety with major bleeding complications and no significant differences between the clopidogrel groups and the placebo^[17].

Solinas *et al.*^[18] randomized patients with NSTEMI-ACS undergoing PCI to be treated with clopidogrel 600 mg, tirofiban and tirofiban plus clopidogrel 300 mg. The authors analysed P-selectin expression and platelet aggregation. Treatment with clopidogrel 600 mg significantly reduced P-selectin expression in comparison with tirofiban alone. However tirofiban inhibited platelet aggregation significantly more than clopidogrel during the first 6 hours, and the addition of clopidogrel 300 mg did not inhibit platelet aggregation any more than tirofiban alone throughout the 24 hours. Clinical outcomes were not observed^[18].

CONCLUSION

In patients with high-risk NSTEMI-ACS, the use of clopidogrel or tirofiban in the first 24 hours of admission were similar and the result did not show statistical significance difference between groups regarding mortality and MACE, despite higher tendency of that in tirofiban group.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

- 1 Angiolillo DJ. The evolution of antiplatelet therapy in the treatment of acute coronary syndromes: from aspirin to the present day. *Drugs* 2012; **72**(16): 2087-2116
- 2 Bolognese L, Falsini G, Liistro F, Angiolini P, Ducci K, Taddei T, Tarducci R, Cosmi F, Baldassarre S, Burali A. Randomized comparison of upstream tirofiban versus downstream high bolus dose tirofiban or abciximab on tissue level perfusion and troponin release in high-risk acute coronary syndromes treated with percutaneous coronary interventions – The EVEREST Trial. *J Am Coll Cardiol* 2006; **47**(3): 522-528
- 3 Bolognese L. The emerging role of platelet glycoprotein IIb/IIIa inhibitors in managing high-risk patients with non-ST segment elevation acute coronary syndromes. *Curr Med Res Opin* 2007; **23**(6): 1217-1226

- 4 Hamm CW, Bassand J, Agewall S, Bax J, Boersma E, Buena H, Caso P, Dudek D, Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns W, Zahger D. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2011; **32**: 2999–3054
 - 5 Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE Jr, Ettinger SM, Fesmire FM, Ganiats TG, Lincoff AM, Peterson ED, Phillippides GJ, Theroux P, Wenger NK, Zidar JP. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non–STelevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2012; **126**: 875–910
 - 6 Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, Jones RH, Kereiakes D, Kupersmith J, Levin TN, Pepine CJ, Schaeffer JW, Smith EE, Steward DE, Theroux P, Gibbons RJ, Alpert JS, Faxon DP, Fuster V, Gregoratos G, Hiratzka LF, Jacobs AK, Smith SC Jr. ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-STsegment elevation myocardial infarction--summary article: a report of the American College of Cardiology/American Heart Association task force on practice guidelines (Committee on the Management of Patients With Unstable Angina). *J Am Coll Cardiol* 2002; **40**(7): 1366-1374
 - 7 Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, Mautner B, Corbalan R, Radley D, Braunwald E. The TIMI risk score for unstable angina/non- ST elevation MI: A method for prognostication and therapeutic decision making. *JAMA* 2000; **284**(7): 835-842
 - 8 Geeganage C, Wilcox R, Bath PMW. Triple antiplatelet therapy for preventing vascular events: a systematic review and meta-analysis. *BMC Medicine*. 2010;8:36.
 - 9 Tao L, Ying X, Yu-jie Z, Yue-ping L, Han-ying M, Yong-he G, Liu YY, Zhao YX, Shi DM. Effects of upstream tirofiban versus downstream tirofiban on myocardial damage and 180-day clinical outcomes in highrisk acute coronary syndromes patients undergoing percutaneous coronary interventions. *Chin Med J* 2009; **122**(15): 1732-1737
 - 10 Ivandic BT, Kurz K, Keck F, Staritz P, Lehrke S, Katus HA, Giannitsis E. Tirofiban optimizes platelet inhibition for immediate percutaneous coronary intervention in high-risk acute coronary syndromes. *Thromb Haemost* 2008; **100**: 648–654
 - 11 Kimmelstiel C, Badar J, Covic L, Waxman S, Weintraub A, Jacques S, Kullopulos A. Pharmacodynamics and pharmacokinetics of the platelet GPIIb/IIIa inhibitor tirofiban in patients undergoing percutaneous coronary intervention: implications for adjustment of tirofiban and clopidogrel dosage. *Thromb Res* 2005; **116**(1): 55-66
 - 12 Leoncini M, Toso A, Maioli M, Bellandi F, Badia T, Politi A, De Servi S, Dabizzi RP. Effects of tirofiban plus clopidogrel versus clopidogrel plus provisional abciximab on biomarkers of myocardial necrosis in patients with non-ST-elevation acute coronary syndromes treated with early aggressive approach. Results of the CLOpidogrel, upstream TIrofiban, in cath Lab Downstream Abciximab (CLOTILDA) study. *Am Heart J* 2005; **150**(3): 401
 - 13 Nazif TM, Mehran R, Lee EA, Fahy M, Parise H, Stone GW, Kirtane AJ. Comparative effectiveness of upstream glycoprotein IIb/IIIa inhibitors in patients with moderate- and high-risk acute coronary syndromes: An Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) substudy. *Am Heart J* 2014; **167**(1): 43-50
 - 14 Gibson CM, Goel M, Murphy SA, Dotani I, Marble SJ, Deckelbaum LI, Dodge JT, King SB 3rd. Global impairment of coronary blood flow in the setting of acute coronary syndromes (a RESTORE substudy). Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis. *Am J Cardiol* 2000; **86**(12):1375-1377
 - 15 Saucedo JF. Balancing the benefits and risks of antiplatelet agents in patients with non-ST-segment elevated acute coronary syndromes and undergoing percutaneous coronary intervention. *J Thromb Thrombolysis*. 2010;30(2):200-9.
 - 16 Juergens CP, White HD, Belardi JA, Macaya C, Soler-Soler J, Meyer BJ, Levy RD, Bunt T, Menten J, Hermann HC, Adgey AA, Tamesby G. A multicenter study of the tolerability of tirofiban versus placebo in patients undergoing planned intracoronary stent placement. *Clin Ther* 2002; **24**(8): 1332-1344
 - 17 Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. Clopidogrel in unstable angina to prevent recurrent events trial (CURE) investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet* 2001; **358**: 527-533
 - 18 Solinas E, Gobbi G, Dangas G, Mehran R, Fahy M, Ippolito L, Bolognesi MG, Ruenes R, Merlini PA, Ardissino D, Vitale M. Comparison of the effects of pretreatment with tirofiban, clopidogrel or both on the inhibition of platelet aggregation and activation in patients with acute coronary syndromes. *J Thromb Thrombolysis*. 2009; **27**(1): 36-43
- Peer reviewer:** Javier Mariani, Coordinator of Coronary Unit, Department of Cardiology, Hospital El Cruce, Florencio Varela, Buenos Aires, Argentina.