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Artículo:

Relevance of the combined TIMI flow/perfusion index to effective assessment of reperfusion regimens with or without tirofiban in ST-elevation myocardial infarction

Relevance of the combined TIMI flow/perfusion index to effective assessment of reperfusion regimens with or without tirofiban in ST-elevation myocardial infarction

Insights from SASTRE-STEMI study, a randomized clinical trial Safety and efficacy of a conjunctive Strategy for Reperfusion Enhancement (SASTRE) in ST-elevation MI

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Summary

Beyond successful epicardial reperfusion (TIMI 3 flow), *optimal myocardial reperfusion* for ST-elevation myocardial infarction also requires a complete reestablishment of blood flow at the coronary microvasculature (TMP grade 3). In this Study, Tirofiban as conjunctive therapy for lytic and stenting regimens, improved not only the TIMI 3 flow rates, but also the TMPG 3 rates, which were related with a better clinical outcome without an increase in the risk of major bleeding. This study supports the hypothesis that platelets play a key role not only in the atherothrombosis process, but also in the disturbances of microcirculation and tissue perfusion. TIMI flow/perfusion index (TFP) is proposed to be used for the analysis of any new reperfusion regimen.

Resumen

EL ÍNDICE DE FLUJO TIMI/PERFUSIÓN EN EL INFARTO AGUDO DEL MIOCARDIO SIN ELEVACIÓN DEL SEGMENTO ST. UN AUXILIAR EFICAZ EN LA VALORACIÓN DE LOS REGÍMENES DE REPERFUSIÓN CON Y SIN TIROFIBAN.

Más allá de una reperfusión epicárdica exitosa, la reperfusión miocárdica para la elevación de la onda ST, requiere también de un restablecimiento completo del flujo sanguíneo en la microvasculatura coronaria. En este estudio, el tirofiban como terapia conjunta en los regímenes de lisis y de stent, no sólo mejoró el flujo de reperfusión epicárdica, sino también las velocidades de tales reperfusiones, los cuales fueron relacionados con un mejor resultado clínico sin incrementar el riesgo de un sangrado importante. Este estudio apoya la hipótesis del papel fundamental de las plaquetas no solamente en el proceso aterotrombótico, sino también en otros eventos. Por ello, se propone que el índice de reperfusión epicárdica/índice de perfusión sea empleado en el análisis de todo nuevo régimen de reperfusión.

Key words: Thrombolysis. Myocardial infarction. Platelet aggregation inhibitors. Tirofiban. Platelets. Reperfusion.
Palabras clave: Trombólisis. Infarto al miocardio. Inhibidores de la agregación plaquetaria. Tirofiban. Plaquetas. Reperfusión.

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Introduction

Optimal myocardial reperfusion is the cardinal therapeutic end point for patients with ST-elevation myocardial infarction (STEMI). Current fibrinolytic regimens achieve in less than two-thirds of patients a Thrombolysis in Myocardial Infarction (TIMI) grade 3 blood flow, and thus resulting in a limited myocardial reperfusion that has been associated to cardiac death and congestive heart failure.[1-3] Moreover, even if TIMI 3 flow is obtained, in some cases tissue flow can be impaired, as with the "nonreflow" phenomenon;[4] also, tissue perfusion does not necessarily imply patency of the infarct-related artery (IRA), as myocardial tissue is sometimes supplied by collateral vessels. Thus, failed thrombolysis may be a consequence of two mechanisms: resistance to thrombolysis, and/or resistance to achieve perfusion at tissue level.[5-7] Cumulative evidence suggests that in both mechanisms, platelets may play a key role.[8-11] Thus, new reperfusion paradigms are required to encompass improvement of artery recanalization, patency and tissue perfusion, as soon as possible. The use of platelet glycoprotein (GP) IIb/IIIa inhibitors alone or in combination with thrombolytic therapy or primary stenting percutaneous coronary intervention (PCI), have been recently proposed as alternatives to improve the results offered by current available reperfusion regimens.[12-15] A facilitated lytic process and a reduction in re-thrombosis and embolization of platelet aggregates with improvement in the coronary microcirculation using platelet GP IIb/IIIa inhibitors in combination with a low-dose of thrombolytic therapy or PCI, makes pathophysiological sense for enhancing myocardial reperfusion. However, the efficacy and safety from the different available platelet GP IIb/IIIa inhibitors as a conjunctive reperfusion therapy remain to be clarified.

We sought to determine if a conjunctive strategy for reperfusion using the combination of nonpeptide glycoprotein IIb/IIIa inhibitor (Tirofiban) plus either reduced-dose of Alteplase or primary stenting PCI improves TIMI flow and TIMI myocardial perfusion (TMP) scores, when compared with the usual strategies of either full-dose of Alteplase, or primary stenting PCI alone, without a significant increase in the risk of bleeding.

Methods

This is a multicenter, prospective, two-parallel, phase II open-label, randomized angiographic trial with a balanced design to define the safety and efficacy of a conjunctive reperfusion strategy with Tirofiban, in both lytic and PCI therapy for treating an acute MI. The trial was conducted between April 2000 and June 2002 at 7 enrolling national centers. The protocol was reviewed and approved at each institution by the appropriate ethics/investigation committee. The central units and the Angiographic Core Laboratory are described in the Appendix.

Patients aged over 18 years old were included if they presented with typical chest pain lasting more than 30 minutes within the prior 6 h and a ST-segment elevation greater than 0.1 mV in two or more contiguous ECG leads and were candidates for either fibrinolytic therapy or PCI. For those patients assigned to PCI the major angiographic inclusion criterion was the finding of a native coronary artery with a lesion no longer than 40 mm with a reference diameter $\geq$ 2.5 mm. The stents used were Jostent[16] (Jomed, Rancho Cordova, Calif.) Patients were excluded if they had any of the following findings: Usual contraindications for fibrinolytic therapy; previous MI; cocaine or amphetamine-induced MI; prior history of left ventricular dysfunction or multiple and advanced coronary artery disease; valvular disease with significant hemodynamic repercussion; cancer; advanced renal, pulmonary or liver failure; previous coronary surgical revascularization; left bundle branch block; cardiogenic shock at entry, or pulmonary edema requiring mechanical support; intolerance to aspirin or heparin, use of heparin 24 h before randomization; and incapacity to provide written informed consent. For the purpose of this study, after randomization, those patients assigned to PCI were excluded for ending comparative analysis if they had coronary lesions anatomically inadequate for intervention, or those in which a multivessel interventional procedure was required. Nevertheless, they received appropriate treatment.

Study groups

After screening, optimizing the baseline condition, and meeting all inclusion criteria, patients were randomized via a central randomization center to receive: Usual therapy (Group A) with either Alteplase alone or primary stenting PCI; or conjunctive therapy with a nonpeptide glycoprotein IIb/IIIa inhibitor, Tirofiban (Group B), in both low-dose of Alteplase and PCI subgroups. After the randomization procedure for assign-

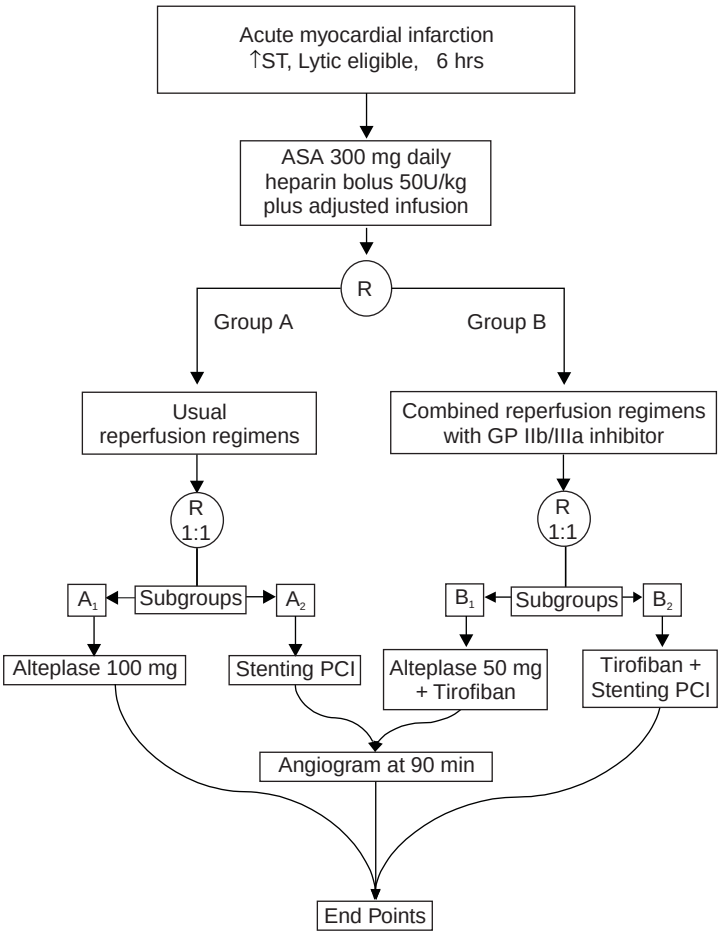

Fig. 1. Study design.

ment to group A or B, patients of each group were again randomized (1:1 fashion) to receive either Thrombolytic or PCI reperfusion regimen *(Fig. 1)*.

Initial medical management

All patients received aspirin 325 mg and intravenous heparin bolus of 50 U/kg with a maximum of 5,000 U followed by an initial maintenance infusion of 10 U/kg/h, titrated to an activated partial thromboplastin time of approximately 60 to 75 seconds. Group A1, received intravenous Alteplase bolus over 5 minutes of 20 mg, followed by an infusion of 80 mg over 60 minutes;[17] Group A2, received usual primary stenting PCI; Group B1, received intravenous Alteplase bolus of 20 mg and 30 mg over 30 min, followed by an intravenous loading of Tirofiban of 0.4 µg/kg/min over 30 min followed by a maintenance infusion of 0.1 min/kg/min for a minimum of 36 h. Tirofiban was administrated immediately after (within 30 min) Alteplase; and Group B2, received the same scheme of Tirofiban plus primary stenting PCI. Additional medical therapy with beta-blocker, nitrate, calcium antagonist, and cholesterol-lowering agent was left to the discretion of the participating investigator. ECG recordings and blood samples were obtained on admission, and at 6, 12 and 24 h. Platelet and blood cell counts were measured daily until hospital discharge or on day 5, whichever came first.

Angiographic procedures

Coronary angiography was performed at 90 min following administration of thrombolytic therapy in groups A1 and B1, unless the investigator considered the need for urgent interventional procedure. After a complete angiographic study including standardized views, the quality of digital recording was verified. Adjunctive/rescue stenting procedure of the IRA was performed at the discretion of the investigator. For groups A2 and B2 the stenting PCI procedure was performed within 90 minutes after the loading infusion of Tirofiban. An independent and validated angiographic core laboratory adjudicated all films with respect to TIMI flow and TMP grades, and the reviewers were blind to reperfusion regimen assignment. Because of TIMI flow and TMP angiographic indexes, separately, have been validated and strongly related with the clinical outcome after a ST-elevation MI,[18-20] we did a post-hoc analysis stratifying by combined scores of both angiographic indexes.

Primary and Secondary end points

Efficacy

The primary angiographic efficacy end point was the incidence of TIMI flow grade 3 in the IRA at 90 min following administration of corresponding lytic regimen. A secondary planned angiographic endpoint of efficacy consisted of the TIMI 2/3 flow rates (artery patency). Myocardial perfusion in the infarct-related zone was analyzed for all patients using the TIMI angiographic score system as previously described.[18] Standardized techniques of injection utilizing nonionic material were used by investigators, and ~ 10 cc for each injection was preferred. For those patients randomly assigned to stenting procedures or when a rescue/adjunctive PCI was performed supplemental heparin dosing was administrated with a target of ~ 200 seconds of activated

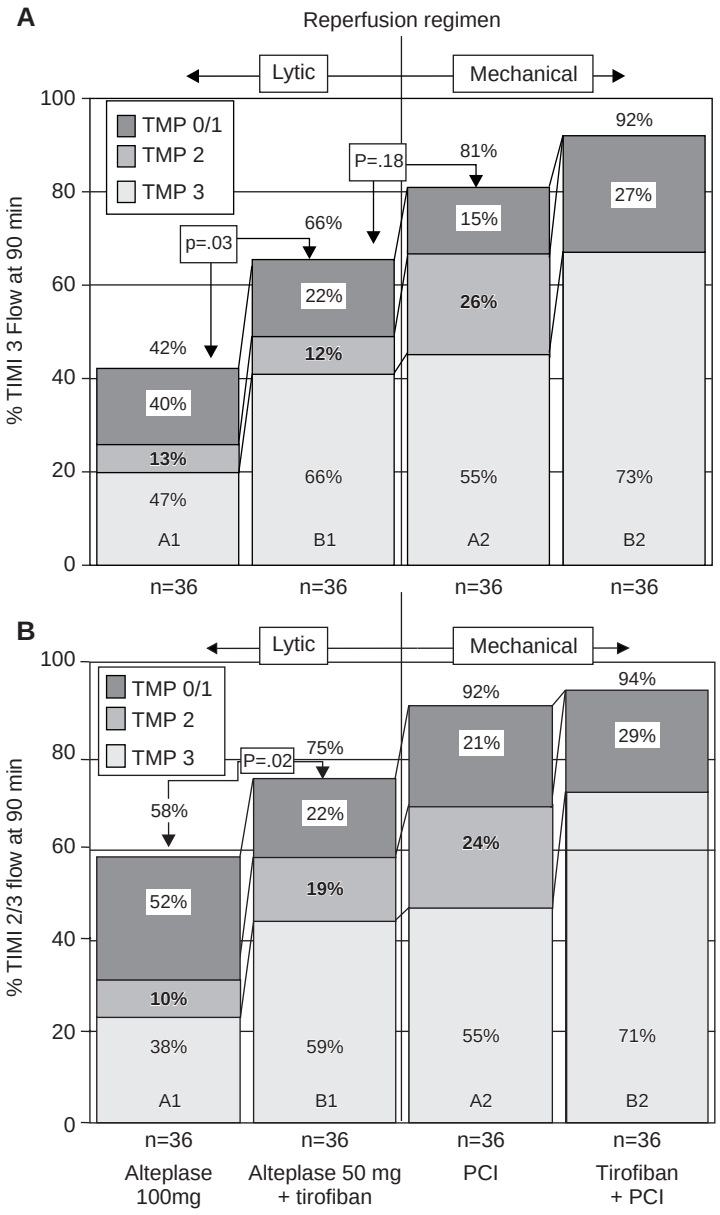

Fig. 2. TIMI flow rates by type of reperfusion regimen. The bars represents the percentages of TIMI 3 flow (2a), and TIMI 2/3 (2b), into the bars is shown the prevalence of the TIMI myocardial perfusion grades.

clotting time. Removal of arterial access sheaths (97%, 6 Fr) was standardized for all patients until the activated clotting time was less than 150 seconds. Closure devices or mechanical compressors were not permitted, and special attention for any evidence of active bleeding on the femoral injection site was recommended for at least 8 h after procedure.

The clinical efficacy endpoint was the time for a first event of a composite index of major cardiovascular events including death (cardiac or no cardiac), reinfarction, stroke (hemorrhagic or nonhemorrhagic), need of percutaneous or surgical coronary revascularization, development of heart failure, new episode of refractory ischemia or severe ischemic-related hemodynamic instability. Reinfarction was defined if a new sustained and significant ST elevation (> 0.1 mm) occurred with an increase in CK-MB levels to more than 50% of the previous significant drop off peak value in the first 24 hours or re-elevation to above three times normal after 24 hours and until day seven, beyond this time two times normal was required. Refractory ischemia was defined as a new sustained chest pain of 15 to 20 minutes in duration; two episodes or more episodes < 15 minutes within 1-hour period while the patient was receiving optimal adjusted medical therapy; or recurrent ischemia with pulmonary edema or cardiogenic shock.

Safety

Major bleeding conditions included one of the following: a reduction in the blood hemoglobin level of more than 5 g per deciliter; the need for the transfusion of three or more units of blood; the need for corrective surgery; and the occurrence of intracranial or retroperitoneal hemorrhage. TIMI score[13] for major bleeding was also assessed. Platelet counts were monitored daily throughout the infusion; minor thrombocytopenia was defined as a platelet count between 60,000 and 149,000; moderate thrombocytopenia was defined as a platelet count between 25,000 and < 60,000; and severe thrombocytopenia if the platelet count was < 25,000. An independent clinical events committee evaluated all events whose members were unaware of the treatments assignments.

Statistics

A minimum of 32 patients per group allowed for at least 96% probability (one-side) of detecting a TIMI flow grade 3 of at least 70% based on a historical control rate of 54% at 90 min.[21] Enrolling 70 patients in each group ensured at least a probability of 70% of detecting a rate of major bleeding of at least 8% based on a historical control rate of 5%. Thus 72 patients for each group of treatment (Standard *vs* Tirofiban-conjunctive therapy) were enrolled. Data are presented, when appropriate, as mean ± SD or medians with 25th to 75th percentile ranges. Categorical variables

Table I. Baseline characteristics by group and subgroups of treatment (standard or conjunctive reperfusion regimens)

Strategy	Usual reperfusion strategies			Conjunctive reperfusion regimens with tirofiban		
Groups	Total	A_1	A_2	Total	B_1	B_2
Number of patients	72	36	36	72	36	36
Age, y (IR)	61 (53, 68)	60 (52, 70)	61(55, 68)	58 (50, 66)	55 (49, 62)	61 (51, 70)
Gender-Male	58 (81%)	29 (81%)	29 (81%)	63 (87%)	34 (94%)	29 (81%)
Hypertension	25 (35%)	15 (42%)	10 (28%)	32 (44%)	12 (33%)	09 (25%)
Diabetes	11 (15%)	06 (17%)	05 (14%)	17 (24%)	08 (22%)	09 (25%)
Prior angina	27 (38%)	15 (42%)	12 (33%)	24 (33%)	12 (33%)	12 (33%)
Current smoker	20 (28%)	10 (28%)	10 (28%)	21 (29%)	11 (31%)	10 (28%)
Anterior-MI	30 (42%)	12 (33%)	18 (50%)	44 (61%)	21 (58%)	13 (36%)
Height, m	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)	1.7 (1.6, 1.7)
Weight, kg	70 (69, 80)	71 (69, 80)	70 (69, 84)	80 (70, 83)	80 (75, 83)	74 (65, 83)
Heart rate, bpm	80 (70, 89)	80 (70, 85)	84 (74, 90)	80 (70, 85)	80 (70, 85)	80 (71, 92)
SBP on admission, mm Hg	127 (110, 140)	127 (102, 140)	124 (110, 147)	130 (110, 150)	125(110, 148)	130 (110, 150)
Time: Symptom to treatment, h	2.9 (1.5, 4.0)	2.0 (1.4, 4.0)	3.0 (1.8, 4.0)	2.6 (1.4, 3.5)	2.0 (1.3, 3.0)	3.0 (1.5, 4.0)
Time: Randomization to angiogram, h	75 (65, 105)	88 (50, 105)	75 (70, 105)	75 (45, 105)	75 (45, 105)	75 (45, 103)

Data are shown as number (percentage) or medians (25^{th}, 75^{th} percentile values); **A1**, Alteplase 100 mg alone; **A2**, stenting PCI; **B1**, Low-dose of Alteplase plus Tirofiban; **B2**, Tirofiban plus stenting PCI (see figure 1); **MI**, myocardial infarction; **SBP**, systolic blood pressure.

Table II. Endpoints: Standard *vs* conjunctive therapy with tirofiban in ST-elevation myocardial infarction.

End point	n	Reperfusion strategy Standard **Group A** (N = 72)	Conjunctive* **Group B** (N = 72)	**rr**	**(95% CI)**	**p value**
Primary angiographic endpoint at 90 min						
TIMI 3 flow	101	44 (61.1%)	57 (79.2%)	.41	(0.19 – 0.87)	.012
TMP 3 grade	68	28 (38.9%)	40 (55.6%)	.51	(0.26 – 0.99)	.045
Other Angiographic endpoints at 90 min						
TIMI 2/3 flow	115	54 (75.0%)	61 (84.7%)	.54	(0.23 – 1.24)	.146
TIMI 3 flow with TMP 3 grade	62	23 (31.9%)	39 (54.1%)	.40	(0.20 – 0.78)	.007
TMP 0/1 grade	47	32 (44.4%)	15 (20.8%)	3.04	(1.45 – 6.33)	.003
Clinical composite endpoint within 30 days	49	31 (38.9%)	18 (19.4%)	1.85	(1.03 – 3.32)	.036
Death/MI/RI	12	10 (13.9%)	02 (02.8%)	5.82	(1.27 – 26.6)	.023
Revascularization	35	20 (28.0%)	15 (20.8%)	1.40	(0.71 – 2.73)	.323
Heart failure	02	01 (01.4%)	01 (01.4%)	1.00		
Stroke	00					

* Conjunctive with Glycoprotein IIb-IIIa inhibitor (Tirofiban); RI, Recurrent refractory ischemia; rr, risk ratio, logistic Cox univariate models.

are presented as number, frequency or percentages. Pearson Chi square or Fisher exact test, Student t, and Wilcoxon rank-sum tests were performed, as indicated.[22] Kaplan and Meier survival curves were constructed to compare the probabilities of having the composite endpoint among the different groups of study. The univariate hazard risk was assessed by a Cox regression analysis.[23] No adjustment was made for multiple comparisons in subgroups. Caution is recommended in the interpretation of these data as well as the secondary endpoints because of the small sample size. A p value $\leq .05$ was considered for statistical significance. All analyses were performed on the intention-to-treat principle.[24]

Results

Baseline characteristics

The general characteristics of the patients by groups are shown in *Table I*. There was no difference between groups of study with respect to the following demographic and clinical variables: age, sex, blood pressure, pulse rate, risk co-morbid factors, history of angina and infarct location. The mean age (SD) was 59.6 (11.5) years. Twenty percent were women. Diabetes and Hypertension were found in 19.4% and 35% respectively. The mean (SD) time from onset of symptoms to randomization was 2.9 (1.7) hours. Forty nine percent of myocardial infarctions were anterior in location; and 94% of patients were classified as Killip class II or I at entry. Aspirin was administrated to all patients before randomization, ß-adrenergic receptor blockers to 22%, angiotensin-converting enzyme inhibitors to 17% and calcium antagonists to 19%.

Angiographic observations

Seven patients were eliminated after randomization; two patients because of lack of angiograms for medical reasons; three patients (PCI group) because of either the IRA did not have the prespecified anatomical criteria or, multivessel angioplasty was required; and two patients due to failure to receive the reperfusion regimen as specified in the protocol. All excluded patients received appropriate treatment. One of them (assigned to B1 group) died due to rapidly ensuing cardiogenic shock.

TIMI flow rates

TIMI 3 flow rate at 90 min was achieved in 61% of patients treated with conventional reperfusion regimens, whereas it was achieved in 79% of patients treated with conjunctive reperfusion therapy with Tirofiban (risk ratio 0.41, [95%CI, 0.20-0.87], p = 0.02). Conversely, the difference between usual and conjunctive regimens in TIMI2/3 flow did not reach significance (75% *vs* 84.7%, hazard ratio .54 [95% CI, 0.23-1.24] p = 0.15) *(Table II)*. Nonetheless, compared with full-dose of Alteplase alone, the conjunctive reperfusion regimen of low-dose Alteplase (50 mg) and Tirofiban, produced an increase in the rates of both TIMI 3 flow (42% *vs* 66%, p = 0.03), and TIMI 2/3 flow (58% *vs* 75%, p = 0.02). Higher rates of TIMI 3 flow were observed in PCI regimens than with lytic regimens. In the pooled data of PCI groups, 86.5% achieved a TIMI 3 flow rate compared with 54% in the lytic regimens (p < 0.01). However, reperfusion regimens with Tirofiban had incremental benefit not only in establishing a better TIMI 3 flow rate, but also a better TMP grade *(Figs. 2a and 2b)*.

TIMI Myocardial perfusion grades

According with the original angiographic myocardial perfusion stratification proposed by the TIMI group,[19] patients enrolled in the usual reperfusion regimens achieved a 38.9% TMPG 3 rate *vs* 55.6% in the conjunctive reperfusion strategies (p = .045). The pooled data for lytic reperfusion regimens showed a 34.7% TMPG 3 compared with 59.7% of the pooled data of PCI groups (p = 0.045). From lytic groups (A1 and B1), however, TMPG 3 in the full Alteplase regimen achieved a 25% compared with 44.4% of the conjunctive regimen with Tirofiban (p = .08). From PCI groups (A2 and B2) TMP 3 grade was observed in 53% and 67% for usual and conjunctive regimens respectively (p = 0.16). The difference of TMPG 3 rate between full Alteplase alone and Tirofiban-PCI regimen was statistically significant (25% *vs* 67%, p < .01), however, the difference between the conjunctive Alteplase + Tirofiban regimen (B1) *versus* PCI alone (A2) regimen was numerically minimal and did not appear to offer incremental benefit for PCI strategy in terms of TMP 3 grade (44.4% *vs* 52.8%, p = 0.6).

Relationship between TIMI flow and TMP grades by reperfusion regimens

Although, increasingly higher rates of TMP 3 grade were found with better TIMI flow score, important differences were observed. The distribution of TMP grades in each reperfusion regimen is shown in *Figure 2a* for those patients who reached TIMI 3 flow, and in *Figure 2b* for TIMI 2/3 flow. The pooled data for the standard reperfusion regimens (group A) that reached TIMI 3 Flow showed a rate of TMPG 3 of 38.9%, however, it was higher in the conjunctive reperfusion strategies (55.6%), representing a relative 30% of increasing; p = 0.02. From Stenting PCI groups with TIMI 3 flow (60/72, 83.3%), a TMP 3 grade was observed in 59.2% and 72.7% for standard and conjunctive strategies respectively.

Clinical outcomes

The overall probability of having composite endpoint within 30 days by the principal reperfusion stra-

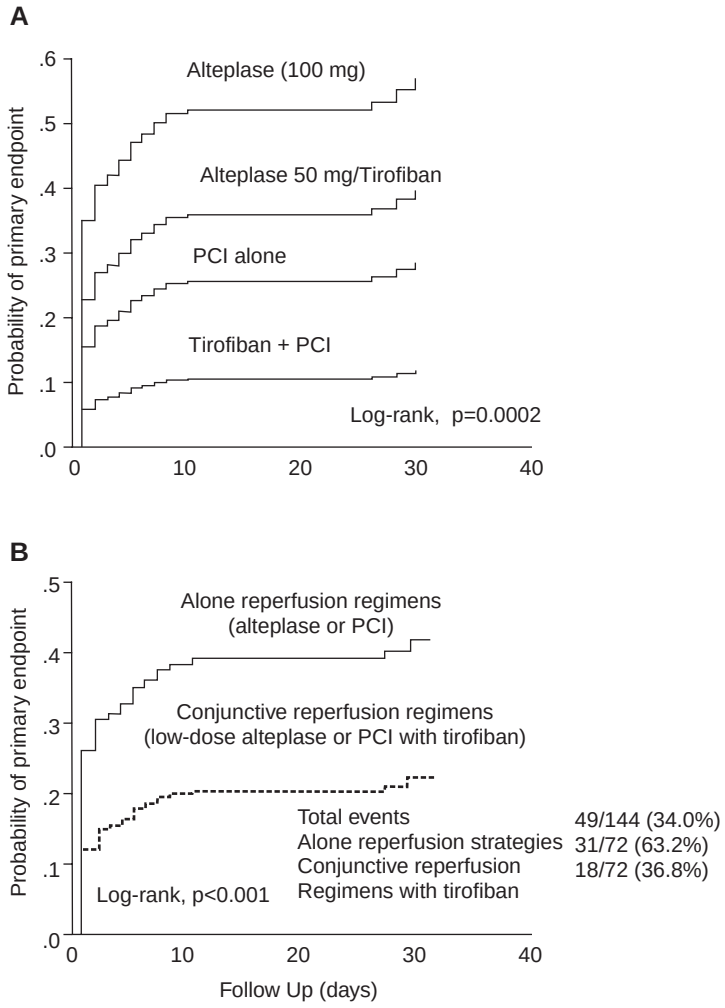

Fig. 3. Probability curves for having the primary end point (major cardiovascular events). 3a, it shows the probability by type of reperfusion regimen, notably, the higher probability observed was for Alteplase alone. 3b, the pooled data for usual and conjunctive strategies with Tirofiban for reperfusion are depicted and show its differences. The curves are separated principally within 24 to 48 h.

tegies is shown in *Figure 3a*. This probability at 30 days was 59% in the lytic A1 group *versus* 38% in the lytic B1 group (36% of relative risk reduction). The pooled data for usual reperfusion regimens *(Table II)* showed a significant increase in the probability of composite endpoint at 30 days, from 39% *versus* 19% in the conjunctive-Tirofiban reperfusion strategies (risk ratio, 1.85; 95% confidence interval, 1.04 to 3.36; p = .036, *Fig. 3b*). Specific comparisons between usual and conjunctive reperfusion strategies in both lytic and interventional arms are summarized in *Table III*.

Regardless of reperfusion regimen, the probability of composite endpoint at 30 days was decreasingly associated with a higher TIMI flow score. However, this probability was also directly associated with a higher TMP score. Interestingly, and even in those patients who reached TIMI 3 or TIMI 2/3 flow, their clinical outcome was depending on the degree of TIMI myocardial perfusion grade *(Fig. 4)*.

Based on these findings an acceptable angiographic index for risk stratification by combining both TIMI flow and TMPG scores was constructed ("TFP index"); then probability curves for having the composite endpoint were performed *(Fig. 5)*.

Safety

The use of Tirofiban did not appear to be associated with excess bleeding complications. Safety observations are summarized in *Table IV*. The overall rate of major bleeding was 2.1% and there was no difference between usual and conjunctive strategies.

Discussion

Thrombolytic therapy for acute myocardial infarction has demarked one of the most extraordinary advances in medical history and remains the most commonly reperfusion treatment, however, it has well documented limitations.[3,6,7] Consequently, a dramatic expansion in the scope of reperfusion regimens including mechanical and pharmacological strategies for opening occluded arteries has been developed.[11,25,26] Nevertheless, optimal myocardial reperfusion is still far from ideal with the current reperfusion regimens, and considerable debate remains regarding the optimal management strategy.[27-29] Excessive time delays to open the IRA, may contribute to extensive myocardial damage, myocardial edema, vasospasm, leukostasis, and immuno-inflammatory changes that may result in an additional impaired tissue perfusion, in spite of having achieved restoration of epicardial flow. Thus, beyond TIMI flow grade 3, "optimal myocardial reperfusion" implies a full, sustained, and suitable time-dependent reestablishment of flow not only at the epicardial level of the IRA, but also at tissue level.

On the other hand, even if early recanalization of the infarct related artery is obtained, multiple elements may participate in the heterogeneity of clinical outcomes including ischemic preconditioning, collateral circulation, molecular responses, genetic polymorphisms, co-morbid disease

Table III. Composite endpoint at 30 days by subgroups of treatment.

End Point	Reperfusion strategy Standard **Group A1** (N = 36)	 Combined* **Group B1** (N = 36)	**HR**	**p value**
LYTHIC THERAPY				
Composite endpoint				
At 30 days	**21 (58.3%)**	**14 (39.0%)**	**1.65**	**.14**
Death/MI/RI	5 (13.9%)	1(02.8%)	5.72	.11
Revascularization	16 (49.4%)	13 (36.1%)	1.34	.43
Heart Failure	———	———	———	
Stroke	———	———	———	
	Group A2 (N = 36)	**Group B2** (N = 36)	**HR**	**p value**
STENTING PCI				
Composite endpoint				
At 30 days	**10 (27.8%)**	**4 (11.1%)**	**2.67**	**.09**
Death/MI/RI	5 (13.9%)	1 (02.8%)	5.72	.11
Revascularization	4 (11.1%)	2 (05.6%)	2.00	.67
Heart failure	1 (02.8%)	1(02.8%)	1.00	
Stroke	———	———		

* Combined with Glycoprotein IIb-IIIa inhibitor (Tirofiban); RI, Recurrent refractory ischemia

(diabetes), signaling cascades at both inter and intracellular level, oxidative stress, electrical membrane stability, inflammatory response and other factors.[4]

Although platelets have been recognized to be crucial to the process of atherothrombosis, they seem to have mechanisms by which participate in the subsequent micro vascular events beyond thrombotic obstruction.[11,30] Despite all the above-mentioned evidence that lends strong support to the hypothesis that any reperfusion regimen should include a Gp IIb/IIIa inhibitor, controversies remain to be clarified.[31,32] These controversies, however, have been based principally on clinical trials that do not include angiograms at 60 or 90 minutes. Conversely, in the randomized angiographic trials the results are irrefutable, in that the use of GP IIb/IIIa as a conjunctive therapy improves TIMI 3 flow rate in both lytic and mechanical reperfusion strategies. The discrepancy between these studies may be related to differences in trial design rather than sampling error. The true benefit could not be found because of the critical determinant in improving survival is not only the early patency of IRA but also an effective and sustained tissue perfusion which is dependent on many other mechanisms. Angiographic studies in this sense have demonstrated that a rescue/adjunctive PCI may be used in more than 40% of patients within 90 minutes,[33] therefore even if the hemodynamic and ECG indicate stability and improvement after a lytic reperfusion regimen, early coronary angiography with a possible coronary intervention might be the new paradigm. Although our results confirm the superiority of stenting procedures rather than lytic reperfusion regimens for obtaining TIMI 3 flow, the later improved when Tirofiban was used. Notably, those patients who received Tirofiban + low-dose Alteplase achieve a 64% of TIMI 3 flow rate, compared with 75% of those patients who received PCI alone. However, the myocardial perfusion rate (TMPG 3) was similar in both groups.

Traditionally TIMI 3 flow has been used as the principal angiographic index to determine efficacy of a reperfusion strategy, however, cumulative evidence have demonstrated that patency does not necessarily mean tissue perfusion. Multiple time-depending interactions occur beyond the anatomical obstruction of the IRA during an ST-elevation myocardial infarction, and therefore new alternatives need to be explored for correcting both situations. Our study supports this hypothesis and has provided validation for an alternative reperfusion strategy. Conjunctive reperfusion regimen with Tirofiban increased not only TIMI 3 flow rate, but also the myocardial reperfusion rate (TMPG 3). This study suggests that platelets are involved in both processes, oc-

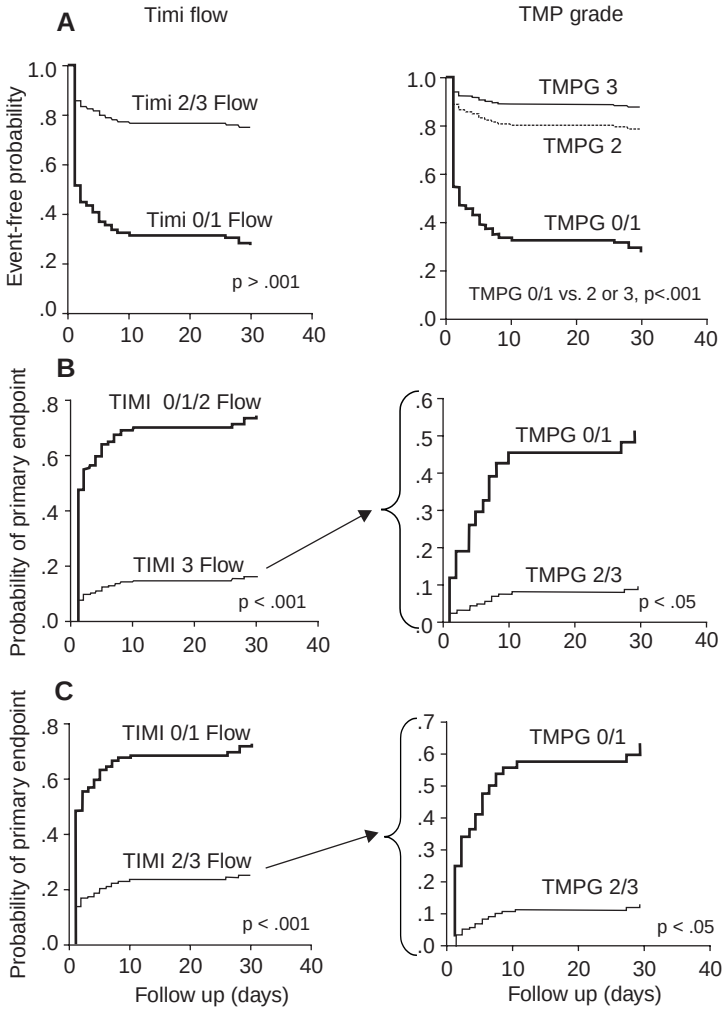

Fig. 4. Kaplan-Meier curves. 4a, event-free probability of having the clinical primary end/point by TIMI flow and TIMI myocardial perfusion scores. 4b, probability curves of primary endpoint. Interestingly, even in those patients who reached TIMI 3 flow, this probability was also clearly related with the TIMI myocardial perfusion grade. The same finding was observed in those patients with TIMI 2/3 flow (4c).

clusion/re-occlusion of the IRA and the vascular/tissue reactivity beyond occlusion. The question is: who is failing, the reperfusion regimen or our perception of the reperfusion process? Definitely, an early and sustained re-opening of the IRA is the best way to achieve the reestablishment of tissue reperfusion, but this is not sufficient, because of the multiple reactions and dynamic mechanisms that are occurring beyond the occlusion should be considered. In addition, we need to keep in mind that more than 40% of patients sooner or later will require a revascularization therapy, therefore, any lytic reperfusion regimen is only a temporary opportunity-window for a true long-term optimal myocardial reperfusion, however, as better, earlier and longer the window is obtained by the lytic reperfusion regimen, the opportunities for better clinical outcomes will increase. Gusto V trial is a clear evidence on this temporary opportunity-window. "Open" the artery-related is not enough, the process is dynamic and if we do not give the next step soon (angiography study) to see the anatomical state, The re-occlusion and its consequences may be mask the real impact of the new conjunctive strategies for myocardial reperfusion. Open the artery is only the first step. In this study, the patients included into the lytic arms a rescue/adjunctive PCI was required in ~ 40%.

Based on our angiographic findings, we developed a combined index using the TIMI flow and perfusion scores (TIMI flow/perfusion, "TFP index"). Regardless of reperfusion regimen, those patients who achieved the combination of TIMI 3 flow and TMP grade 3, had the lowest probability of having the composite endpoint. However, even if a TIMI flow grade 3 was achieved, when TMPG was < 2, the risk for having the com-

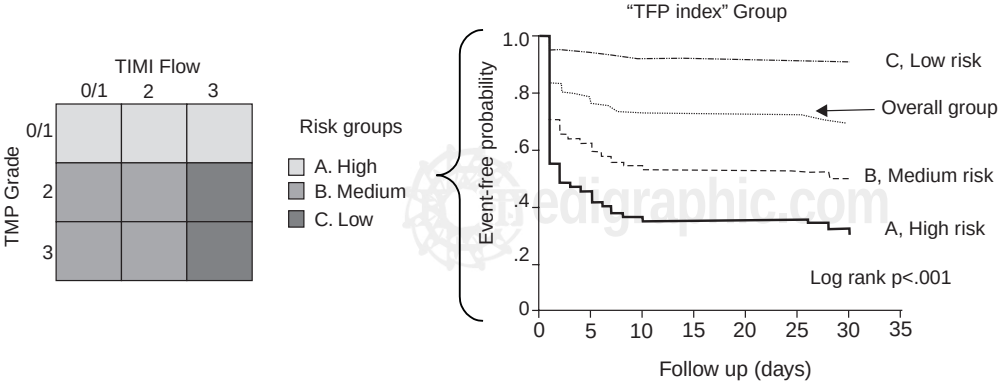

Fig. 5. TIMI flow/perfusion index (TFP). According with the results and frequencies of the primary end point, a combined index using both TIMI flow and myocardial perfusion scores was developed. Survival curves (right) using the TFP were performed and the important differences are shown

Table IV. Safety endpoints.

			Groups of study			
		Total Group	**A1**	**A2**	**B1**	**B2**
Number of patients		144	36	36	36	36
Events						
Bleeding		**12 (8.3)**	**3 (8.3)**	**3 (8.3)**	**2 (5.6)**	**4 (11.1)**
Minor	(non-transfusion)	04 (2.8)	1 (2.8)	1 (2.8)	1 (2.8)	1 (2.8)
Moderate	(≤ 3 units)	06 (4.2)	1 (2.8)	2 (5.6)	1 (2.8)	2 (5.6)
Severe	(> 3 units)	02 (1.4)	1 (2.8)	———	———	1 (2.8)
TIMI Major bleeding criteria†		03 (2.1)	1 (2.8)	1 (2.8)	———	1 (2.8)
Thrombocytopenia		**04 (2.8)**	**1 (2.8)**	**1 (2.8)**	**1 (2.8)**	**1 (2.8)**
Minor	(> 60,000 - < 150,000)	03 (2.1)	1 (2.8)	1 (2.8)	1 (2.8)	———
Moderate	(> 25,000 - ≤ 60,000)	00 (0.0)	———	———	———	———
Severe	(< 25,000)	01 (.07)	———	———	———	1 (2.8)
Intracranial hemorrhage		**00 (0.0)**	———	———	———	———
Total		**16 (10.4)**	**4 (11.1)**	**4 (11.1)**	**3(8.3)**	**5 (13.8)**

Data presented as n (%); †, Decrease in hemoglobin > 5g/dL or Intracranial bleed,[13] other abbreviations as table I

posite endpoint at 30 days was drastically increased. The probability curves of having the composite endpoint are shown in *Figure 5*.

Safety

Eight cases required transfusion but only two cases required transfusion of > 3 units. Although special care was given to the arterial access, two thirds of hemorrhages occurred at these sites, however, our complication rate was similar to other trials.[12,13,15] We did not have any intracranial hemorrhage or stroke. Thrombocytopenia occurred in 2.8% but only one had less than 25,000 (12,000) and was associated with a moderate groin bleeding and required the transfusion of 2 blood units. The overall rate for the combination of death/reinfarction/refractory ischemia was higher in standard *vs* conjunctive reperfusion strategies. These differences were statistically significant and are shown in *Table II*. However, larger sample size from registries and phase III trials is needed for a more statistically robust estimate of the risk of major bleeding such as intracranial hemorrhage with this new regimen for reperfusion.

Limitations

This is a phase II angiographic trial that limits our conclusion in terms of clinical outcomes. In order to reduce heterogeneity in the sample size we selected cases with a first myocardial infarction because of the higher probability of having cases with multivessel disease as has been previously informed. However a contribution of our study was to demonstrate the efficacy and safety of a conjunctive reperfusion regimen using Tirofiban. Nevertheless important clinical observations were detected and represent a further advance on the assessment of effective myocardial reperfusion.

Conclusion

Compared with usual regimens for reperfusion, in patients with ST-Elevation myocardial infarction, a conjunctive strategy with Tirofiban in both low-dose Alteplase and stenting PCI regimens leads to a greater rate not only of TIMI 3 flow, but also TMPG 3, without an increasing rate of major bleeding or adverse outcomes. The current trial emphasizes that the lower probability for having a composite endpoint at 30 days was clearly associated with the capability of each reperfusion regimen for obtaining not only a greater TIMI flow, but also a greater TMP. These data suggest that in ST-elevation myocardial infarction the paradigm of "optimal tissue reperfusion" rather than "patency" should be used in order to evaluate the true efficacy of reperfusion regimens. We suggest that TFP index may be a good alternative when an early angiographic study is available.

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