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A randomized trial comparing clopidogrel versus ticlopidine therapy in patients undergoing infarct artery stenting for acute myocardial infarction with abciximab as adjunctive therapy

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Aim To evaluate the impact of a clopidogrel therapy on the effectiveness of myocardial reperfusion in patients with ST-segment elevation acute myocardial infarction (AMI) undergoing routine infarct-related artery (IRA) stent implantation and receiving routine abciximab therapy.

Background Inflammatory processes after mechanical restoration of flow in AMI play a central role in decreasing the effectiveness of reperfusion at microcirculatory level. Several studies suggest that clopidogrel may exert a protective effect against adverse cardiovascular events by virtue of its anti-inflammatory properties.

Methods A total of 133 patients with a first ST-elevation AMI were randomized to clopidogrel (600-mg loading dose before IRA stenting followed by 75 mg daily, n = 66) or ticlopidine (500 mg before IRA stenting followed by 250 mg twice daily, n = 67). The primary end point was scintigraphic infarct size at 1 month. The secondary end points were ST-segment elevation resolution within 3 hours of procedure and 1-month clinical outcome, as a composite of death, reinfarction, target vessel revascularization, and stroke within 1 month of the index procedure.

Results The 1-month technetium 99m sestamibi scintigraphy revealed similar infarct size (16.2% ± 14.6% vs 15.0% ± 14.1%, $P = .703$) and severity (0.48 ± 0.18 vs 0.49 ± 0.15, $P = .592$) in the clopidogrel group as compared with the ticlopidine group. Three-hour ST-segment resolution rate was similar in the 2 study groups (86% vs 89%, $P = .642$). At 1 month, there was no difference in major cardiovascular adverse event rate (3% vs 3%, $P = .988$). Discontinuation of thienopiridine therapy within the first month occurred in no patient randomized to clopidogrel and in 3 (4.5%) patients randomized to ticlopidine ($P = .082$).

Conclusion Clopidogrel has no impact on the effectiveness of myocardial reperfusion in patients with AMI treated routinely with stenting and abciximab. However, clopidogrel, administered as a 600-mg loading dose followed by 75 mg daily, is safe and at least as effective as the standard ticlopidine therapy in this subgroup of patients. (Am Heart J 2005;150:220.e1-220.e5.)

Inflammatory processes after mechanical restoration of flow in acute myocardial infarction (AMI) play a central role in decreasing the effectiveness of reperfusion at microcirculatory level. Some effective pharmacologic therapies in patients with AMI provide a benefit that is related to their anti-inflammatory properties that are distinct from their perceived primary mechanism of action. This is the case of abciximab that provides an early protective effect against stented vessel failure due to the inhibition of IIb/IIIa platelet receptor and a relevant effect at microcirculatory level with the inhibition of the inflammatory cascade started by atherothrombotic and platelet aggregates at microcirculatory level and subsequent leukocytes activation, resulting in increased myocardial salvage and smaller infarcts.[1,2]

Several studies suggest that the antiplatelet agent clopidogrel may exert a protective effect against adverse cardiovascular events by virtue of its anti-inflammatory properties as well. Recently, it has been shown that clopidogrel may reduce platelet-leukocyte aggregates and P-selectin expression.[3,4] Formation of

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platelet-leukocyte aggregates through the CD62 ligand is one of the mechanisms by which leukocytes contribute to inflammation, and clopidogrel may inhibit the expression of CD62 ligand.[4] Thus, there is the potential for a synergistic anti-inflammatory effect of clopidogrel as adjunctive treatment to abciximab.[5]

To evaluate the impact of clopidogrel therapy (600-mg loading dose followed by 75 mg daily) on effectiveness of myocardial reperfusion in patients with ST-segment elevation AMI undergoing routine infarct-related artery (IRA) stent implantation and receiving routine abciximab therapy, we performed an unblinded randomized trial comparing clopidogrel with standard ticlopidine therapy.

We chose to treat control arm patients with ticlopidine (250 mg twice daily) because it has became the reference antithrombotic therapy after coronary stenting, although full effect requires a few days because of the delayed onset of action.[6] On the contrary, clopidogrel (an antiplatelet agent closely related to ticlopidine in chemical structure and action) does not cause the adverse events that limit ticlopidine therapy and has a faster onset of action, especially when early activity is achieved by a clopidogrel loading dose.[7]

Methods

Study population

Criteria for enrolment included (1) chest pain persisting >30 minutes associated with ST-segment elevation of at least 0.1 mV in ≥2 contiguous electrocardiographic leads and (2) admission within 12 hours of symptom onset. Patients with cardiogenic shock due to predominant ventricular failure were included. Cardiogenic shock due to predominant ventricular failure was defined as systolic blood pressure <90 mm Hg (without inotropic or intra-aortic balloon support) that is thought to be secondary to ventricular dysfunction and associated with signs of end-organ hypoperfusion such as cold or diaphoretic extremities or altered mental status or anuria. The exclusion criteria included ongoing thienopiridine therapy, previous myocardial infarction, previous administration of fibrinolytic therapy, participation in another study, inability to obtain informed consent, and a reference IRA diameter <2.5 mm. Evidences of massive coronary thrombus, diffuse disease, a major branch involved in the culprit lesion, or severe vessel tortuosity were not considered contraindications to IRA stenting. The use of thrombectomy and direct stenting was at discretion of the operator.

Before catheterization, patients received 250 mg of aspirin intravenously.

After coronary angiography, patients were randomly assigned to clopidogrel (600 mg) or ticlopidine (500 mg). Randomization was carried out by computer-generated sequence, and assignment was performed using a closed envelope system. Thienopiridine loading dose was administered immediately before the intervention.

All randomized patients received abciximab if not contraindicated (ReoPro, Centocor, Malvern, Pa) immediately before the procedure as a bolus of 0.25 mg/kg of body weight followed by a 12-hour infusion at a rate of 0.125 μg/kg per minute. Heparin was given as an initial bolus of 70 U/kg, and additional boluses were administered during the procedure to achieve an activated clotting time of 200 to 300 seconds.

Patients were thereafter treated with aspirin (325 mg/d indefinitely), and ticlopidine (250 mg twice daily for 6 months) or clopidogrel (75 mg daily for 6 months), as previously assigned. The use of atorvastatin was strongly encouraged at discharge. The study protocol was approved by the institutional Ethical Committee and patient's informed consent was obtained.

End points and outcome measures

The primary end point of the study was infarct size as assessed by technetium 99m (^{99m}Tc) sestamibi scintigraphy at 1 month. The secondary end points were (1) the effectiveness of myocardial reperfusion as assessed by ST-segment elevation resolution analysis within 3 hours of procedure and (2) 1-month clinical outcome, as a composite of death from any cause, reinfarction, target vessel revascularization, and stroke within 1 month of the index procedure (patients with >1 event were assigned the highest-ranked event according to the previous list).

The 1-month ^{99m}Tc sestamibi scintigraphic determinations of infarct size and severity at 1 month were performed as previously described.[8]

A 12-lead electrocardiogram was recorded before procedure and 3 hours after IRA recanalization. The ST-segment changes were evaluated in the single lead with the most prominent ST-segment elevation before mechanical intervention. The ST-segment elevation was measured to the nearest 0.5 mm at 60 milliseconds after the J point with the aid of handheld calipers. According to a previous report,[9] early ST-segment elevation resolution was defined as ≥50% decrease in ST-segment elevation after IRA recanalization. Investigators who were unaware of patient treatment assignment and clinical outcome performed independent analyses of the electrocardiograms, scintigraphies, and angiographies.

Creatine kinase (CK), white blood cell, and platelet count measurements were systematically performed on admission and every 3 hours for the subsequent 24 hours and then every 12 hours for 2 days. The peak value of CK and the time-to-peak CK was estimated for each patient. Blood samples for C-reactive protein and creatinine measurements were drawn on patient's admission.

Reinfarction was defined as recurrent chest pain with ST-segment or T-wave changes and recurrent elevation of cardiac enzymes. Repeat target vessel revascularization was defined as coronary angioplasty or coronary surgery performed because of restenosis or reocclusion of the IRA. Stroke was defined as an acute neurologic defect that lasts >24 hours and results in death or inability to perform normal activities.

Statistical analysis

The sample size was calculated on the assumption that clopidogrel therapy reduces 1-month scintigraphic infarct size by 30%. To detect a difference with 80% power and a type I error (α) of .05, 200 patients per group were required. Interim analyses were planned after one third (N = 133) of study patient enrollment. Discrete data are summarized as frequencies, whereas continuous as mean ± SD. χ^2 Test analysis was used for comparison of categorical variables. Student *t* test was used

Table I. Baseline characteristics

	Clopidogrel (n = 66)	Ticlopidine (n = 67)	P
Age (y)	66 ± 12	69 ± 13	.154
Male	47 (71)	45 (67)	.613
Current smoker	18 (27)	26 (39)	.158
Hypertension	31 (47)	31 (47)	.935
Cholesterolemia >200 mg/dL	27 (41)	18 (27)	.087
Diabetes mellitus	8 (12)	14 (21)	.173
Anterior infarct location	35 (53)	29 (43)	.261
Cardiogenic shock	5 (8)	5 (8)	.980
Infarct artery			.471
Left anterior descending artery	35 (53)	29 (43)	
Right coronary artery	24 (36)	31 (46)	
Circumflex coronary artery	7 (11)	6 (9)	
Venous graft	0 (0)	1 (2)	
Multivessel disease	37 (56)	34 (51)	.539
Preprocedural TIMI grade flow 0-1	53 (80)	52 (78)	.703
Time of ischemia (h)	3.5 ± 2.0	3.1 ± 1.8	.225
C-reactive protein (mg/L)	3.32 ± 4.43	2.44 ± 3.00	.286
White blood cell count (10^9/L)	10.9 ± 3.8	11.4 ± 3.6	.434
Creatinine (mg/dL)	1.18 ± 0.99	1.11 ± 0.39	.579

Values are presented as number (%) or mean ± SD.

to test differences among continuous variables. Because of the asymmetrical distribution of infarct size values, the Mann-Whitney *U* test was used for the primary end point. All analyses were conducted according to the intention-to-treat principle. $P < .05$ was considered significant. Analyses were performed with SPSS for Windows, version 11.5 (SPSS Inc, Chicago, Ill).

Results

Between December 2003 and August 2004, a total of 133 patients were randomized to clopidogrel (n = 66) or ticlopidine (n = 67) therapy. The trial was stopped prematurely (after the enrollment of one third of the planned patients) because of no detectable trend toward infarct size reduction by clopidogrel treatment.

The reasons for exclusion of 32 patients from randomization were ongoing thienopiridine therapy (9 patients), previous myocardial infarction (9), participation in another study (7), IRA diameter <2.5 mm (4), and inability to obtain informed consent (3).

Table I summarizes the baseline patient characteristics and Table II the procedural data. Patients randomized to clopidogrel were younger and had a greater incidence of dyslipidemia and a lower incidence of diabetes and smoking, but all these differences did not reach statistical significance. There were no differences in procedural success between the 2 groups. All study patients had IRA stenting. Nearly all patients of both groups received abciximab treatment.

Table II. Procedural data

	Clopidogrel (n = 66)	Ticlopidine (n = 67)	P
Intra-aortic balloon counterpulsation	6 (9)	4 (6)	.495
Abciximab administration	63 (96)	66 (99)	.303
Rheolytic thrombectomy	25 (38)	27 (40)	.775
Infarct artery stenting	66 (100)	67 (100)	1.000
Direct stent implantation	38 (58)	40 (60)	.803
Multiple stents implantation	12 (24)	13 (26)	.817
Procedural success	64 (97)	66 (98)	.221
Peak CK value (U/L)	2886 ± 2768	2585 ± 2381	.503
Time-to-peak CK (h)	6.6 ± 4.6	6.5 ± 3.9	.942
Bleeding complications	2 (3)	1 (2)	.550
Neutropenia (<1.5 × 10^9/L)	0 (0)	0 (0)	1.000
Thrombocytopenia (<100 × 10^9/L)	1 (2)	1 (2)	.990
ACE inhibitors recommended at discharge	57 (86)	56 (86)	.972
β-Blockers recommended at discharge	25 (38)	19 (29)	.295
Statins recommended at discharge	60 (92)	55 (82)	.121

Values are presented as number (%) or mean ± SD. *ACE*, Angiotensin-converting enzyme.

Table III. One-month outcomes

	Clopidogrel (n = 66)	Ticlopidine (n = 67)	P
^{99m}Tc sestamibi infarct size (%)	16.2 ± 14.6	15.0 ± 14.1	.703
^{99m}Tc sestamibi infarct severity	0.48 ± 0.18	0.49 ± 0.15	.592
3-hour ST-segment elevation resolution	50 (86)	49 (89)	.642
Death	1 (1.5)	2 (3)	.568
Reinfarction	1 (1.5)	0 (0)	.312
Target vessel revascularization	0 (0)	0 (0)	1.000
Stroke	0 (0)	0 (0)	1.000
Composite 1-month adverse events	2 (3)	2 (3)	.988

Values are presented as number (%) or mean ± SD.

Bleeding complications requiring blood transfusion, neutropenia (<1.5 × 10^9/L), and thrombocytopenia (<100 × 10^9/L) occurred in 3%, 0%, and 1% of the patients randomized to clopidogrel and in 2%, 0%, and 2% of the patients randomized to ticlopidine, respectively (P = NS).

Discontinuation of thienopiridine therapy within the first month occurred in no patient randomized to clopidogrel and in 3 (4.5%) patients randomized to ticlopidine ($P = .082$). The causes for discontinuation were gastrointestinal disorder (n = 2) and bleeding (n = 1).

The end point rates and outcomes are summarized in Table III. The 1-month ^{99m}Tc sestamibi scintigraphy revealed similar infarct size and severity in the clopidogrel

group as compared with the ticlopidine group. Three-hour ST-segment resolution rate was similar in the 2 study groups. At 1 month, there were no differences in major cardiovascular adverse event rates. The causes of death were free wall rupture in 1 patient randomized to clopidogrel and refractory heart failure in 2 patients randomized to ticlopidine. Reinfarction occurred at day 4 in 1 patient randomized to clopidogrel due to subacute stent thrombosis treated with thrombectomy and a new angioplasty procedure.

Discussion

Catheter-based reperfusion with adjunctive abciximab therapy is considered nowadays as the preferred reperfusion therapy for patients with AMI.[10,11] In fact, abciximab provides an early protective effect against stented vessel failure due to the inhibition of IIb/IIIa platelet receptor, and a relevant effect at microcirculatory level with the inhibition of the inflammatory cascade. In clinical practice, clopidogrel, an antiplatelet agent with anti-inflammatory properties, is frequently administered in patients undergoing coronary stent implantation. Thus, there is the potential for a synergistic anti-inflammatory effect during the reperfusion phase, of abciximab and clopidogrel, at least when early activity is achieved by a clopidogrel loading dose.

The present study is the first randomized trial to evaluate the clopidogrel additive anti-inflammatory impact on myocardial reperfusion in patients with AMI undergoing routine primary infarct artery stenting with abciximab as adjunctive therapy.

This trial was stopped prematurely because of the evidence of no clopidogrel treatment effect on the primary end point (final infarct size) at the interim analysis. We found no difference in final infarct size and severity as well as ST-segment elevation resolution, a reliable parameter of reperfusion at tissue level,[12,13] between patients randomized to clopidogrel and those randomized to ticlopidine. Likely, the well-known benefit of clopidogrel treatment in patients with acute coronary syndromes is not related to an increased myocardial salvage and to smaller infarcts. However, the results of this negative study allow some speculations.

Secondary end point data are consistent with the hypothesis that 1-month adverse event rates, including stent thrombosis and recurrent ischemic events, are similar in patients treated with clopidogrel as compared with those treated with ticlopidine. Clopidogrel (with a loading dose) and ticlopidine therapy seems to provide comparable efficacy in patients with AMI undergoing routine infarct artery stenting, with abciximab as adjunctive therapy. The dose of thienopiridine given at the time of primary stenting appears to have no impact on clinical outcomes in patients routinely treated with abciximab.

Clopidogrel treatment showed once again its good tolerability. These results, achieved in patients with ST-elevation AMI undergoing IRA primary stenting, are consistent with previous randomized trials comparing the outcome of clopidogrel and aspirin with ticlopidine and aspirin in unselected patients undergoing intracoronary stent implantation.[14-17]

Study limitations

First, the present study was not powered to draw definitive conclusions on clinical outcome and the patient population was at relatively low risk (first AMI). A large-scale, multicenter, randomized trial is needed to evaluate the impact on clinical outcome of clopidogrel treatment after IRA stenting. Second, a longer follow-up period would be required to evaluate the actual long-term benefit of clopidogrel treatment in patients with ST-elevation AMI.[18,19] Third, the medication use was not blind. However, the end point measurements were evaluated by investigators who were unaware of patient's treatment assignment.

Clinical implications

The results of the present trial underline that clopidogrel, administered as a 600-mg loading dose followed by 75 mg daily, is safe and at least as effective as the standard ticlopidine therapy in patients with ST-elevation AMI treated routinely with stenting and abciximab. In fact, even without an impact on the effectiveness of myocardial reperfusion, this therapeutic regimen was very well tolerated, had a zero side effect–related discontinuation rate, and did not increase the risk of bleeding.

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Appendix A

The following investigators and institutions participated in the CLOTIC trial. Data monitoring: GM Santoro (Director) and E Taddeucci, ARCARD Foundation (Careggi Hospital, Florence, Italy); G Moschi (Director) and G Memisha, ECG Core Laboratory (Division of Cardiology, Careggi Hospital, Florence, Italy); and A Pupi (Director) and R Sciagrà, Nuclear Medicine Core Laboratory (Nuclear Medicine Unit, University of Florence, Florence, Italy).