Benefit of Clopidogrel in Patients With Acute Coronary Syndromes Without ST-Segment Elevation in Various Risk Groups

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Background—The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial demonstrated that clopidogrel, given early and continued long term, was superior to placebo in patients with non-ST–elevation acute coronary syndromes receiving aspirin. The purpose of the present analysis was to estimate the treatment effect of clopidogrel in patients who were stratified according to their risk of future cardiovascular events.

Methods and Results—Patients (n = 12,562) who presented within 24 hours after the onset of symptoms were randomized to receive clopidogrel (300 mg followed by 75 mg daily) or placebo in addition to aspirin for 3 to 12 months. Treatment effect was analyzed in various risk groups according to the Thrombolysis in Myocardial Infarction (TIMI) risk score. The TIMI risk model was validated in the CURE population (C statistic, 0.634). The primary composite outcome of cardiovascular death, myocardial infarction, or stroke increased proportionally with increasing risk according to the TIMI risk score. The impact of clopidogrel versus placebo on the rate of the primary outcome was as follows: low-risk group (TIMI score 0 to 2), 4.1% versus 5.7% (relative risk [RR], 0.71; 95% confidence interval [CI], 0.52 to 0.97; P < 0.04), intermediate-risk group (TIMI score 3 to 4), 9.8% versus 11.4% (RR, 0.85; 95% CI, 0.74 to 0.98; P < 0.03), and high-risk group (TIMI score 5 to 7), 15.9% versus 20.7% (RR, 0.73; 95% CI, 0.60 to 0.90; P < 0.004). There was no evidence of statistical heterogeneity among the groups.

Conclusions—The benefit of clopidogrel demonstrated in the CURE trial is consistent in low-, intermediate-, and high-risk patients with acute coronary syndromes (as stratified by TIMI risk score), thus supporting its use in all patients with documented non–ST elevation acute coronary syndromes. (Circulation. 2002;106:1622-1626.)

Key Words: angina ■ platelet aggregation inhibitors ■ drugs ■ risk factors

Despite considerable advances in therapy, acute coronary syndromes (ACS) are associated with high mortality and morbidity.1 Risk stratification of patients with ACS enables the identification of patients at various levels of risk of recurrent events who may benefit from more aggressive use of pharmacological and nonpharmacological interventions. In ACS without ST-segment elevation, a variety of factors predicting the risk of subsequent clinical events have been recognized, including baseline demographic variables,2 symptoms,3 electrocardiographic changes,4 and levels of serum cardiac and other biochemical markers.5–8

Several algorithms integrating these variables have been proposed to risk-stratify patients with non–ST elevation ACS.9–11 The Thrombolysis In Myocardial Infarction (TIMI) risk score12 is one such tool; it has been shown to predict both prognosis and response to new therapies12,13 and interventions.14

The Clopidogrel in Unstable angina to prevent Recurrent ischaemic Events (CURE) trial demonstrated a significant 20% risk reduction in the composite outcome of cardiovascular death, nonfatal myocardial infarction, or stroke with clopidogrel compared with placebo in patients with non–ST elevation ACS who were receiving aspirin.15 Benefit was observed in almost every subgroup examined. Patients undergoing percutaneous coronary interventions had a 31% relative risk reduction.16

The purpose of the present analysis was to estimate the treatment effects of clopidogrel in patients who were stratified according to TIMI risk score.
TABLE 1. Distribution of TIMI Risk Factors in Placebo and Clopidogrel Groups

<table>
<thead>
<tr>
<th>Factor</th>
<th>Overall (n=12 562)</th>
<th>Placebo (n=6303)</th>
<th>Clopidogrel (n=6259)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age≥65</td>
<td>6565 (52.3)</td>
<td>3287 (52.1)</td>
<td>3278 (52.4)</td>
</tr>
<tr>
<td>≥3 CAD risk factors</td>
<td>1831 (14.6)</td>
<td>866 (14.1)</td>
<td>945 (15.1)</td>
</tr>
<tr>
<td>Known CAD (/&gt;50% stenosis)</td>
<td>3155 (25.1)</td>
<td>1602 (25.4)</td>
<td>1553 (24.8)</td>
</tr>
<tr>
<td>Aspirin use in past 7 days</td>
<td>8302 (66.1)</td>
<td>4134 (65.6)</td>
<td>4168 (66.6)</td>
</tr>
<tr>
<td>Severe angina within 24 h</td>
<td>12 317 (98.0)</td>
<td>6184 (98.1)</td>
<td>6133 (98.0)</td>
</tr>
<tr>
<td>ST deviation (0.5 mm)</td>
<td>6275 (50.0)</td>
<td>3127 (49.6)</td>
<td>3148 (50.3)</td>
</tr>
<tr>
<td>Elevated cardiac markers</td>
<td>3176 (25.3)</td>
<td>1592 (25.3)</td>
<td>1584 (25.3)</td>
</tr>
</tbody>
</table>

Values are number of patients (%).

Methods

Patients, Study Treatment, and Outcomes

The CURE trial is a randomized, double-blind, placebo-controlled study comparing clopidogrel with placebo in patients with ACS without ST-segment elevation. The design, rationale, and results of the study have been reported previously.15–17

Patients were recruited between December 1998 and September 2000 at 482 centers in 28 countries. Patients could be included in the study if they had been hospitalized within 24 hours after the onset of symptoms and had ischemic changes on ECG but not ST-segment elevation (initially patients ≥60 years of age without new ECG changes but with a history of coronary artery disease [CAD] were enrolled) or already elevated cardiac enzymes or markers to at least twice the upper limit of normal. The exclusion criteria included contraindications to antithrombotic or antiplatelet therapy, high risk for bleeding, requirement for long-term oral anticoagulants, coronary revascularization in the previous 3 months, or administration of intravenous glycoprotein IIb/IIIa inhibitors in the previous 3 days.

Patients were randomly assigned to either the clopidogrel group (loading dose of 300 mg followed by 75 mg daily) or the placebo group; the duration of treatment was 3 to 12 months (mean, 9 months). Aspirin (in the dose range of 75 to 325 mg) was administered concomitantly in both groups.

The primary outcome was the composite of cardiovascular death, nonfatal myocardial infarction, or stroke, and the co-primary outcome was the composite of the primary outcome or refractory angina. The safety-related outcomes were bleeding complications, which were categorized as major (which included life-threatening) or minor. The definitions of outcomes have been described elsewhere.15–17 All primary outcomes and major bleeding complications were adjudicated.

The ethics review board at each participating center approved the study; and the patients gave informed consent.

Approach to Statistical Analysis

The TIMI risk score for non–ST elevation ACS was applied to the CURE patient population.12 Treatment effects were analyzed in various risk groups.

TIMI risk score is based on the following 7 independent risk predictors: (1) age ≥65 years, (2) ≥3 CAD risk factors (family history of CAD, hypertension, hypercholesterolemia, diabetes, and/or current smoking), (3) documented CAD (>50% stenosis on coronary angiography), (4) aspirin use 7 days before hospitalization, (5) at least 2 episodes of angina within 24 hours before hospitalization, (6) ST-segment deviation ≥0.5 mm, and (7) elevated cardiac markers. Some slight modifications of these variables were necessary due to the unavailability or different coding of data in the CURE case report forms. The data on family history of CAD were not available. The results of coronary angiography were derived from the questions “cardiac catheterization showing significant CAD in past history” or “PTCA performed in past history” or “CABG performed in past history.” The use of aspirin was derived from the question “aspirin use regularly prior to randomization,” and episodes of angina were determined from the inclusion criteria “ischemic chest pain or symptoms occurring at rest or with minimal exercise (>5 minutes or requiring nitroglycerin for relief of pain), <24 hours since onset.” ST-segment deviation was coded as “ST depression ≥1 mm, any other ST depression, ST elevation ≤1 mm, or transient ST elevation >2 mm,” and elevated cardiac markers were determined from “any cardiac enzymes elevated to at least twice the upper limit of normal at randomization.”

A full TIMI risk score (points 0 to 7) was calculated separately for placebo and clopidogrel-assigned groups and for all patients. The treatment effects at 12 months were analyzed in each risk subgroup and in categories of low (TIMI score 0 to 2), intermediate (TIMI score 3 to 4), and high (TIMI score 5 to 7) risk.

Statistical Analysis

Descriptive statistics (percentages for discrete variables and mean±SD for continuous variables) were generated for baseline characteristics, TIMI risk score, and predictors in TIMI risk score. Comparisons between placebo and clopidogrel-assigned groups were performed using χ² tests for differences in the proportions of categorical variables and Student’s t test for continuous variables. All tests were 2-sided and considered significant at P<0.05.

The discriminative power of the TIMI risk model was assessed by the mean of the area under the receiver-operating characteristic curve (C statistic).18

The frequencies of outcomes in various risk groups were compared using χ² tests for trends (Coherman-Armitage trend test).19 Tests for heterogeneity were performed to compare the treatment effects in various risk groups. Treatment effects, as measured by relative risk (RR) and 95% confidence interval (CI), were derived with Cox’s proportional hazard model.

All statistical analyses were done using SAS version 8.0 software.

TABLE 2. Validation of TIMI Risk Score/Event Rate in Various Risk Groups at 9 Months

<table>
<thead>
<tr>
<th>Events</th>
<th>0–1 (n=752)</th>
<th>2 (n=2524)</th>
<th>3 (n=3730)</th>
<th>4 (n=3567)</th>
<th>5 (n=1593)</th>
<th>6–7 (n=396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, or stroke</td>
<td>26 (3.5)</td>
<td>136 (5.4)</td>
<td>326 (8.7)</td>
<td>448 (12.6)</td>
<td>275 (17.3)</td>
<td>90 (22.7)</td>
</tr>
<tr>
<td>CV death, MI, stroke, or refractory ischemia</td>
<td>85 (11.3)</td>
<td>274 (10.9)</td>
<td>593 (15.9)</td>
<td>732 (20.5)</td>
<td>420 (26.4)</td>
<td>118 (29.8)</td>
</tr>
<tr>
<td>CV death</td>
<td>10 (1.3)</td>
<td>45 (1.8)</td>
<td>167 (4.5)</td>
<td>245 (6.9)</td>
<td>150 (9.4)</td>
<td>46 (11.6)</td>
</tr>
<tr>
<td>MI</td>
<td>13 (1.7)</td>
<td>87 (3.5)</td>
<td>179 (4.8)</td>
<td>251 (7.0)</td>
<td>158 (9.9)</td>
<td>55 (13.9)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (0.5)</td>
<td>20 (0.8)</td>
<td>40 (1.1)</td>
<td>57 (1.6)</td>
<td>32 (2.0)</td>
<td>9 (2.3)</td>
</tr>
<tr>
<td>Refractory ischemia</td>
<td>61 (8.1)</td>
<td>152 (6.0)</td>
<td>321 (8.6)</td>
<td>357 (10.0)</td>
<td>198 (12.4)</td>
<td>42 (10.6)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>14 (1.9)</td>
<td>59 (2.3)</td>
<td>109 (2.9)</td>
<td>127 (3.6)</td>
<td>73 (4.6)</td>
<td>18 (4.6)</td>
</tr>
</tbody>
</table>

Values are number of patients (%). CV indicates cardiovascular; MI, myocardial infarction.
Results

Key demographic and clinical characteristics of the 12,562 patients enrolled in the CURE trial have been published previously.\textsuperscript{15,17} There were no differences in baseline characteristics between the clopidogrel and placebo groups.

Prediction of Events

The validated TIMI risk model demonstrated moderately good discriminative power in the CURE population (C statistic, 0.634 for the primary outcome at 9 months).

Distribution of factors predicting risk with the use of TIMI risk score is shown in Table 1. The variables proven to be independent predictors of future cardiovascular events were equally distributed in the placebo and clopidogrel groups. The median TIMI risk score for the total CURE population and for the clopidogrel and placebo groups was 3.

In the total study group, all outcomes at 9 months (namely the primary and co-primary composites and their components of cardiovascular death, myocardial infarction, stroke, and refractory angina, as well as major bleeding) increased proportionally with increasing risk, according to TIMI risk score. The data are presented in Table 2 and Figure 1.

Impact of Clopidogrel by Risk Group

Assessment of treatment effects according to TIMI risk score revealed the benefit of clopidogrel in all categories. The effect was significant for the primary and co-primary end points in the majority of categories. There was a consistent benefit of clopidogrel in all risk groups, with no evidence of statistical heterogeneity. The number of patients needed to treat to prevent one event was 63 for the low-risk group, 63 for the intermediate-risk group, and 21 for the high-risk group; clopidogrel was favored in each group. The results are presented in Figures 2 and 3.

The risk of bleeding also increased proportionally with the increase of TIMI risk score. The results concerning bleeding complications with regard to TIMI risk score are presented in Table 3.

Discussion

Our study of therapy with clopidogrel in addition to aspirin in non–ST elevation ACS patients has demonstrated that the TIMI risk score had moderately good discriminative power when applied to the CURE population and that there were consistent and significant benefits of clopidogrel in patients in all risk groups.

Our analysis demonstrated a significant increase of event rate with increasing risk score. The primary and co-primary end points occurred in 3.5% and 11.3% of the patients in the lowest risk group (score 0 to 1) and in 22.7% and 26.4% of patients in the highest risk group (score 6 to 7). The differences existed for each component of composite outcome and were 9-fold for cardiovascular death, 8-fold for myocardial infarction, 5-fold for stroke, and 1-fold for refractory ischemia.

The treatment effect of clopidogrel demonstrated in CURE was consistent in all risk categories. Tests for interactions did not demonstrate significant heterogeneity. However, the absolute benefit increased with increasing TIMI score. This indicates that although all categories of patients will benefit from clopidogrel, the greatest absolute benefit will be in high-risk subjects.

The TIMI risk score has not been evaluated with regard to bleeding complications. However, in our analysis, major bleeding occurred more frequently with increasing risk score. The excess of bleeding with clopidogrel compared with placebo was similar in each category of risk. The tests for interactions for excess of bleeding in each risk group were not
significant. The risk of bleeding in the entire clopidogrel-treated group was proportional to the benefit of this treatment across all categories of risk. The excess hemorrhagic complications did not include life-threatening bleeding. The benefit was also consistent for the composite outcomes of cardiovascular death, myocardial infarction, stroke, and refractory ischemia. Therefore, it seems that the benefit/risk ratio of clopidogrel therapy is maintained across all categories of risk stratification.

The TIMI risk score has been applied to analyze treatment effects in other studies. Stratification according to this algorithm revealed a highly significant gradient of increasing risk for composite outcomes and a strong pattern of increasing benefit of treatment with rising risk. Low-molecular-weight heparin (enoxaparin), a glycoprotein IIb/IIIa inhibitor (tirofiban), and an invasive strategy were effective treatments in the intermediate- and high-risk groups of non–ST elevation ACS patients but not in the low-risk group. Low risk according to TIMI risk score is effective in the low-risk group; this may be explained by prolonged treatment, which enables benefit and delays potential rebound effects.

Risk stratification of the trial population relates to inclusion/exclusion criteria and event rate. Low-risk patients according to the definitions provided by the American College of Cardiology/American Heart Association (ACC/AHA) guidelines were deliberately not recruited into the CURE trial. Similarly, the TIMI 11B and Efficacy and Safety of Clopidogrel in Various Risk Groups (ESSENCE) trial populations, on which the TIMI risk model was built and validated, did not include such low-risk patients. The 1-year event rate of the CURE and ESSENCE trials is similar and relatively high. For CURE, the 9-month rate of cardiovascular death/myocardial infarction was 10.3% in the clopidogrel group and 12.2% in the placebo group; for the ESSENCE trial, the rate of death/myocardial infarction was 11.5% in the enoxaparin group and 13.5% in the heparin group. Low risk according to TIMI risk score can mean intermediate or even high risk by ACC/AHA definition.

Our study has some limitations. This is a retrospective subgroup analysis, but the consistency of the results across different risk categories decreases the probability of bias. There were also some discrepancies in the coding of the TIMI risk score variables due to differences between the CURE, TIMI 11B, and ESSENCE data sets. The model, however, has been statistically validated in the CURE population.

We think that our analysis provides important clinical implications. Clopidogrel should be administered in patients with non–ST elevation ACS who fulfill the inclusion/exclusion criteria of the CURE trial, regardless of their risk characteristics.

In conclusion, the benefit of therapy with clopidogrel in addition to aspirin demonstrated in the CURE trial is consistent and significant in low-, intermediate-, and high-risk patients with non–ST elevation ACS (with risk stratified by the TIMI risk score). High-risk patients derived the greatest absolute benefit.

Acknowledgments

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References


### TABLE 3. Major Bleeding Complications in Low-, Intermediate-, and High-Risk Groups in Placebo- and Clopidogrel-Treated Patients

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Placebo</th>
<th>Clopidogrel</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>32/1674 (1.9)</td>
<td>41/1602 (2.6)</td>
<td>1.34</td>
<td>0.85–2.11</td>
<td>0.21</td>
</tr>
<tr>
<td>Intermediate</td>
<td>96/3626 (2.6)</td>
<td>140/3671 (3.8)</td>
<td>1.44</td>
<td>1.12–1.86</td>
<td>0.005</td>
</tr>
<tr>
<td>High</td>
<td>41/1003 (4.1)</td>
<td>50/986 (5.1)</td>
<td>1.24</td>
<td>0.63–1.86</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Values are number of events/number of patients (%).

Test for interaction for major bleeding, P=0.830.


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