Early and Late Effects of Clopidogrel in Patients With Acute Coronary Syndromes

Salim Yusuf, MBBS; Shamir R. Mehta, MD; Feng Zhao, MSc; Bernard J. Gersh, MB, ChB; Patrick J. Commerford, MB, ChB; Mel Blumenthal, MD; Andrzej Budaj, MD; Thomas Wittlinger, Dr Med; Keith A.A. Fox, MB, ChB; on Behalf of the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) Trial Investigators*

Background—The risk of ischemic events is high, both early and late after acute coronary syndromes (ACS). We examine the benefits and risks associated with the use of adding clopidogrel to aspirin within the first 30 days and later (31 days to 12 months) in 12,562 patients with ACS.

Methods and Results—A total of 12,562 ACS patients were randomized to receive clopidogrel (300 mg initially followed by 75 mg/d) or placebo for 3 to 12 months. The proportion of patients experiencing cardiovascular death, myocardial infarction, or strokes (primary outcome) at 30 days was 5.4% in the placebo group and 4.3% in the active group (relative risk 0.79, 95% CI 0.67 to 0.92). Beyond 30 days, the corresponding rates were 6.3% versus 5.2% (relative risk 0.82, 95% CI 0.70 to 0.95). There was no significant excess in life-threatening bleeds in each period (0.97% versus 1.28%, relative risk 1.32, 95% CI 0.95 to 1.84 for 0 to 30 days; 0.83% versus 0.91%, relative risk 1.09, 95% CI 0.75 to 1.59 for 31 days to 12 months). Further subdivision of the early data indicates benefits within 24 hours with consistently lower rates of the primary outcome in combination with refractory or severe ischemia.

Conclusions—Clopidogrel reduces the risk of ischemic vascular events, with the benefits emerging within 24 hours of initiation of treatment and continuing throughout the 12 months (mean 9 months) of the study. (Circulation. 2003;107: 966-972.)

Key Words: coronary disease ■ prevention ■ platelets

Although unstable angina (UA) and non–ST-elevation myocardial infarction (NSTEMI) are generally considered as acute coronary syndromes (ACS), such patients have a high risk of death, myocardial infarction (MI), or stroke not only early in the hospital phase but also late during the subsequent months and years. Therefore, strategies that prevent these events both early and late are required. The Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) Trial demonstrated the benefits of clopidogrel when added to standard therapy that included aspirin in patients with an ACS. Treatment was initiated within 24 hours of symptom onset and then continued up to 1 year. The present study explores the rapidity with which treatment was effective and its sustainability over 1 year. In addition, we explored the rates of bleeding over the same periods.

Methods
Details of the CURE study design and methods have been published previously. Briefly, CURE was a randomized, double-blind, placebo-controlled trial that compared clopidogrel with placebo in patients with ACS, without ST-segment elevation, who presented to a hospital within 24 hours. After written informed consent had been obtained, 12,562 patients were randomized to receive clopidogrel at an initial dose of 300 mg, followed by 75 mg/d orally or equivalent placebo, for a minimum of 3 months and a maximum of 12 months (mean of 9 months). Approximately 5000 patients were eligible to receive treatment for 1 year. Aspirin was started or continued at doses (75 to 325 mg/d) chosen by the treating physician. All other treatments were at the discretion of individual physicians. Each institution approved the study, and patients provided written informed consent.

The first primary outcome was the composite of cardiovascular death, MI, or stroke; the second primary outcome was the above composite plus refractory ischemia. The definition of refractory ischemia differed in hospital and after discharge. During hospital-
TABLE 1. Effects of Clopidogrel Compared to Placebo by Time Periods

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>% Events</th>
<th>RR (95% CI)</th>
<th>% Events</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death/MI/stroke</td>
<td>Placebo</td>
<td>5.4</td>
<td>Clopidogrel</td>
<td>4.3</td>
</tr>
<tr>
<td>Refractory ischemia</td>
<td>Placebo</td>
<td>4.3</td>
<td>Clopidogrel</td>
<td>3.7</td>
</tr>
<tr>
<td>Severe ischemia†</td>
<td>Placebo</td>
<td>5.0</td>
<td>Clopidogrel</td>
<td>3.8</td>
</tr>
<tr>
<td>CV death/MI/stroke/refractory ischemia</td>
<td>Placebo</td>
<td>9.2</td>
<td>Clopidogrel</td>
<td>7.7</td>
</tr>
<tr>
<td>CV death/MI/stroke/in-hospital severe ischemia</td>
<td>Placebo</td>
<td>11.7</td>
<td>Clopidogrel</td>
<td>9.6</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any major bleeds‡</td>
<td>1.54</td>
<td>2.01</td>
<td></td>
<td>1.31 (1.01–1.70)</td>
</tr>
<tr>
<td>Life-threatening bleeds</td>
<td>0.97</td>
<td>1.28</td>
<td></td>
<td>1.32 (0.95–1.84)</td>
</tr>
<tr>
<td>TIMI major bleeds</td>
<td>0.57</td>
<td>0.58</td>
<td></td>
<td>1.01 (0.64–1.60)</td>
</tr>
<tr>
<td>GUSTO severe/life-threatening bleeds</td>
<td>0.57</td>
<td>0.70</td>
<td></td>
<td>1.23 (0.79–1.91)</td>
</tr>
</tbody>
</table>

RR indicates relative risk; CV, cardiovascular.

*The entire difference in refractory ischemia is due to a difference in events occurring in hospital, with little effect later. Note that the definitions for refractory ischemia during the initial hospitalization and after discharge are quite dissimilar.
†Severe ischemia includes refractory ischemia.
‡Includes life-threatening bleeds.

Results
The characteristics of patients have been described in detail previously. Briefly, the mean age was 64.2 ± 11.3 years, 38.5% were women, and the mean time from pain onset to randomization was 14.2 hours. Baseline characteristics were similar between those randomized to clopidogrel or to placebo. Aspirin was used in 99.8% of patients in hospital, 94.0% at 30 days, 95.6% at 6 months, and 93.5% at study end. Unfractionated or low-molecular-weight heparin was used in 91.4% of patients in hospital. The proportion of patients receiving blinded medication was 88.4% in the clopidogrel group and 87.0% in the placebo group at hospital discharge, 82.9% and 82.1% at 30 days, and 92.2% and 92.1% by study end, respectively. The use of open-label thiopentopyridines/ clopidogrel was 10.7% in the clopidogrel group and 12.1% in the placebo group at hospital discharge, 13.0% and 13.7% at 30 days, and 2.9% and 3.1% at study end.

Overall, 9.3% of patients experienced cardiovascular death, MI, or strokes in the clopidogrel group compared with 11.4% in the placebo group (relative risk 0.80, 95% CI 0.72 to 0.90, \(P<0.0001\)). The results were consistent and statistically significant, both early (≤30 days; relative risk 0.79, \(P<0.004\)) and late (≥30 days; relative risk 0.82, \(P<0.01\); Table 1).

Early Effects of Clopidogrel (0 to 30 Days After Randomization)

Efficacy
From randomization to 30 days, 343 patients (5.4%) developed cardiovascular death, MI, or stroke in the placebo group compared with 270 (4.3%) in the clopidogrel group (relative risk 0.79, 95% CI 0.67 to 0.92; \(P<0.004\); Figure 1). There was also a significant reduction in the composite outcome...
that included cardiovascular death, MI, stroke, or refractory ischemia: 580 (9.2%) in the placebo group versus 480 (7.7%) in the clopidogrel group (relative risk 0.83, 95% CI 0.73 to 0.93, \(P<0.002\)). Addition of severe ischemia to this composite also showed consistent and clear benefits for clopidogrel (740 [11.7%] versus 602 [9.6%], relative risk 0.81, 95% CI 0.73 to 0.90, \(P<0.0001\)).

To explore the rapidity of onset of effects, the expanded composite outcome of the primary outcome plus refractory or severe ischemia was used. Further subdivision of the data indicated a consistent benefit within the first 7 days and between days 8 and days 30 (Table 2). Detailed examination of the data during the first 24 hours after randomization (Tables 3 and 4) indicated a 20% relative risk reduction in the primary outcome and a 34% relative risk reduction in the expanded composite. The latter difference was statistically significant (\(P<0.003\)) even within this relatively brief period. Examination of Figure 2 indicates the very rapid emergence of the treatment benefit, with the curves diverging as early as 4 hours after randomization. Although there was a clear impact in reducing in-hospital refractory ischemia (126 [2.0%] versus 85 [1.4%]; relative risk 0.68, 95% CI 0.52 to 0.90), there was no impact on rehospitalization for unstable angina between discharge and 30 days (143 [2.3%] versus 145 [2.3%]; relative risk 1.02, 95% CI 0.81 to 1.29).

### Bleeding

There was no excess in major bleeds within the first 24 hours with clopidogrel (Table 3). The relative risk of major bleeds was 1.18 (95% CI 0.80 to 1.75, absolute excess 0.13%) at 0

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**TABLE 2. Effects of Clopidogrel Compared With Placebo Within the First Week and Subsequent 3 Weeks**

<table>
<thead>
<tr>
<th>% Events</th>
<th>0 to 7 Days</th>
<th>8 to 30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Clopidogrel</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death/MI/stroke</td>
<td>2.5</td>
<td>2.1</td>
</tr>
<tr>
<td>CV death/MI/stroke/refractory ischemia</td>
<td>4.2</td>
<td>3.5</td>
</tr>
<tr>
<td>CV death/MI/stroke/severe ischemia</td>
<td>6.7</td>
<td>5.2</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CURE criteria for</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeds</td>
<td>0.73</td>
<td>0.86</td>
</tr>
<tr>
<td>Life-threatening bleeds</td>
<td>0.44</td>
<td>0.48</td>
</tr>
<tr>
<td>TIMI major bleeds</td>
<td>0.17</td>
<td>0.19</td>
</tr>
<tr>
<td>GUSTO severe/life-threatening bleeds</td>
<td>0.21</td>
<td>0.21</td>
</tr>
</tbody>
</table>

RR indicates relative risk; CV, cardiovascular.
Late Effects of Clopidogrel (31 Days to 12 Months)

**Efficacy**
During this period, there was a further 18% relative risk reduction in the primary outcome of cardiovascular death, MI, or stroke ($P \leq 0.01$; Figure 1). There was no impact on rehospitalizations for unstable angina with ECG changes (314 [5.2%] clopidogrel versus 318 [5.3%] placebo; relative risk 0.99, 95% CI 0.85 to 1.16) during this period.

**Bleeding**
When the CURE criteria were used, 1.18% of placebo patients and 1.75% of clopidogrel patients experienced a major bleed (relative risk 1.48, 95% CI 1.1 to 1.99, absolute excess 0.57%) over a mean of 8 months. The rate of life-threatening bleeds was 0.83% in the placebo group compared with 0.91% in the clopidogrel group (relative risk 1.09, 95% CI 0.75 to 1.59, absolute excess 0.08%). With the TIMI or the GUSTO criteria, there was no apparent excess in bleeds.

**Benefit-to-Risk Ratio, Overall and by Period**
The number of major vascular events prevented during any period was much greater than the risk of bleeding (life-threatening bleeding was given the same weight as death, MI, or stroke) requiring intervention (Figure 3). Overall, there were 664 patients with one of the above events in the clopidogrel group (10.6%) compared with 785 (12.5%) in the placebo group (relative risk 0.84, 95% CI 0.76 to 0.93, $P < 0.001$). Subdivision of data into events that occurred during the first 30 days (relative risk 0.85, 95% CI 0.74 to 0.99) and beyond (relative risk 0.83, 95% CI 0.72 to 0.96) indicated consistency in results.

**Discussion**
We have demonstrated the consistency of the benefits of clopidogrel both early and late after acute coronary syndromes. In particular, the benefits emerged very rapidly after the first oral administration of clopidogrel, and the absolute difference continued to widen throughout the period of the study. The data are presented separately at 30 days and beyond because this time point has been used previously to evaluate the effects of a number of short-term treatments. The early data were split into narrower intervals to explore the rapidity of benefit. The data beyond 30 days provide information on the incremental benefits beyond the acute phase.

The very rapid emergence of benefit after the oral dose of 300 mg of clopidogrel parallels the rapid impact on inhibition of platelet function. In addition, these effects were achieved on top of aspirin and a thrombin inhibitor and against a broad range of clinical practices in multiple countries. Overall, 99.8% of patients received aspirin, 91.4% received heparin or low-molecular-weight heparin, 78.5% received a β-blocker, 4.5% received intravenous glycoprotein IIb/IIIa inhibitors (approximately two thirds with angioplasty), 46.6% received a lipid-lowering agent, and 36.4% underwent a revascularization procedure. The results were consistent across subgroups defined as those receiving or not receiving these

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**TABLE 3. Effects of Clopidogrel Versus Placebo in First 24 Hours After Randomization**

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo (%)</th>
<th>Clopidogrel (%)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, or stroke</td>
<td>34 (0.5)</td>
<td>27 (0.4)</td>
<td>0.80 (0.48–1.32)</td>
</tr>
<tr>
<td>CV death, MI, stroke, or refractory ischemia</td>
<td>70 (1.1)</td>
<td>53 (0.8)</td>
<td>0.76 (0.53–1.09)</td>
</tr>
<tr>
<td>CV death, MI, stroke, severe ischemia†</td>
<td>135 (2.1)</td>
<td>89 (1.4)</td>
<td>0.66 (0.51–0.86)</td>
</tr>
</tbody>
</table>

**TABLE 4. Effects of Clopidogrel on Day 1, Day 2, and Day 3**

<table>
<thead>
<tr>
<th>Event</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI or stroke</td>
<td>34 vs 27 (0.80)</td>
<td>67 vs 54 (0.81)</td>
<td>89 vs 75 (0.85)</td>
</tr>
<tr>
<td>CV death, MI, stroke, or severe ischemia</td>
<td>135 vs 89 (0.66)†</td>
<td>233 vs 162 (0.70)†</td>
<td>288 vs 217 (0.75)†</td>
</tr>
</tbody>
</table>

CV indicates cardiovascular.
†$P < 0.01$; †$P < 0.001$. 

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interventions. By 24 hours, there was a clear and statistically significant reduction in the risk of the composite outcome of cardiovascular death, stroke, MI, or refractory or severe ischemia, which emphasizes the value of initiating treatment with clopidogrel without delay. During the first 24 hours, the rates of major or life-threatening bleeding were extremely low and were similar in the clopidogrel and placebo groups, which indicates the safety of early initiation of therapy with clopidogrel. Thus, the benefit-versus-risk ratio is clearly favorable even during the first 24 hours, when practically all patients received aspirin and >90% received a thrombin inhibitor. Although the protocol excluded patients who had received an intravenous glycoprotein IIb/IIIa inhibitor before randomization, there were no restrictions on the use of these drugs subsequent to randomization. The benefits of clopidogrel were consistent among the 823 patients who received this class of agent, with no apparent excess of bleeding with clopidogrel versus placebo. These data are consistent with information from studies of patients undergoing PTCA and suggest that clopidogrel and intravenous glycoprotein IIb/IIIa inhibitors can be used safely together.

During the first 7 days, consistent benefits were observed, with ≈20% relative risk reductions in the 2 primary composite outcomes (4 and 7 events prevented per 1000, respectively) and in the secondary composite outcome that included severe ischemia (15 events prevented per 1000). The benefits clearly outweighed the risks, with no apparent excess in life-threatening bleeds and only a small (1 per 1000) excess in other major bleeds. These benefits continued to increase to 30 days with about the same relative risk reductions but larger absolute risk reductions (for every 1000 patients treated, a further 7 cardiovascular deaths, MIs, or strokes were prevented). Therefore, the total number of major vascular events prevented by 30 days was several times larger (11 first primary events plus 6 cases of refractory ischemia for a total of 17 major vascular events prevented) than the risk of bleeding (5 major or life-threatening bleeds). The data in Tables 3 and 4 and Figure 2 indicate that with delays of even 1 day in initiating therapy, approximately one fourth of the benefits related to preventing the primary outcome and half of the 7-day benefits related to preventing the composite that included cardiovascular death, MI, strokes, and severe ische-
mia would be lost. Given that event rates are highest during the first day, this is the period during which maximum absolute benefit for any given day of treatment can be obtained. This emphasizes the importance of starting treatment with clopidogrel as early as possible.

Beyond 30 days, benefits of clopidogrel continued to be evident, with a further one-fifth decrease (11 per 1000) in the risk of cardiovascular death, MI, and stroke, which was by itself statistically significant. During this period, there was no significant excess in life-threatening bleeds (1 per 1000 over 8 months), but there was an excess of other major bleeds (5 per 1000 over 8 months). These data again indicate that the benefits of treatment outweigh the risks during this late phase beyond 30 days after presentation. Our approach of separately analyzing the data beyond 30 days may potentially underestimate the late benefits of clopidogrel for 2 reasons. First, patients who had events within the first 30 days were not included, and so the impact of preventing early recurrent events was not taken into consideration. Second, because clopidogrel was effective in the first 30 days, more high-risk patients (in whom an event was prevented with clopidogrel) remained in the clopidogrel group than in the control group. Therefore, the real benefit of clopidogrel is likely to be somewhat larger than that apparent by the present analysis.

Subdivision of the data beyond 30 days is not presented because there is neither an obvious cutoff in the Kaplan-Meier rates during this period nor any biological or clinical rationale that the atherothrombotic process varies at any time after 30 days. Furthermore, censoring data before any cut point after randomization may create even more imbalances in numbers and biases in the types of patients who remain in the analysis beyond this time point, with these problems becoming worse the later censoring occurs. Moreover, statistical power is compromised because the number of events available for analysis decreases dramatically. Nevertheless, as indicated by Figures 2 and 3, benefits were seen throughout this period. Figure 3 demonstrates that a substantial part of the benefit is achieved by 3 months, with further small benefits over the remaining period of the study. These data support the recent guidelines recommending the use of clopidogrel (and aspirin) for \( \approx \)9 months in ACS.

The exact duration of therapy cannot be deduced reliably from a trial with the design of CURE, because even “parallel” event rates (or survival curves) may reflect continuing benefit as the group with the active treatment would be expected to include individuals in whom an event was prevented at an earlier time point. The only way to reliably estimate the exact length of time that various treatments in any condition should be given is by prospectively randomizing patients to various durations of therapy. However, such trials would have to be much larger than current studies and are unlikely to be conducted.

Our definition of life-threatening bleeding in the CURE study may be broader than that defined by the TIMI or GUSTO studies. The CURE definition of life-threatening bleeding produced event rates that were twice those seen with the TIMI or GUSTO criteria in the present trial. Therefore, in comparing bleeding rates across studies, it is important to use definitions that are similar. Because these latter 2 definitions have been commonly used in other studies in ACS, we reanalyzed our data utilizing these criteria. This resulted in no excess bleeding risk with clopidogrel and much lower bleeding rates in both the active and control groups. There are several implications of this observation. First, comparison of the bleeding from CURE with that of other trials requires caution, because it is likely that trials with other agents (eg, glycoprotein IIb/IIIa inhibitors or thrombin inhibitors) may have underestimated the absolute bleeding risks because of differing criteria for bleeding. This suggests the need for commonly agreed-upon standards and definitions for reporting bleeding to be used across various studies in ACS. Furthermore, differences in patient characteristics (eg, age), and cointerventions (eg, surgery) that affect bleeding rates should be considered and data across studies interpreted with considerable caution.

The excess risk of bleeding that we observed in CURE was similar to the risks associated with aspirin in the Antiplatelet Trialists’ Collaboration, although in CURE, the use of other agents (aspirin or heparin) or interventions that also increase the risk of bleeding was more common. The risk of bleeding with clopidogrel was similar to that observed with low-molecular-weight heparin versus placebo (0.8% versus 0.5%) in the FRISC (Fragmin During Instability in Coronary Artery Disease) study but lower than that observed in the trials of intravenous (2.4% versus 1.4%) or oral (4.1% versus 2.4%) glycoprotein IIb/IIIa inhibitors. Furthermore, several of the above treatments were given for relatively short periods of time (eg, 3 days to a few weeks), and the bleeding events were mainly counted during this period. Therefore, based on these indirect comparisons, the risk-benefit balance over time with clopidogrel is at least similar (and may even be better) to that seen with other agents proven to be effective in ACS.

Other than aspirin, clopidogrel is the only antithrombotic agent that has been demonstrated to be of benefit both in the early phase and during long-term treatment in ACS. Other oral antithrombotic therapies have been found to be harmful (eg, oral glycoprotein IIb/IIIa inhibitors), ineffective, or poorly tolerated (eg, oral anticoagulants). Therefore, both aspirin and clopidogrel should be initiated early (along with thrombin inhibitors and glycoprotein IIb/IIIa inhibitors in those undergoing interventions) and continued for the long term (with statins, ACE inhibitors, and, where appropriate, \( \beta \)-blockers). The combined use of these treatments will lead to the greatest benefits in the largest number of patients.

Acknowledgments

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