Superiority of Clopidogrel Versus Aspirin in Patients With Prior Cardiac Surgery

Deepak L. Bhatt, MD; Derek P. Chew, MBBS; Alan T. Hirsch, MD; Peter A. Ringleb, MD; Werner Hacke, MD; Eric J. Topol, MD

Background—After coronary artery bypass surgery, patients have a high cumulative rate of graft closure and recurrent ischemic events. We sought to determine whether antiplatelet therapy with clopidogrel would be more effective than aspirin, the accepted standard, in these patients.

Methods and Results—The event rates for all-cause mortality, vascular death, myocardial infarction, stroke, and rehospitalization were determined for the 1480 patients with a history of cardiac surgery randomized to either clopidogrel or aspirin in a trial of 19 185 patients. The event rate per year of vascular death, myocardial infarction, stroke, or rehospitalization was 22.3% in the 705 patients randomized to aspirin and 15.9% in the 775 patients randomized to clopidogrel ($P=0.001$). A risk reduction was also seen in each of the individual end points examined, including a 42.8% relative risk reduction in vascular death in patients on clopidogrel versus aspirin ($P=0.030$). In a multivariate model incorporating baseline clinical characteristics, clopidogrel therapy was independently associated with a decrease in vascular death, myocardial infarction, stroke, or rehospitalization in patients with a history of cardiac surgery, with a 31.2% relative risk reduction (95% CI, 15.8 to 43.8; $P=0.0003$). Although clopidogrel therapy was efficacious in the entire Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) population, multivariate analysis demonstrated that patients with previous cardiac surgery derived particular benefit ($P=0.015$).

Conclusion—Compared with aspirin, clopidogrel therapy results in a striking reduction in the elevated risk for recurrent ischemic events seen in patients with a history of prior cardiac surgery, along with a decreased risk of bleeding. (Circulation. 2001;103:363-368.)

Key Words: aspirin □ bypass □ grafting □ platelets

ABG is the definitive surgical approach for the treatment of ischemic heart disease, with $>400 000$ procedures performed annually in the United States alone.

Secondary prevention with aspirin has been proven effective in patients who have undergone cardiac surgery. The Antiplatelet Trialists’ Collaboration demonstrated a significant benefit of aspirin versus placebo in maintaining graft patency. Despite the benefit of aspirin, a large number of recurrent events occur. Although aspirin can successfully block thromboxane A$_2$ production, there are other pivotal pathways to platelet activation, such as that resulting from ADP. Furthermore, a cohort of patients appears to be “aspirin resistant,” as defined by lacking significant, detectable platelet inhibition after receiving aspirin therapy for $\geq 1$ week.

The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study was a large-scale, multicenter, blinded, randomized trial that compared the ADP receptor antagonist clopidogrel with aspirin in 19 185 patients. The trial showed modest superiority of clopidogrel for reducing recurrent ischemic events, with fewer bleeding complications. We sought to determine whether clopidogrel would be more effective than aspirin in reducing recurrent ischemic events in patients with previous cardiac surgery.

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Dr Topol has received honoraria for educational programs and lecture presentations related to this study. Regarding Sanofi-Synthelabo and Bristol-Myers Squibb, Dr Bhatt has received honoraria from both firms, and Dr Hirsch has received research grants and honoraria as well. In addition, Dr Hacke serves as a consultant to Sanofi Winthrop, which has also provided remuneration for lecture presentations.

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TABLE 1. Baseline Characteristics of Patients with a History of Prior Cardiac Surgery Who Were Randomized to Clopidogrel or Aspirin

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel</th>
<th>Aspirin</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.3</td>
<td>63.9</td>
<td>0.23</td>
</tr>
<tr>
<td>Male, %</td>
<td>83</td>
<td>84</td>
<td>0.69</td>
</tr>
<tr>
<td>White, %</td>
<td>95</td>
<td>97</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>30</td>
<td>27</td>
<td>0.27</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>64</td>
<td>55</td>
<td>0.001</td>
</tr>
<tr>
<td>Elevated cholesterol, %</td>
<td>56</td>
<td>55</td>
<td>0.84</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>14</td>
<td>14</td>
<td>0.83</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>59</td>
<td>56</td>
<td>0.23</td>
</tr>
<tr>
<td>Stable angina, %</td>
<td>60</td>
<td>57</td>
<td>0.31</td>
</tr>
<tr>
<td>Unstable angina, %</td>
<td>37</td>
<td>35</td>
<td>0.28</td>
</tr>
<tr>
<td>Prior stroke, %</td>
<td>10</td>
<td>11</td>
<td>0.53</td>
</tr>
<tr>
<td>Prior TIA, %</td>
<td>10</td>
<td>11</td>
<td>0.58</td>
</tr>
<tr>
<td>Intermittent claudication, %</td>
<td>9</td>
<td>6</td>
<td>0.06</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>20</td>
<td>20</td>
<td>0.85</td>
</tr>
</tbody>
</table>

Methods

Study Population
Details of the CAPRIE study have been published elsewhere.11 Briefly, patients with a recent MI or ischemic stroke or objective evidence of lower extremity ischemia were included. Exclusion criteria included a history of bleeding disorders, uncontrolled hypertension, or severe renal or hepatic dysfunction. Prior informed consent was required of all enrolled patients. Patients with a previous history of cardiac surgery were identified at enrollment. Rates of all-cause mortality, vascular death, MI, ischemic or hemorrhagic stroke, and all-cause rehospitalization were determined. Rates of hospitalization for ischemic events (unstable angina, TIA, limb ischemia) or for bleeding events were also analyzed. Rates of rehospitalization were collected from forms documenting serious adverse events, which were required to be reported within 24 hours of occurrence. Rehospitalization was defined as new hospitalization or extension of the duration of an existing hospitalization. If 2 events began on the same day and both led to rehospitalization, then this was considered 1 hospitalization. Importantly, rehospitalization data for the primary outcomes of nonfatal MI and stroke were not reported again as serious adverse events; thus, there was no double-counting of events by including hospitalization data from the serious adverse events. For example, a rehospitalization for an MI would be counted as only 1 event, an MI, and not rehospitalization and an MI. Because the CAPRIE database did not specifically delineate the type of cardiac surgery, all analyses were repeated after exclusion of the 9% of patients who had a history of valvular heart disease to exclude patients who possibly had valve surgery and to attempt to identify those with only CABG.

Statistical Analysis
Kaplan-Meier event rate estimates for the clopidogrel and aspirin groups were used to assess the cumulative risk for the primary composite end point of vascular death, ischemic or hemorrhagic stroke, MI, or rehospitalization for ischemia or bleeding over a period of 3 years (average treatment duration, 1.6 years). Survival curves for the 2 treatment groups were compared by a 2-sided Mantel-Haenszel (stratified log-rank) test, and the relative risk reduction (RRR) and 95% CIs were calculated from the Cox proportional-hazards model. The proportion of patients hospitalized for various reasons was compared between treatment groups by use of the Pearson χ² test. A multivariate Cox proportional-hazards model was also used to adjust for baseline characteristics, including age, weight, race, sex, hypertension, prior MI, prior cerebrovascular event, congestive heart failure, smoking, diabetes, claudication, and angina. A significance level of P=0.05 was used for all analyses. Because data on hospitalizations were collected only during study drug treatment, all analyses were on-treatment analyses in which the number of events continued to be counted against the patient’s allocated treatment up to 28 days after the early permanent discontinuation of study drug but not beyond the closing date of the study. All statistical calculations were performed with SAS software (version 6.12, SAS Institute Inc).

Results

Baseline Characteristics
The baseline characteristics of the 775 patients with a history of cardiac surgery randomized to clopidogrel or the 705 patients randomized to aspirin were well balanced (Table 1). There were no significant differences in age, sex, or prevalence of diabetes, elevated cholesterol, heart failure, prior MI or stroke, angina, or smoking. There was a higher proportion of patients with a history of hypertension in the clopidogrel compared with aspirin group (64% versus 55%, P=0.001). There was also a lower proportion of white patients in the clopidogrel group and a trend toward a higher prevalence of a history of claudication in the clopidogrel group. Table 2 depicts the significant differences in those patients with prior cardiac surgery. As would be expected, the patients with prior cardiac surgery had a greater prevalence of risk factors.

Individual and Composite End Points
Figure 1 depicts the RRRs and 95% CIs for each end point, as well as a composite of ischemic and bleeding events, for clopidogrel versus aspirin. There were statistically significant RRRs in vascular death and MI. All-cause death was also reduced in the group randomized to clopidogrel, although this did not achieve statistical significance. The reduction in ischemic or hemorrhagic stroke also did not reach statistical significance. Hospitalization for ischemic events or bleeding was significantly reduced, as was all-cause hospitalization.

TABLE 2. Baseline Characteristics of Patients With a History of Prior Cardiac Surgery Versus Those Without Such a History

<table>
<thead>
<tr>
<th></th>
<th>Cardiac Surgery</th>
<th>No Cardiac Surgery</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>63.6</td>
<td>62.4</td>
<td>0.0001</td>
</tr>
<tr>
<td>Male, %</td>
<td>84</td>
<td>71</td>
<td>0.001</td>
</tr>
<tr>
<td>White, %</td>
<td>96</td>
<td>95</td>
<td>0.036</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>29</td>
<td>20</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>60</td>
<td>51</td>
<td>0.001</td>
</tr>
<tr>
<td>Elevated cholesterol, %</td>
<td>55</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td>14</td>
<td>5</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>58</td>
<td>13</td>
<td>0.001</td>
</tr>
<tr>
<td>Stable angina, %</td>
<td>58</td>
<td>19</td>
<td>0.001</td>
</tr>
<tr>
<td>Unstable angina, %</td>
<td>36</td>
<td>6</td>
<td>0.001</td>
</tr>
<tr>
<td>Prior stroke, %</td>
<td>11</td>
<td>9</td>
<td>0.005</td>
</tr>
<tr>
<td>Prior TIA, %</td>
<td>11</td>
<td>8</td>
<td>0.001</td>
</tr>
<tr>
<td>Intermittent claudication, %</td>
<td>7</td>
<td>4</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>20</td>
<td>30</td>
<td>0.001</td>
</tr>
</tbody>
</table>
The composite end point of death, MI, ischemic or hemorrhagic stroke, or rehospitalization per year was significantly reduced from 52.9% to 39.7% (RRR = 22.4%; 95% CI, 10.4 to 32.8; \( P = 0.001 \)). The rate per year of vascular death, MI, ischemic or hemorrhagic stroke, or rehospitalization was 22.3% in the patients randomized to aspirin and 15.9% in the patients randomized to clopidogrel (RRR = 28.9%; 95% CI, 13.1 to 14.8; \( P = 0.001 \)). The rate per year of death, MI, stroke, or rehospitalization specifically for ischemia was reduced from 21.8% to 15.7% (RRR = 27.8%; 95% CI, 13.3 to 42.3; \( P = 0.0008 \)). Figure 2A depicts the Kaplan-Meier curve for vascular death, and Figure 2B depicts the Kaplan-Meier curve for vascular death, MI, stroke, or rehospitalization for ischemia or bleeding.

**CAPRIE End Point**

The composite end point used in the main CAPRIE trial—vascular death, MI, or ischemic stroke—was examined in those patients with a history of cardiac surgery (Figure 1). A 36.3% RRR (95% CI, 13.4 to 53.1) was seen with clopidogrel (5.8% event rate per year) compared with aspirin (9.1% event rate per year, \( P = 0.004 \)). Similarly, there was a 31.8% RRR (95% CI, 8.2 to 49.4) in all-cause death, MI, or all-cause stroke (\( P = 0.011 \)).

**Rehospitalization Rates**

The number of patients hospitalized for ischemic events (unstable angina, TIA, limb ischemia), bleeding events, either ischemic or bleeding events, and all causes combined was reduced with clopidogrel therapy (Table 3). The reduction in all-cause hospitalization was driven principally by the reduction in hospitalization for ischemic events. Although not statistically significant, the rate of study drug discontinuation was lower for clopidogrel versus aspirin (28.8% versus 30.4%, \( P = 0.29 \)).

**Multivariate Modeling**

Table 4 contains the multivariate model for the end point of all-cause death, MI, ischemic or hemorrhagic stroke, or all-cause rehospitalization. Compared with aspirin, the RRR of an adverse event in patients randomized to treatment with clopidogrel was 22.8% (95% CI, 10.7 to 33.2; \( P = 0.001 \)). Significant predictors of adverse events included age, diabetes, congestive heart failure, angina, claudication, and prior cerebrovascular event. The interaction term for the benefit of clopidogrel for this composite end point in patients with a history of previous cardiac surgery was highly significant (\( P = 0.0014 \)). When the multivariate analysis was confined to those ischemic and bleeding end points that clopidogrel therapy might be expected to influence, the benefit over aspirin was even more robust; the RRR with clopidogrel for the composite end point of vascular death, MI, stroke, or rehospitalization for ischemia or bleeding was 31.2% (95% CI, 15.8 to 43.8; \( P = 0.0003 \)). The interaction term for the benefit of clopidogrel for this composite end point was also significant (\( P = 0.015 \)).

**Discussion**

The present analysis demonstrates the superiority of clopidogrel over aspirin in patients with previous cardiac surgery. The consistent reduction in events was seen across a variety of different end points, including all-cause mortality, vascular death, MI, stroke, rehospitalization for ischemic events or bleeding, and all-cause rehospitalization. Although a reduction in ischemic events may be expected from the more potent antiplatelet effect provided by clopidogrel compared with aspirin, the significant reduction in all-cause hospitalization is noteworthy.
This study confirms that patients who have undergone previous cardiac surgery are at very high risk for recurrent vascular events. Graft closure, superimposed on progression of native coronary artery disease, can occur. In the patients receiving aspirin, 18.9% were rehospitalized for ischemic events; even with the significant reduction by clopidogrel, the rate was still 14.8%. In addition to recurrent cardiac events, other arterial beds, in particular the cerebral vasculature, are in jeopardy in these patients. Bleeding episodes from prolonged antiplatelet therapy are an additional concern. Compared with aspirin, clopidogrel significantly reduces rehospitalization for angina, TIA, and peripheral arterial disease, the respective precursors to MI, stroke, and amputation, while causing fewer bleeding episodes. A previous analysis of CAPRIE demonstrated the value of rehospitalization for ischemic events and bleeding as an end point in comparing antiplatelet therapies.12

**The Need for Antithrombotic Therapy**

Thrombotic occlusion of vein grafts is almost inevitable with the passage of a sufficient period of time.5,13,14 Long-term anticoagulant therapy, which is associated with substantial bleeding risks, has not been definitively shown to prevent graft closure.15–19 Antiplatelet therapy, however, can delay this occurrence.4,5,20,21 Spontaneous embolization of atherothrombotic material also occurs in saphenous vein grafts.22 Antiplatelet agents may play a role in preventing the initial thrombus formation at the site of plaque and may minimize the impact of any embolization that does occur by preventing secondary thrombotic occlusion of the microvasculature.53 Additionally, ADP receptor blockade has been shown to inhibit shear stress–induced platelet aggregation more effectively than aspirin.24–28 This latter mechanism may be particularly relevant in surgical conduits, which are more likely to have perturbed blood flow patterns. Progression of native disease may also occur and predispose to a thrombotic event, again creating a role for the more potent antiplatelet effect of clopidogrel in these patients. There is also mounting evidence that a significant proportion of patients undergoing CABG may be aspirin resistant.10,29 Depending on the population studied and the specific definition of aspirin resistance, anywhere from 10% to 40% of patients appear to have an inadequate antiplatelet response to aspirin. The ADP antagonist ticlopidine has been evaluated in small studies and found to be efficacious in patients with CABG.30,31 However,
the unfavorable side effect profile and small, but real, possibility of thrombotic thrombocytopenic purpura make this drug unappealing for long-term secondary prevention.32–36 Thus, because of its efficacy, safety, and tolerability, clopidogrel may be the ideal antiplatelet agent for post-CABG patients.

Dual Therapy With Clopidogrel and Aspirin

Furthermore, the combination of aspirin plus ADP antagonist may result in even better outcomes than with clopidogrel alone. Several experimental studies support the synergy of dual therapy with an ADP antagonist and aspirin.37–43 The combination of aspirin plus an ADP antagonist decreases fibrinogen binding and platelet aggregation significantly more than either agent alone. The present study shows that long-term therapy with clopidogrel is superior to aspirin in patients who have had previous cardiac surgery, without an increase in bleeding risks. Therefore, a randomized trial of long-term therapy with clopidogrel plus aspirin versus aspirin (or clopidogrel) alone after CABG may be warranted.

Study Limitations

The current subgroup analysis was not prespecified. However, treatment with clopidogrel or aspirin was randomized. Data on revascularization procedures during the study period were incomplete. The exact date of the previous surgery was unknown; therefore, the mean age of the bypass grafts could not be determined. The CAPRIE database only identified patients as having a history of previous cardiac surgery, without identifying the exact type of operative procedure. The proportion of patients receiving either venous or arterial grafts could not be determined. Currently, there is greater use of arterial grafts than at the time of this study. Thus, the benefit of clopidogrel over aspirin may be more (greater effect on platelet-rich arterial thrombus) or less (fewer recurrent ischemic events in those with arterial grafts) than seen in this analysis. Finally, all patients enrolled in CAPRIE had a qualifying ischemic event, perhaps identifying a somewhat higher-risk group than the typical cardiac surgery patient.

Conclusions

Although in the overall trial of patients with atherosclerosis the advantage of clopidogrel over aspirin was modest, the high-risk population of prior cardiac surgery patients derived particular and substantial benefit. These findings lend support for the superiority of more potent antiplatelet antagonism induced by ADP receptor blockade by clopidogrel over thrombomodulin inhibition by aspirin in an appropriately selected population at high risk for recurrent vascular events. The promise of further event reduction with dual antiplatelet therapy may establish a new benchmark for optimal secondary prevention in patients at elevated risk for ischemic events.

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References


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