The Role of Clopidogrel in Early and Sustained Arterial Patency After Fibrinolysis for ST-Segment Elevation Myocardial Infarction

The ECG CLARITY–TIMI 28 Study

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OBJECTIVES
This study was designed to determine the relationship between clopidogrel and early ST-segment resolution (STRes) and the interaction of the two with clinical outcomes after fibrinolysis.

BACKGROUND
ST-segment resolution is an early noninvasive marker of coronary reperfusion. The CLARITY–TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28) trial randomized 3,491 patients with ST-segment elevation myocardial infarction (STEMI) undergoing fibrinolysis to clopidogrel versus placebo. ST-segment resolution was defined as complete (>70%), partial (30% to 70%), or none (<30%).

RESULTS
Electrocardiograms were valid for interpretation in 2,431 patients at 90 min and 2,087 at 180 min. There was no difference in the rate of complete STRes between the clopidogrel and placebo groups at 90 min (38.4% vs. 36.6% at 90 min). When patients were stratified by STRes category, treatment with clopidogrel resulted in greater benefit among those with evidence of early STRes, with greater odds of an open artery at late angiography in patients with partial (OR 2.0, p < 0.001) STRes, but no improvement in those with no STRes at 90 min (OR 0.89, p = 0.48) (p for interaction = 0.003). Clopidogrel was also associated with a significant reduction in the odds of an in-hospital death or myocardial infarction in patients who achieved partial (OR 0.30, p = 0.003) or complete STRes at 90 min (OR 0.49, p = 0.056), whereas clinical benefit was not apparent in patients who had no STRes (OR 0.98, p = 0.95) (p for interaction = 0.027). By 30 days, the clinical benefit of clopidogrel was predominately seen in patients with complete STRes.

CONCLUSIONS
Clopidogrel appears to improve late coronary patency and clinical outcomes by preventing reocclusion of open arteries rather than by facilitating early reperfusion. (J Am Coll Cardiol 2006;48:37–42) © 2006 by the American College of Cardiology Foundation

The principal goals in the treatment of patients presenting with ST-segment elevation myocardial infarction (STEMI) with fibrinolytic agents are to achieve early reperfusion and to sustain arterial patency in the days following presentation (1). The resolution of ST-segment elevation on serial electrocardiogram (ECG) has been shown to be a simple surrogate of epicardial and myocardial reperfusion (2–6) and improved ST-segment resolution (STRes) is a marker of good short- and long-term prognosis (3,7–10). Maintaining sustained patency after fibrinolysis is clinically important because patients remain at risk for recurrent ischemia, myocardial infarction (MI), or death, likely due to abrupt reocclusion of the infarct related artery (11,12).

In the CLARITY–TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction-28) trial, clopidogrel in combination with fibrinolytic treatment was shown to reduce the rate of occluded infarct-related artery, death, or MI, with no associated increase in the rate of TIMI major and minor bleeding (13). There are several potential mechanisms by which clopidogrel may have improved both coronary artery flow on late angiography and clinical outcomes. One possibility is that, like the glycoprotein IIb/IIIa inhibitors (14), clopidogrel facilitated initial fibrinolysis and thereby improved early reperfusion. Conversely, clopidogrel may have not improved initial fibrinolysis but instead maintained patency over the days following fibrinolysis in arteries that were completely or partially opened. The CLARITY–TIMI 28 trial offers the ability to understand better the beneficial mechanism of action of clopidogrel by using early STRes as a marker of early reperfusion and using late angiography to determine the rate of late infarct-related artery patency (Fig. 1).

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Manuscript received January 6, 2006; revised manuscript received February 9, 2006, accepted February 14, 2006.

Acute Myocardial Infarction
METHODS
Patient selection and procedures. The CLARITY–TIMI 28 trial enrolled 3,491 patients who presented with ischemic discomfort at rest within 12 h before randomization, had ST-segment elevation of at least 0.1 mV in at least two contiguous limb leads, ST-segment elevation of at least 0.2 mV in at least two contiguous precordial leads, or left bundle-branch block that was not known to be old. Inclusion and exclusion criteria have been described previously (13,15). Patients were randomly assigned in a 1:1 ratio to receive either clopidogrel (300 mg loading dose followed by 75 mg once daily) or placebo for up to and including the day of coronary angiography. All patients were to be treated with a fibrinolytic agent (selected by the treating physician); aspirin; and, for those receiving a fibrin-specific lytic agent, heparin for 48 h. As part of a prespecified substudy, ECGs were performed at baseline before fibrinolysis at 90 min and 180 min after the administration of the loading dose of study drug.

Outcomes. Each ECG was analyzed by two investigators at TIMI ECG Core Laboratory, who were blinded to study treatment and outcomes, using a hand-held electronic caliper (Fowler Inc., Newton, Massachusetts). The ST-segment deviation was measured 20 ms after the J point in all leads. For anterior MI, the sum of ST-segment elevation in leads V1 to V6, I, and aVL was added to the sum of ST-segment depression in leads II, III, and aVF. For inferior MI, the sum of ST-segment elevation in leads II, III, aVF (and I, aVL, V5, and V6, if present) was added to the sum of ST-segment depression in leads V1 to V4.

Reciprocal ST-segment depression was used only in leads with ≥0.1 mV of ST-segment depression at baseline (7). The percent resolution of ST-segment deviation from baseline to 90 was calculated and categorized according to a previously described three-component definition: complete (>70%) STRes, partial (30% to 70%) STRes, and no (<30%) STRes (7). All coronary angiograms were analyzed in the TIMI Angiographic Core Laboratory by readers blinded to treatment assignment, STRes, and clinical end points. Flow in the infarct-related artery was reported using the TIMI flow grading system, where an occluded infarct related artery is defined as TIMI flow grade 0 or 1 (16). The definitions of recurrent MI and other efficacy end points have been described previously (15). Coronary angiography was performed during the index hospitalization 48 to 192 h (median 84 h) after the start of study medication to assess for late patency of the infarct-related artery. Patients were followed clinically for 30 days.

Statistical analysis. For the comparison of baseline characteristics between treatment groups, a chi-square test was performed for categorical variables and a Wilcoxon rank-sum test for continuous variables. All comparisons between treatment groups were performed with a prospectively defined logistic regression model that included terms for the treatment group, the type of fibrinolytic agent used, the type of heparin used, and the location of the infarct (13). The interactions among treatment strategy, STRes category, and outcomes were analyzed using the previous described multivariable model with addition of an interaction term of treatment strategy × STRes variables. The statistical significance for interaction was derived from the difference in the likelihood ratios between the logistic regression models with and without the interaction terms.

RESULTS
Of the 3,491 patients enrolled in the CLARITY–TIMI 28 trial, 2,431 (70%) had ECGs both at baseline and 90 min that were valid for interpretation and were included in this analysis. Patients were excluded if their ECG had insuffi-
cient ST-segment deviation, revealed a left bundle-branch block or accelerated idioventricular rhythm, or were determined to be unreadable due to poor quality. There were no important differences in baseline characteristics and initial therapy between the two treatment groups among the 2,431 patients in whom 90-min STRes could be calculated (Table 1), nor between those with and without evaluable serial ECGs (data not shown).

Effect of clopidogrel on STRes. There was no difference at 90 min in the degree of mean STRes between the clopidogrel and the placebo groups (40.4% vs. 39.5% resolution, p = NS), which corresponded to similar rates of complete STRes (38.4% vs. 36.6%, respectively [adjusted odds ratio [OR] 1.08, 95% confidence interval [CI] 0.91 to 1.29]), partial STRes (31.9% vs. 35.7%), or no STRes (29.9% vs. 28.9%). There was greater STRes among all patients at 180 min but, again, no difference in terms of mean STRes (55.0% vs. 57.1% resolution, p = NS) or rates of complete STRes (52.4% vs. 53.6%, p = NS).

Treatment effect of clopidogrel according to STRes category. To examine the relationship between treatment with clopidogrel and outcomes according to the presence of early reperfusion, patients were stratified according to STRes category at 90 min. Clopidogrel resulted in improved epicardial flow (TIMI flow grade 2 or 3) at late angiography in all STRes categories (95.2% vs. 88.7%, adjusted OR 2.6, 95% CI 1.5 to 4.3, p = 0.001 for complete STRes; 87.7% vs. 83.4%, adjusted OR 1.4, 95% CI 0.94 to 2.1, p = 0.09 for partial STRes; and 80.2% vs. 73.0%, adjusted OR 1.5, 95% CI 1.0 to 2.2, p = 0.03 for no STRes, p for interaction = 0.89) Importantly, clopidogrel resulted in greater odds of optimal epicardial flow (TIMI flow grade 3) in patients with complete or partial STRes, but no improvement in those with no STRes (p for interaction = 0.003) (Fig. 2).

In terms of clinical events, clopidogrel significantly reduced the odds of in-hospital death or MI in patients who achieved partial STRes (adjusted OR 0.30, 95% CI 0.13 to 0.67, p = 0.003) and was associated with a strong trend in reduced risk in patients with complete STRes (adjusted OR 0.49, 95% CI 0.24 to 1.02, p = 0.056), whereas the clinical benefit of clopidogrel over placebo was not apparent in patients who had no STRes (adjusted OR 0.98, 95% CI 0.58 to 1.68, p = 0.95, interaction p = 0.027) (Fig. 3).

By 30 days, treatment with clopidogrel resulted in a significantly lower odds of death or MI in patients with complete STRes (Fig. 4A). A similar relationship was seen for both MI and mortality alone. Patients with complete STRes had more than 60% reduction in the odds of a recurrent MI (adjusted OR 0.37, 95% CI 0.20 to 0.71, p = 0.002), whereas a more modest benefit was observed in those with partial STRes (adjusted OR 0.67, 95% CI 0.32

### Table 1. Baseline Characteristics and Initial Treatment in Patients With Baseline and 90-min Electrocardiograms Valid for ST-Segment Resolution Analysis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Clopidogrel (n = 1,239) %</th>
<th>Placebo (n = 1,192) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean)</td>
<td>57.6</td>
<td>57.3</td>
</tr>
<tr>
<td>Age &gt;65 yrs old</td>
<td>27.3</td>
<td>24.8</td>
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<tr>
<td>Male</td>
<td>81.0</td>
<td>81.0</td>
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<tr>
<td>Caucasian</td>
<td>89.4</td>
<td>88.9</td>
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<td>Hypertension</td>
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<td>44.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15.6</td>
<td>17.2</td>
</tr>
<tr>
<td>Prior aspirin</td>
<td>15.0</td>
<td>16.8</td>
</tr>
<tr>
<td>Prior lipid-lowering agent</td>
<td>13.8</td>
<td>14.4</td>
</tr>
<tr>
<td>Presentation</td>
<td></td>
<td></td>
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<tr>
<td>SBP (mean)</td>
<td>134.4</td>
<td>135.3</td>
</tr>
<tr>
<td>HR (mean)</td>
<td>75.1</td>
<td>75.6</td>
</tr>
<tr>
<td>Anterior infarct location</td>
<td>41.8</td>
<td>41.0</td>
</tr>
<tr>
<td>High TIMI risk score (≥5)</td>
<td>14.1</td>
<td>13.0</td>
</tr>
<tr>
<td>Initial treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time for symptom onset to lytic, h (median)</td>
<td>2.72</td>
<td>2.72</td>
</tr>
<tr>
<td>Time from lytic to study drug, min (median)</td>
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<td>10</td>
</tr>
<tr>
<td>Time from baseline ECG to lytic, min (median)</td>
<td>33</td>
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<td>Before-hospital randomization</td>
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<tr>
<td>Fibrin specific lytic</td>
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<td>65.4</td>
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<tr>
<td>Initial heparin</td>
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<tr>
<td>Unfractionated heparin</td>
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<tr>
<td>Low-molecular-weight heparin</td>
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<td>28.4</td>
</tr>
<tr>
<td>No heparin</td>
<td>20.9</td>
<td>22.1</td>
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<tr>
<td>Subsequent Treatment</td>
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<td></td>
</tr>
<tr>
<td>PCI during index hospitalization</td>
<td>53.8</td>
<td>52.5</td>
</tr>
<tr>
<td>Open-label clopidogrel after discharge</td>
<td>51.8</td>
<td>51.3</td>
</tr>
<tr>
<td>Open-label ticlodipine after discharge</td>
<td>3.2</td>
<td>3.3</td>
</tr>
</tbody>
</table>

The p values for all comparisons are nonsignificant.
ECG = electrocardiogram; HR = heart rate; PCI = percutaneous coronary intervention; SBP = systolic blood pressure; TIMI = Thrombolysis In Myocardial Infarction.
to 1.36, \( p = 0.27 \) and no clear benefit in patients with no STRes (adjusted OR 0.80, 95% CI 0.44 to 1.45, \( p = 0.46 \)) (interaction \( p = 0.93 \)). The 30-day mortality rate was low among patients with complete STRes who received clopidogrel (0.6%), though the benefit of clopidogrel in patients with complete STRes was borderline (\( p = 0.058 \)) and interaction was not significant (Fig. 4B). Similar results were seen with the 180-min ECGs.

**DISCUSSION**

In this study, we demonstrate the significant interaction between early STRes and the benefit of clopidogrel on late angiographic and clinical outcomes. Specifically, clopidogrel did not appear to facilitate early reperfusion as determined by STRes, but late optimal arterial flow (TIMI flow grade 3) was improved with significantly greater efficacy in patients with complete STRes. Analogously, and consequently, clopidogrel significantly reduced death or recurrent MI in patients who achieved early STRes. Thus, our data suggest clopidogrel improves clinical outcomes by preventing reocclusion rather than by facilitating early reperfusion.

The pharmacokinetics of clopidogrel may explain how this drug led to significant clinical benefit by preventing reocclusion of open arteries without facilitating early reperfusion as detected by STRes. In platelet aggregation studies, a loading dose of 300 mg of clopidogrel begins to exert its full antiplatelet effects after a few hours, but this effect is not maximal by 90 or 180 min when the serial ECGs were recorded. Thus, the lack of benefit on early reperfusion was...
likely due to the modest additional platelet inhibition at the time of peak fibrinolytic activity. In prior studies of intravenous glycoprotein IIb/IIIa inhibitors, greater platelet receptor occupancy and inhibition was associated with improved STRes and angiographic findings (17) and reduced reinfarction (18), so it is not surprising that the relatively lower platelet inhibition seen within the first hours after 300 mg of clopidogrel did not result in improved reperfusion. Clopidogrel significantly improved late infarct-related arterial patency at a median of 3.5 days—when clopidogrel’s full effect on inhibition of platelet inhibition has been reached—with greater benefit in those with early STRes. This speaks to both the dynamic nature of thrombotic occlusions in the hours following fibrinolysis and the benefit of sustained antiplatelet effect after reperfusion. Longer follow-up may be required to detect the clinical benefit of an open artery in those patients with poor early STRes (19).

The relationship between STRes and mortality is even more striking in regards to clopidogrel versus placebo. Patients who achieved complete STRes by 90 min and received clopidogrel had a 30-day mortality rate of only 0.6%, compared with 2.3% in patients receiving a placebo; thus, patients presenting with STEMI who achieve early complete STRes and receive clopidogrel can be identified within the first hours of hospitalization and appear to represent a very low-risk population. Conversely, patients with failed STRes may require immediate angiography.

It should be noted that the clinical benefit of clopidogrel was apparent within the first few days of hospitalization in the overall CLARITY–TIMI 28 trial with an early separation of the event curves (13). Moreover, pretreatment with
Clopidogrel in patients undergoing PCI, including within 6 h of randomization, resulted in a significant clinical benefit (20). Finally, a statistically significant clinical benefit of clopidogrel was also observed within the first day in the COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction) trial, in which 45,852 patients with STEMI were randomized to 75 mg of clopidogrel or placebo (21). Therefore, early use of 300 mg of clopidogrel should be given at the time of presentation in patients without contraindications in order to prevent reocclusion and thus death and ischemic complications.

**Study limitations.** Although the percentages of interpretable ECGs were similar in the two treatment arms, STREs were similar in the two treatment arms, STRes studies (8,18).

**Clinical implications.** The addition of clopidogrel to fibrinolytic agents improves angiographic and clinical outcomes predominantly in those patients who achieve early STREs by maintaining arterial patency and preventing reocclusion. Because there was no increased risk of bleeding, clopidogrel treatment with a 300-mg loading dose should be considered in all patients younger than 75 years receiving fibrinolysis for STEMI (and 75 mg in all patients with STEMI based on the COMMIT trial [21]). Careful surveillance of STREs in the first hours after receiving clopidogrel and a fibrinolytic agent will identify patients with failed fibrinolysis who require immediate mechanical revascularization to establish myocardial perfusion. On the other hand, patients treated with clopidogrel who achieve early STREs are at very low risk for death or recurrent MI and do not appear to require an early invasive approach.

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**REFERENCES**