# Usefulness of *Clopidogrel* in Abolishing the Increased Risk of Reinfarction Associated With Higher Platelet Counts in Patients With ST-Elevation Myocardial Infarction (Results from CLARITY-TIMI 28)

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**Previous studies have demonstrated an association between increased baseline platelet counts and poorer clinical and angiographic outcomes in patients with ST-elevation myocardial infarction (STEMI). We hypothesized that antiplatelet therapy would mitigate the effect of high baseline platelet counts on clinical outcomes. Data were obtained from 3,491 patients with STEMI in the CLARITY-TIMI 28 trial. Patients were categorized into 3 groups based on their baseline platelet counts: $<200 \times 10^3/\mu l$ (group 1), 200 to $300 \times 10^3/\mu l$ (group 2), and $>300 \times 10^3/\mu l$ (group 3). Among placebo-treated patients, reinfarction rates increased in a stepwise fashion as platelet counts increased (3.6%, 5.4%, and 9.0%, respectively, p for trend = 0.0025). When confounders of high platelet counts and correlates of reinfarction were adjusted for in a multivariate model, high platelet counts remained independently associated with increased rates of reinfarction at 30 days in placebo-treated patients; using group 1 as a reference group, multivariate odds ratios were 1.45 (95% confidence interval 0.91 to 2.31, p = 0.119) for patients in group 2 and 1.78 (95% confidence interval 1.03 to 3.08, p = 0.038) for patients in group 3. In contrast, among clopidogrel-treated patients, there was no increase in the risk of reinfarction as the platelet count increased (3.2%, 4.1%, and 3.3%, respectively; p for trend = 0.9073, p for interaction = 0.064). In conclusion, among patients with STEMI who are treated with aspirin and a fibrinolytic agent, high platelet counts on presentation are independently associated with increased rates of reinfarction. Clopidogrel therapy abolishes this increase in the risk of reinfarction as platelet counts increase. These data are consistent with a putative role of platelets in reinfarction.**  **(Am J Cardiol 2006;98: 761–763)**

Improved outcomes in the setting of ST-elevation myocardial infarction (STEMI) are related to early, full, and sustained coronary blood flow. Reinfarction and failure to sustain early restoration of full patency are associated with a doubling of mortality by 2 years.[1] Unfortunately, it is difficult based on clinical characteristics alone to identify patients at risk for reinfarction.[1,2] One simple, easily measurable laboratory test that may aid in this risk assessment is the platelet count, which has been associated with a higher risk of persistent thrombus and recurrent myocardial infarction (MI) after fibrinolytic therapy.[3] Elevated platelet volume has also been associated with a higher risk of adverse outcomes.[4] Previous studies have demonstrated an association between high baseline platelet counts and poorer clinical and angiographic outcomes in patients with STEMI.[3] Consistent with the putative role of platelets in reinfarction, we hypothesized that antiplatelet therapy would mitigate the effect of high baseline platelet counts on clinical outcomes.

## Methods and Results

The study design and the patient population has been previously described in detail elsewhere.[5,6] In brief, the Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction (CLARITY-TIMI) 28 trial randomized, in a 1:1 manner, 3,491 patients presenting with STEMI in a double-blind fashion to the administration of clopidogrel (a 300-mg loading dose to be followed by 75 mg/day) or placebo. In addition, patients were treated with a fibrinolytic agent (choice at the discretion of the treating physician), aspirin (150 to 325 mg on the first day to be followed by 75 to 162 mg/day thereafter), and unfractionated heparin for 48 hours (in patients treated with fibrin-specific fibrinolytic agents). Subsequently, protocol-mandated coronary angiography was performed within 48 to 192 hours after study inclusion. Patients received study

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Table 1
Baseline characteristics by platelet count groups

| Platelet Counts on Presentation | Group 1 (≤200) (n = 734) | Group 2 (201–300) (n = 1,923) | Group 3 (>300) (n = 651) | p Value for Trend |
|---|---|---|---|---|
| Age (yrs) | 60 (52, 68) | 57 (50, 65) | 56 (48, 65) | <0.001 |
| Female gender | 14.3% | 18.3% | 29.3% | <0.001 |
| History of hyperlipidemia* | 39.0% | 39.0% | 36.5% | 0.568 |
| History of hypertension* | 50.6% | 42.1% | 41.5% | <0.001 |
| History of diabetes* | 21.5% | 16.3% | 13.2% | <0.001 |
| Previous MI | 9.8% | 9.2% | 8.3% | 0.621 |
| Smoker | 47.7% | 50.8% | 52.5% | 0.181 |
| Previous percutaneous coronary intervention | 5.6% | 4.7% | 4.3% | 0.474 |
| Anterior MI | 40.7% | 39.6% | 41.8% | 0.602 |
| Previous use of aspirin | 17.4% | 15.1% | 16.6% | 0.308 |
| Type of lytic used | | | | 0.013 |
| Fibrin specific | 63.2% | 69.0% | 70.1% | |
| Nonfibrin specific | 36.5% | 30.6% | 30.0% | |
| None | 0.3% | 0.4% | 0.0% | |
| Time to lytic therapy (h) | 2.9 (1.9, 4.3) | 2.7 (1.8, 4.1) | 2.6 (1.7, 4.3) | 0.04 |
| Killip's class II–IV | 7.8% | 7.6% | 8.5% | 0.779 |
| TIMI STEMI risk score | | | | <0.001 |
| 0–2 | 50.6 | 35.0 | 14.4 | |
| 3–4 | 60.4 | 27.1 | 12.5 | |
| ≥5 | 59.0 | 26.3 | 14.7 | |

* Self-reported.

medication daily up to and including the day of coronary angiography. Percutaneous coronary intervention was performed at the discretion of the investigator. The primary study end point was a composite of occluded infarct-related artery on angiography or death or recurrent infarction before angiography. The trial was approved by each participating center's institutional review board. Written informed consent was obtained from all participating patients.

Platelet counts were obtained at enrollment and were analyzed at the clinical site. For the purpose of this analysis, platelet counts were divided into subgroups of hundreds multiplied by $10^3/\mu$l (group 1 $<200 \times 10^3/\mu$l, group 2 201 to $300 \times 10^3/\mu$l, group 3 $>300 \times 10^3/\mu$l).

Continuous variables are expressed as medians and interquartile ranges. The chi-square test was used for analysis of baseline categorical variables and platelet group. Test for trend across ordered groups was performed for the association of the 3 platelet groups and clinical and angiographic outcomes. A test for interaction was performed for the relation to reinfarction between platelet group and randomized treatment.

A multivariate logistic regression model was used for the analysis of 30-day reinfarction. This model was adjusted for baseline characteristics that significantly differed across platelet groups on univariate analysis (including age, female gender, history of hypertension, history of diabetes, smoking status, time from symptom onset to fibrinolytic treatment, and initial type of heparin used) and clinical correlates of poorer outcomes in STEMI (including anterior infarction, systolic blood pressure on presentation, and Killip's class on presentation). Higher platelet groups were compared with the reference group of patients with a platelet count $<200 \times 10^3/\mu$l. All analyses were performed with STATA 8.2 (STATA Corp., College Station, Texas).

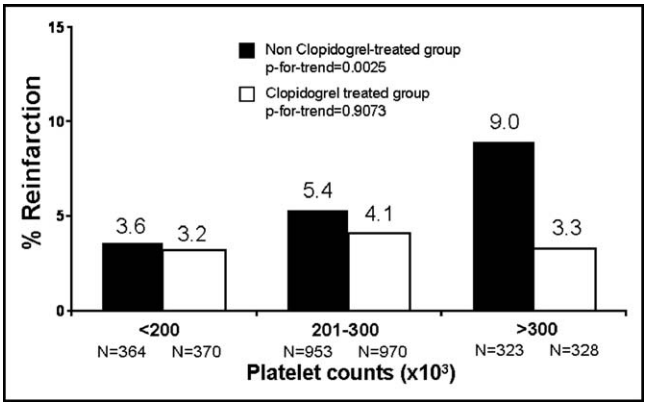


Figure 1. Comparison of association of platelet levels with reinfarction at 30 days among patients who received placebo with those who received clopidogrel. Rates of reinfarction increased in a stepwise fashion with increasing levels of circulating platelets in placebo-treated patients, whereas rates did not differ by increasing levels of circulating platelets in clopidogrel-treated patients.

No significant difference was found between clopidogrel- and placebo-treated patients in the distribution of platelet count groups at baseline (clopidogrel 22.2% in group 1, 58.2% in group 2, and 19.7% in group 3; placebo 22.2%, 58.1%, and 19.7%, respectively) or in median platelet count (clopidogrel median $242.5 \times 10^3/\mu$l, interquartile range 205.5 to 289; placebo median $244 \times 10^3/\mu$l, interquartile range 206 to 287.5). Baseline characteristics of platelet groups are presented in Table 1. The group with increasing platelet count was associated with younger age, more women, fewer patients with history of hypertension

and diabetes, and a shorter time from symptom onset to fibrinolytic therapy (Table 1).

Rates of reinfarction increased in a stepwise fashion with increasing levels of circulating platelets in placebo-treated patients (3.6% in group 1, 5.4% in group 2, and 9.0 in group 3, p for trend = 0.0025; Figure 1). This relation was not evident in clopidogrel-treated patients (3.2% in group 1, 4.1% in group 2, and 3.3% in group 3, p for trend = 0.9073; Figure 1). The interaction term relating reinfarction, platelet group, and randomized treatment was of borderline significance (p = 0.064).

In a multivariate model that was adjusted for age, female gender, history of hypertension, history of diabetes, smoking status, anterior infarction, time from symptom onset to fibrinolytic therapy, systolic blood pressure on presentation, Killip's class on presentation, and initial type of heparin used, high platelet count remained independently associated with increased rates of reinfarction at 30 days. With a reference group with a platelet count of $<200 \times 10^3/\mu$l, the multivariate odds ratios for reinfarction were 1.45 (95% confidence interval 0.91 to 2.31, p = 0.119) for platelet counts between 200 and 300 $\times$ $10^3/\mu$l and 1.78 (95% confidence interval 1.03 to 3.08, p = 0.038) for platelet counts $>300 \times 10^3/\mu$l.

## Discussion

The present study confirms previous observations regarding the independent association of increased platelet levels on presentation with an increased risk of adverse events, particularly the risk of reinfarction in the setting of STEMI. Clopidogrel therapy abolishes this increase in the risk of reinfarction as platelet counts increase. These data are consistent with a role for platelets in reinfarction.

Although the present study demonstrates the putative role of platelets in reinfarction, the role of platelets in the onset of myocardial infarction was demonstrated in a similar fashion in the Physicians' Health Study, a randomized, double-blind, placebo-controlled trial of alternate-day aspirin intake (325 mg) among 22,071 United States male physicians.[7] Physicians randomized to received placebo demonstrated a circadian variation in onset of MI, with a primary peak between 4:00 and 10:00 A.M. (p <0.001). In the aspirin group, however, this circadian variation was minimal, which was predominantly due to a marked decrease in the morning peak of infarction. The greatest decrease was observed during the 3-hour interval immediately after awakening, a period during which the risk of infarction is 2 times that of any other comparable interval (p <0.001). Data from the Physicians' Health Study support the hypothesis that increased platelet aggregability in the morning contributes to the onset of MI and that aspirin decreases the risk of STEMI by inhibiting platelet aggregation during these critical periods.[7]

The present study is a retrospective analysis of data obtained from a single randomized trial (TIMI 28-CLARITY study). Insofar as inclusion and exclusion criteria were applied, the present results apply to the trial's patient population and may not be generalizable to all patients who are encountered in clinical practice.


1. Gibson CM, Karha J, Murphy SA, James D, Morrow DA, Cannon CP, Giugliano RP, Antman EM, Braunwald E. Early and long-term clinical outcomes associated with reinfarction following fibrinolytic administration in the Thrombolysis In Myocardial Infarction trials. *J Am Coll Cardiol* 2003;42:7–16.
2. Hudson MP, Granger CB, Topol EJ, Pieper KS, Armstrong PW, Barbash GI, Guerci AD, Vahanian A, Califf RM, Ohman EM. Early reinfarction after fibrinolysis: experience from the global utilization of streptokinase and tissue plasminogen activator (alteplase) for occluded coronary arteries (GUSTO I) and Global Use of Strategies to Open occluded coronary arteries (GUSTO III) trials. *Circulation* 2001;104: 1229–1235.
3. Turakhia MP, Murphy SA, Pinto TL, Antman EM, Giugliano RP, Cannon CP, Braunwald E, Gibson CM. Association of platelet count with residual thrombus in the myocardial infarct-related coronary artery among patients treated with fibrinolytic therapy for ST-segment elevation acute myocardial infarction. *Am J Cardiol* 2004;94:1406–1410.
4. Martin JF, Bath PM, Burr ML. Influence of platelet size on outcome after myocardial infarction. *Lancet* 1991;338:1409–1411.
5. Sabatine MS, Cannon CP, Gibson CM, Lopez-Sendon JL, Montalescot G, Theroux P, Claeys MJ, Cools F, Hill KA, Skene AM, et al, for the CLARITY-TIMI 28 Investigators. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005;352:1179–1189.
6. Sabatine MS, McCabe CH, Gibson CM, Cannon CP. Design and rationale of Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis In Myocardial Infarction (CLARITY-TIMI) 28 trial. *Am Heart J* 2005; 149:227–233.
7. Ridker PM, Manson JE, Buring JE, Muller JE, Hennekens CH. Circadian variation of acute myocardial infarction and the effect of low-dose aspirin in a randomized trial of physicians. *Circulation* 1990;82:897–902.