Clopidogrel has been evaluated in clinical trials that included cardiovascular patients with different risk levels for a cardiovascular event. We reviewed the results of the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) and Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trials, with special emphasis on comparing the outcomes in high-risk patients with those of the total populations in the trials. The results in the high-risk subgroups and total populations were compared by recording total event rates, absolute risk reduction, relative risk reduction, and number needed to treat. In the CAPRIE trial, the efficacy of clopidogrel was compared with acetylsalicylic acid (ASA) in the following subgroups: total population, previous coronary bypass surgery, history of more than 1 ischemic event, multiple vascular beds involvement, diabetes, and hypercholesterolemia. In the CURE trial, the combination of clopidogrel and ASA was compared with ASA alone. The results in the CURE study were compared in patients who did and did not have a coronary intervention procedure, in patients with different levels of risk based on the Thrombolysis in Myocardial Infarction score and in patients with and without a history of a revascularization procedure. High-risk subgroups of patients participating in the CAPRIE and CURE studies were more responsive to the beneficial effects of clopidogrel compared with the study population as a whole. High-risk groups in the CAPRIE and CURE studies would be expected to derive enhanced benefit from treatment with clopidogrel over that achieved by ASA.

The important role of antiplatelet therapy for the prevention and treatment of thrombotic complications of atherosclerotic disease is well established. In their most recent meta-analysis, the Antiplatelet Trialists’ Collaboration group reported a 22% overall odds reduction of serious vascular events in patients receiving antiplatelet therapy. Currently, the antiplatelet agents in common clinical use are clopidogrel and acetylsalicylic acid (ASA). The first antiplatelet agent to be evaluated, ASA is inexpensive, relatively safe, and widely used. It produces its platelet effect by irreversibly inactivating platelet cyclooxygenase in platelets, thereby inhibiting thromboxane A₂–mediated platelet activation. Clopidogrel and its precursor ticlopidine are thienopyridines. They produce their antiplatelet effect through active metabolites that irreversibly modify the adenosine diphosphate (ADP) receptor (the P2Y₁₂ receptor) on platelets, thereby inhibiting ADP-mediated platelet activation. Clopidogrel, the safer and more convenient of the 2 thienopyridines, was approved in 1997 for the prevention of thrombotic complications of atherosclerotic disease. It is at least as safe as aspirin but more expensive.

The efficacy and safety of clopidogrel have been compared with ASA in 3 clini-
cal trials. In the first, the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study, 3 clopidogrel was compared with ASA in a broad spectrum of patients with atherothrombosis. In the other 2, the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study 4 and the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, 5 the combination of clopidogrel and ASA was compared with ASA alone. The CURE study was performed in patients with unstable angina and non-ST-segment elevation myocardial infarction (MI), whereas the CREDO trial included patients who were likely to undergo percutaneous coronary intervention (PCI).

In an analysis of CAPRIE and CURE, subgroups of patients have been identified who experienced higher than average event rates while receiving ASA therapy alone. These higher-risk patients also appeared to derive greater benefit from clopidogrel compared with the general patient populations. The results of these trials are important from 2 viewpoints. First, they provide information on the relative importance of blocking platelet activation mediated by thromboxane A2, by ADP, or by the combination of the 2 antagonists. Second, the clinical trials provide information that assists clinicians in choosing the most appropriate antiplatelet therapy in different clinical settings. The present article reviews the results of CAPRIE and CURE, with special emphasis on subgroup analyses of high-risk patients.

Four terms are used in this review to compare the efficacy of clopidogrel with ASA: event rate (ER), absolute risk reduction (ARR), relative risk reduction (RRR), and number needed to treat (NNT). The ARR is the absolute arithmetic difference in event rates between experimental and control groups, calculated as ER experimental minus ER control. The RRR is the proportional reduction in event rates between experimental and control group, calculated as event rate ER experimental minus ER control divided by ER control, expressed as a percentage. The NNT is the number of patients that must receive a particular intervention, for a specified length of time, to prevent 1 bad outcome, which is calculated by dividing the ARR into 100.

**CAPRIE**

The CAPRIE study was conducted to evaluate the relative efficacy and safety of clopidogrel compared with ASA in reducing the risk of occurrence of the composite primary outcome cluster of ischemic stroke (IS), MI, or vascular death (VD), in patients at risk of ischemic events. 3 CAPRIE randomized 19 185 patients (with IS in the past 6 months, or MI within 35 days of randomization, or atherosclerotic peripheral arterial disease) to clopidogrel, 75 mg/d, or ASA, 325 mg/d, and followed-up these patients for 1 to 3 years.

The ER in the ASA group was 5.8%. Patients assigned to clopidogrel had a modest but statistically significant benefit, with an RRR of 8.7%, an ARR of 0.51%, and an NNT of 196 over 1 year to prevent an event (IS, MI, or VD). A review of the CAPRIE database identified the following 5 clinically defined high-risk groups in whom an amplified absolute and relative risk reduction is seen with clopidogrel treatment: patients with a history of coronary artery bypass grafting (CABG); 6 those with a history of more than 1 ischemic event; 7 individuals with involvement of multiple vascular beds; 8 patients with diabetes; 9 and those with hypercholesterolemia. 9

Furthermore, a subsequent analysis of the CAPRIE database found a significant reduction in rehospitalization for ischemic events (unstable angina, transient ischemic attack, and peripheral limb ischemia) or bleeding events in patients treated with clopidogrel over aspirin. 10 This benefit was in addition to the risk reduction seen in the main composite end point of VD, MI, or IS, with no double counting of events. In fact, the composite of VD, MI, IS, or rehospitalization for ischemia or bleeding was reduced from 13.67% to 12.57%—a RRR of 7.9%, an ARR of 1.1%, and an NNT over 1 year of 91. Thus, the true impact of clopidogrel on ischemic event reduction is larger than appreciated in the original CAPRIE analysis.

**Patients With a History of More Than 1 Ischemic Event**

Patients who had experienced a prior ischemic event in addition to the qualifying event had a greater risk of experiencing a recurrent ischemic event compared with those who had not. 7 Thus, the annual ER for VD, IS, MI, or rehospitalization for ischemia or bleeding in patients who received ASA was 22.3%, compared with an ER of 15.9% in individuals receiving clopidogrel. Importantly, patients with a history of CABG who received clopidogrel had an RRR of 28.9%, which is considerably higher than the overall RRR in CAPRIE, compared with patients receiving ASA. Therefore, this population not only was at greater risk of an ischemic event but also was more responsive to clopidogrel, with an ARR of 6.4% and an NNT over 1 year of 16.

**Patients With Involvement of Multiple Vascular Beds**

In the CAPRIE study, the risk of an event while receiving ASA therapy increased with the number of vascular beds clinically affected. 3 In patients with multiple vascular bed involvement, the annual ER in patients who received ASA was 19.84%, compared with an ER of 17.39% in individuals receiving clopidogrel. This group also derived greater benefit from clopidogrel treatment than did low-risk patients. Thus, compared with ASA, the RRR for VD, MI, or
Table 1. Enhanced Risk Reduction With Clopidogrel Therapy in High-Risk Patients in the CAPRIE3 Study

<table>
<thead>
<tr>
<th>High-risk Populations</th>
<th>Clopidogrel: ER, %</th>
<th>ASA: ER, %</th>
<th>RRR, %</th>
<th>ARR, %</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CAPRIE population</td>
<td>12.57</td>
<td>13.67</td>
<td>7.9</td>
<td>1.1</td>
<td>91</td>
</tr>
<tr>
<td>Patients with previous CABG</td>
<td>15.9</td>
<td>22.3</td>
<td>28.9</td>
<td>6.4</td>
<td>16</td>
</tr>
<tr>
<td>Patients with a history of ≥1 ischemic event</td>
<td>18.4</td>
<td>20.4</td>
<td>10.0</td>
<td>2.0</td>
<td>50</td>
</tr>
<tr>
<td>Patients with involvement of multiple vascular beds</td>
<td>17.39</td>
<td>19.84</td>
<td>12.4</td>
<td>2.45</td>
<td>41</td>
</tr>
<tr>
<td>Patients with diabetes</td>
<td>15.6</td>
<td>17.7</td>
<td>12.5</td>
<td>2.1</td>
<td>48</td>
</tr>
<tr>
<td>Patients with hypercholesterolemia</td>
<td>12.3</td>
<td>13.6</td>
<td>9.7</td>
<td>1.3</td>
<td>77</td>
</tr>
</tbody>
</table>

Abbreviations: ARR, absolute risk reduction; ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CAPRIE, Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events; ER, event rate; NNT, number of patients needed to treat to prevent an event; RRR, relative risk reduction.

The CAPRIE study population included 2094 patients with hypercholesterolemia who were being treated with lipid-lowering therapy. These patients also formed a high-risk group, with an average ER per year for VD, IS, MI, or rehospitalization for ischemia or bleeding (12.3%) and an ARR of 1.3% and an NNT of 77.

Patients With Diabetes

The CAPRIE trial included 3866 patients with diabetes. The ER was higher in this group than in the general study population. As with other high-risk populations, patients with diabetes derived a greater benefit from clopidogrel treatment than from ASA therapy. The ER for VD, IS, MI, or rehospitalization for ischemia or bleeding was 17.7% in patients with diabetes randomized to ASA and 15.6% in those randomized to clopidogrel—an RRR of 12.5%, with an ARR of 2.1% and an NNT of 48. Clopidogrel prevented 21 more events per 1000 diabetic patients treated than did ASA.

The ER in patients with diabetes receiving insulin was higher than in diabetic patients as a whole, and these patients also achieved an even greater benefit with clopidogrel treatment than did diabetic patients as a whole. In insulin-treated diabetic patients, the ER was 21.5% for those receiving ASA and 17.7% for those receiving clopidogrel—an RRR of 16.7%, with an ARR of 3.8% and an NNT of 26.3. Clopidogrel prevented 38 more events per 1000 diabetic patients receiving insulin than did ASA.

Patients With Hypercholesterolemia

The CAPRIE study population included 2094 patients with hypercholesterolemia who were being treated with lipid-lowering therapy. These patients also formed a high-risk group, with an average ER per year for VD, IS, MI, or rehospitalization for ischemia or bleeding (13.6%). As with other high-risk groups, hypercholesterolemic patients derived greater benefit from clopidogrel therapy than did the general study population. Compared with ASA, the RRR with clopidogrel was 9.7%, with an ARR of 1.3% and an NNT of 77.

Summary: High-Risk CAPRIE Subgroups

A summary of ER and risk reductions in the total CAPRIE population and the high-risk subgroups is contained in Table 1. Interestingly, all 5 subgroups were at least as responsive to clopidogrel as the overall population. In addition, patients with previous CABG, involvement of multiple vascular beds, history of more than 1 ischemic event, or diabetes had an apparent greater RRR with clopidogrel, suggesting that these subgroups may be more responsive to the beneficial effects of clopidogrel compared with the general study population.

CURE

High-risk groups that were more responsive than the study population as a whole were also identified in the CURE trial. The high-risk groups were those with a high TIMI risk score in Myocardial Infarction (TIMI) risk score, those with a history of a revascularization procedure, and most particularly those who had a PCI.

The CURE study randomized 12,562 patients with non–ST-segment elevation acute coronary syndrome, who had presented within 24 hours of symptom onset, to receive clopidogrel, 300 mg immediately then 75 mg/d, or placebo; both groups received a background therapy of ASA, for 3 to 12 months. The first primary outcome was a composite: death from cardiovascular causes, nonfatal MI, or IS. This outcome occurred in 9.3% of patients in the clopidogrel group and in 11.4% of patients in the placebo group, with an RRR of 20% for patients in the clopidogrel group (P<.001). This represents an ARR of 2.1% and an NNT of 48 (Table 2).

High-Risk Groups

Patients at low, intermediate, and high risk, as assessed by the TIMI risk score, all derived significant benefit from clopidogrel therapy, though the greatest absolute risk reductions were seen in patients with high TIMI risk scores. Patients who had a history of a revascularization procedure showed a similar trend for deriving more benefit from clopidogrel, as did those in the CABG group in the CAPRIE study. Thus, patients in the CURE study who had a previous revascularization had an RRR of approximately 45% for clopidogrel compared with placebo.

Patients Undergoing PCI

The PCI-CURE trial was an angio-plasty companion study to the CURE study. The trial enrolled 2658 pa-
Table 2. Enhanced Risk Reduction With Clopidogrel Therapy in the CURE4 and PCI-CURE11 Studies

<table>
<thead>
<tr>
<th>High-Risk Populations</th>
<th>Clopidogrel and ASA: ER, %</th>
<th>ASA: ER, %</th>
<th>Clopidogrel and ASA: RRR, %</th>
<th>ARR, %</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE population</td>
<td>9.2</td>
<td>11.4</td>
<td>20</td>
<td>2.1</td>
<td>48</td>
</tr>
<tr>
<td>PCI-CURE</td>
<td>8.8</td>
<td>12.6</td>
<td>51</td>
<td>3.8</td>
<td>26</td>
</tr>
</tbody>
</table>

Abbreviations: ARR, absolute risk reduction; ASA, acetylsalicylic acid; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Events; ER, event rate; NNT, number needed to treat to prevent an event; PCI-CURE, percutaneous coronary intervention CURE; RRR, relative risk reduction.

There are 2 different end points: for CURE, myocardial infarction, stroke, and cardiovascular death; for PCI-CURE, cardiovascular death and myocardial infarction. For PCI-CURE, the results presented include events before and after PCI. The ER% represents the percentage of patients who had an event during the study and are not the average event rate per year. The NNT therefore has a different interpretation than in the Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events (CAPRIE) section where the average rate per year was presented. Here, the NNT represents the number needed to treat for the average length of follow-up to prevent an event.

patients with non–ST-elevation acute coronary syndrome, who underwent a PCI.11 The aim of PCI-CURE was to determine whether clopidogrel pretreatment followed by long-term therapy is beneficial for patients with non–ST-elevation acute coronary syndrome undergoing PCI.11 At study entry, patients were randomized to receive clopidogrel or placebo; both groups received a background of ASA. Patients randomized to the combination of clopidogrel and ASA, who later underwent PCI, had the procedure on average at 6 days if PCI was performed during hospitalization and on average at 49 days if PCI was performed after hospital discharge. After PCI, approximately 80% of patients in each group received open-label clopidogrel for 4 weeks, after which therapy with the study drug was restarted and continued for a mean of 8 months. The PCI-CURE trial demonstrated that patients undergoing coronary angioplasty and stenting are a high-risk group, with an increased risk of both early and late events. As in other high-risk groups, the ER was dramatically reduced by clopidogrel treatment.

The primary efficacy end point was the composite cardiovascular death, MI, or urgent revascularization of the target vessel required within 30 days after PCI. Pretreatment with the combination of clopidogrel and ASA significantly reduced major procedure-related complications in patients with non–ST-elevation acute coronary syndrome undergoing PCI, compared with treatment with ASA alone. Patients receiving a combination of clopidogrel and ASA experienced a significantly lower ER (4.5%) at 30 days than did patients in the placebo group (6.4%). The combination of clopidogrel and ASA was associated with a small, nonsignificant increase in major bleeding and no increase in life-threatening bleeding. The relative risk of major bleeding was 1.13, with an absolute increase of 0.2%. The relative risk of life-threatening bleeding was 0.92. Therefore, the benefit-risk ratio was clearly in favor of the combination.

In addition, long-term treatment with clopidogrel and standard therapy including ASA for up to 1 year reduced the occurrence of MI and cardiovascular death. Patients treated with clopidogrel experienced an overall RRR of 31% in cardiovascular death or MI compared with patients receiving placebo (P = .002), with an ARR of 3.8% and an NNT of 26.

A comparison of the CURE and PCI-CURE results is given in Table 2. Patients who underwent a PCI had a higher risk of an event compared with the study population as a whole and were considerably more responsive to clopidogrel.

CONCLUSIONS

High-risk subgroups of patients participating in the CAPRIE and CURE studies have been identified. Of importance, all subgroups were at least as responsive to the beneficial effects of clopidogrel, either used alone or in combination with ASA, as the study population as a whole, and some of the identified high-risk groups assigned to clopidogrel showed a greater RRR compared with the population as a whole, suggesting the possibility that these subgroups might be more responsive to the antiplatelet effects of clopidogrel than to ASA. The risk of bleeding was similar with both antiplatelet agents.

The subgroup analysis of the CAPRIE study and of 2 of the groups (high TIMI score and previous revascularization) in the CURE study have limitations because the identified high-risk groups were not pre-specified. Accordingly, the results should be considered as hypothesis forming, and the observed event rates in the identified subgroups could overestimate the real situation. This shortcoming does not apply to the PCI-CURE study, which was a prespecified companion study to CURE. On the other hand, the CAPRA study13 suggests that in the real world, patients with atherosclerosis are at much higher risk compared with those enrolled in clinical trials such as CAPRIE and therefore more likely to derive benefit from effective therapies.

In addressing the question of the relative importance of thromboxane A2- and ADP-mediated platelet activation in thrombogenesis, the clinical trial data indicate that a greater antithrombotic effect is achieved by blocking ADP-mediated activation and that this advantage extends into patient groups with a high baseline risk of thrombotic complications. More importantly, the results of the CURE study indicate that the impressive additive effect that is achieved by blocking both mechanisms of platelet activation also extends to patients with a high baseline risk of thrombotic complications.
From a clinical perspective, the results of subgroup analyses provide data that help the clinician to balance the increased benefit of clopidogrel with the lower cost of ASA and the greater benefit and small increase in major bleeding of the combination of clopidogrel and ASA with the lower cost of ASA. The ongoing Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial will help further define the effectiveness and cost-efficacy of dual antiplatelet therapy vs aspirin monotherapy in secondary prevention of coronary, cerebral, and peripheral arterial diseases, as well as in high-risk primary prevention.

Accepted for Publication: December 16, 2003.

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REFERENCES