The Effect of Clopidogrel in Combination With Aspirin When Given Before Coronary Artery Bypass Grafting

Richard H. Hongo, MD, Jill Ley, RN, MS, CCRN, Stuart E. Dick, MPH, RD, Rupsa R. Yee, MD, FACC
San Francisco, California

OBJECTIVES

This study was designed to evaluate the effect of preoperative clopidogrel on coronary artery bypass graft surgery (CABG) outcomes.

BACKGROUND

Clopidogrel in combination with aspirin, given before percutaneous coronary intervention, has become the standard for stent thrombosis prevention. Some premedicated patients, however, are found to have surgical disease on angiography, and irreversible platelet inhibition becomes a concern for upcoming CABG.

METHODS

We prospectively studied 224 consecutive patients undergoing nonemergent first-time CABG, and compared those with preoperative clopidogrel exposure within seven days ($n = 59$) to those without exposure ($n = 165$).

RESULTS

The groups were comparable in age, gender, body surface area, preoperative hematocrit, preoperative prothrombin time and prior myocardial infarction. The clopidogrel group had higher 24-h mean chest tube output (1,224 ml vs. 840 ml, $p = 0.001$), and more transfusions of red blood cells (2.51 U vs. 1.74 U, $p = 0.036$), platelets (0.86 U vs. 0.24 U, $p = 0.001$) and fresh frozen plasma (0.68 U vs. 0.24 U, $p = 0.015$). Moreover, reoperation for bleeding was 10-fold higher in the clopidogrel group (6.8% vs. 0.6%, $p = 0.018$). The clopidogrel group also had less extubation within 8 h (54.2% vs. 75.8%, $p = 0.002$) and a trend towards less hospital discharge within five days (33.9% vs. 46.7%, $p = 0.094$).

CONCLUSIONS

Clopidogrel in combination with aspirin before CABG is associated with higher postoperative bleeding and morbidity. These findings raise concern regarding the routine administration of clopidogrel before anticipated coronary stent implantation. (J Am Coll Cardiol 2002;40:231–7) © 2002 by the American College of Cardiology Foundation

The early experience of coronary artery stenting was confounded by an unacceptably high rate of stent thrombosis (24%) (1). Today, thrombosis rates are demonstrated to be <2% with elective stent implantation (2–4). The two pivotal changes that have had the greatest impact in decreasing the rate of stent thrombosis have been the implementation of high-pressure balloon stent expansion and the use of enhanced antiplatelet therapy.

Combination antiplatelet therapy with aspirin and ticlopidine, a platelet adenosine diphosphate (ADP) receptor antagonist, emerged as the standard for stent thrombosis prevention after randomized studies (5,6) demonstrated it to be more effective than aspirin-antithrombotic regimens. The use of ticlopidine, however, was not well tolerated because of gastrointestinal and dermatologic side effects, and was complicated by rare but serious occurrences of severe neutropenia and thrombotic thrombocytopenic purpura (7). Clopidogrel, an acetate derivative of ticlopidine, has demonstrated more potent antiaggregant effect (8), more rapid onset of action (9), lower rate of serious side effects (10,11) and better tolerability (11–13). Several randomized studies (11,14,15) have strongly suggested the comparable efficacy of clopidogrel and ticlopidine, and have helped establish the combination of aspirin and clopidogrel as the current standard for coronary stent thrombosis prevention.

Clopidogrel and aspirin are usually given to patients before the diagnostic angiogram whenever there is a possibility of “ad hoc” coronary stent implantation. This practice has evolved in an attempt to ensure adequate platelet inhibition at the time of stent implantation. A number of patients premedicated with this combination, however, are found to have surgical disease on angiography and do not undergo stent implantation. In these patients, enhanced and irreversible platelet inhibition becomes a concern for upcoming coronary artery bypass graft surgery (CABG). The purpose of this study was to better define the effects of preoperative clopidogrel on surgical and clinical outcomes after CABG.

METHODS

The study population consisted of 409 consecutive patients that underwent CABG between March 1999 and June 2000. Patients undergoing emergent surgery, and those with a history of previous cardiac surgery, concomitant valvular
surgery or preoperative exposure to either coumadin or platelet glycoprotein (GP) Ib/IIa inhibitors were excluded (n = 185). In the remaining 224 patients, those with preoperative clopidogrel exposure within seven days of surgery (n = 59) were compared to those without exposure (n = 165) for postoperative bleeding and clinical outcomes.

Patients with clopidogrel exposure were further grouped into those with (n = 51) and without (n = 8) preoperative aspirin exposure within seven days of surgery, and outcomes of these two groups were compared in an effort to isolate the effect of clopidogrel. Patients without clopidogrel exposure were also grouped into those with (n = 78) and without (n = 87) preoperative aspirin exposure, and were compared in an effort to isolate the effect of aspirin.

Chest tube outputs assessed at 8 h and 24 h were the primary measure of postoperative bleeding. Transfusion quantity was recorded for the four main blood product types (red blood cells, platelets, fresh frozen plasma and cryoprecipitate). Clinical outcomes specific to CABG recovery included reoperation for bleeding, severe low cardiac output, mortality, acute myocardial infarction, stroke and postoperative atrial fibrillation. Severe low cardiac output was defined as the need for multiple vasopressors or intra-aortic balloon pump for more than 24 h after surgery. General postsurgical outcomes evaluated were duration of intubation and postoperative length of stay.

Recognized risk factors for perioperative bleeding in cardiac surgery were assessed including advanced age, female gender, small body surface area and renal insufficiency (16,17). Baseline hematocrit and prothrombin time was assessed because of their influence on blood product transfusions. Criteria for emergent status and reoperation for bleeding were in accordance to definitions set out by the Society of Thoracic Surgeons. The study was approved by the Institutional Review Board.

**Statistical analysis.** Continuous variables are expressed as mean ± SD. Dichotomous variables are shown as percentages. Mean differences between the groups were analyzed using the Student t test. Proportional differences were analyzed using the Fisher exact chi-square analysis. A p value of <0.05 was considered statistically significant.

**RESULTS**

The baseline characteristics of those with and without preoperative clopidogrel exposure were comparable in age, gender and body surface area (Table 1). The baseline hematocrit, prothrombin time and creatinine levels were also comparable between the groups. There was a significantly higher prevalence of class III to IV angina (71.1% vs. 47.9%, p = 0.002) in the clopidogrel group. As expected, there was a high prevalence of concomitant aspirin exposure in the clopidogrel group (86.4%). On the other hand, fewer than half of the patients in the group without clopidogrel exposure had exposure to aspirin (47.3%) (p < 0.001).

The postoperative measures of bleeding and blood product transfusions are shown in Table 2. The clopidogrel group had a higher mean chest tube output at both 8 h (775 ml vs. 516 ml, p = 0.005) and 24 h (1,224 ml vs. 840 ml, p = 0.001) after procedure, and a higher mean number of transfusions with each blood product type. Only 15% of patients in the clopidogrel group were free of blood product exposure.

The clinical outcomes are shown in Table 3. The most striking finding was a 10-fold higher incidence of reoperation for bleeding in the clopidogrel group (6.8% vs. 0.6%, p = 0.018). The clopidogrel group was also less likely to be extubated within 8 h of surgery, and was trending towards being less likely to be discharged from the hospital within five postoperative days. There appeared to be less mortality and fewer postoperative myocardial infarctions and strokes.

**Table 1. Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel (n = 59)</th>
<th>No Clopidogrel (n = 165)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>66.9 ± 12.4</td>
<td>67.0 ± 10.6</td>
<td>0.732</td>
</tr>
<tr>
<td>Gender (female)</td>
<td>38.8%</td>
<td>26.1%</td>
<td>0.732</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.85 ± 0.27</td>
<td>1.85 ± 0.27</td>
<td>0.650</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>39.1 ± 3.7</td>
<td>38.6 ± 5.2</td>
<td>0.415</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>11.6 ± 1.2</td>
<td>11.2 ± 1.3</td>
<td>0.091</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>1.03 ± 0.40</td>
<td>1.35 ± 1.59</td>
<td>0.145</td>
</tr>
<tr>
<td>History of MI</td>
<td>52.5%</td>
<td>46.1%</td>
<td>0.448</td>
</tr>
<tr>
<td>History of CVA</td>
<td>10.2%</td>
<td>7.3%</td>
<td>0.576</td>
</tr>
<tr>
<td>History of CHF</td>
<td>13.6%</td>
<td>24.8%</td>
<td>0.097</td>
</tr>
<tr>
<td>Class III to IV angina*</td>
<td>71.1%</td>
<td>47.9%</td>
<td>0.002</td>
</tr>
<tr>
<td>Aspirin therapy</td>
<td>86.4%</td>
<td>47.3%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD or percentages. *Canadian Cardiovascular Society angina class.

**Abbreviations and Acronyms**

ADP = adenosine diphosphate  
CABG = coronary artery bypass graft surgery  
CLASSICS = Clopidogrel Aspirin Stent International Cooperative Study  
CURE = Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events trial  
GP = glycoprotein  
MI = myocardial infarction  
CHF = congestive heart failure  
CVA = cerebral vascular accident  
ADP = adenosine diphosphate  
CABG = coronary artery bypass graft surgery  
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**Table 2. Chest Tube Outputs and Transfusions**

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel (n = 59)</th>
<th>No Clopidogrel (n = 165)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest tube output (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-h</td>
<td>775 ± 727</td>
<td>516 ± 533</td>
<td>0.005</td>
</tr>
<tr>
<td>24-h</td>
<td>1224 ± 1119</td>
<td>840 ± 621</td>
<td>0.001</td>
</tr>
<tr>
<td>Transfusions (U)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red blood cells</td>
<td>2.51 ± 2.41</td>
<td>1.74 ± 2.16</td>
<td>0.036</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.86 ± 1.20</td>
<td>0.24 ± 0.60</td>
<td>0.001</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>0.68 ± 1.69</td>
<td>0.24 ± 0.85</td>
<td>0.015</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>0.19 ± 1.31</td>
<td>0.17 ± 1.20</td>
<td>0.774</td>
</tr>
<tr>
<td>Blood product exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red blood cells</td>
<td>79.7%</td>
<td>58.2%</td>
<td>0.004</td>
</tr>
<tr>
<td>Platelets</td>
<td>50.8%</td>
<td>18.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Any blood product</td>
<td>84.7%</td>
<td>61.3%</td>
<td>0.001</td>
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</tbody>
</table>

Data are shown as mean ± SD or percentages.
Table 3. Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel (n = 59)</th>
<th>No Clopidogrel (n = 165)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reoperation for bleeding</td>
<td>6.8%</td>
<td>0.6%</td>
<td>0.018</td>
</tr>
<tr>
<td>Severe low cardiac output*</td>
<td>6.8%</td>
<td>3.6%</td>
<td>0.296</td>
</tr>
<tr>
<td>Mortality†</td>
<td>1.7%</td>
<td>3.6%</td>
<td>0.576</td>
</tr>
<tr>
<td>MI‡</td>
<td>0%</td>
<td>3.6%</td>
<td>0.434</td>
</tr>
<tr>
<td>CVA</td>
<td>3.4%</td>
<td>4.8%</td>
<td>1.000</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>44.1%</td>
<td>34.5%</td>
<td>0.211</td>
</tr>
<tr>
<td>Deep sternal wound infection</td>
<td>1.7%</td>
<td>1.2%</td>
<td>1.000</td>
</tr>
<tr>
<td>Intubation ≤8 h</td>
<td>54.2%</td>
<td>75.8%</td>
<td>0.002</td>
</tr>
<tr>
<td>Postop length of stay ≤5 days</td>
<td>33.9%</td>
<td>46.7%</td>
<td>0.093</td>
</tr>
</tbody>
</table>

Data are shown as percentages. *Defined as multiple vasopressors or intra-aortic balloon pump >24 h. †Defined as all-cause mortality during hospitalization. ‡Defined as postoperative MI during hospitalization.

CVA = cerebral vascular accident; MI = myocardial infarction.

in the clopidogrel group, but the number of events was small and the results did not reach statistical significance.

Table 4 and Table 5 show the bleeding and transfusion rates for patients with and without clopidogrel exposure, respectively. Within the clopidogrel group, patients with preoperative aspirin exposure appeared to have higher overall chest tube outputs and number of transfusions than those without aspirin exposure. This difference, however, was not statistically significant, possibly because of the small number of patients that received clopidogrel alone. Within the group without clopidogrel exposure, patients with and without preoperative aspirin exposure had no significant difference in chest tube output or number of transfusions.

Figure 1 shows the 24-h chest tube output plotted against time from last clopidogrel dose to surgery in the patients with clopidogrel exposure. There was poor correlation between chest tube output and time of delay to surgery ($R^2 = 0.0011$). Although all reoperations for bleeding were in patients with a delay of three days or less, there were very few patients with a delay of more than three days.

DISCUSSION

In addition to stent thrombosis prevention, the efficacy of clopidogrel therapy has now been demonstrated in the setting of acute coronary syndrome and non-ST elevation myocardial infarction in the recent Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) trial (18). As the indications for clopidogrel expand, the use of aggressive antiplatelet therapy will be seen in an increasing number of patients presenting for CABG. A greater understanding of the effects of clopidogrel on CABG is therefore of paramount importance.

In this study, we found that patients exposed to clopidogrel, mostly in combination with aspirin, before nonemergent first-time CABG had significantly more postoperative bleeding and subsequent transfusions. Only 15% of patients in the clopidogrel group were free of blood product exposure. The most striking finding was a 10-fold higher incidence of reoperation for bleeding in the clopidogrel group (6.8% vs. 0.6%, $p = 0.018$). These findings call into question, in particular, the practice of commencing clopidogrel therapy in addition to aspirin before possible but undecided coronary stent implantation.

The need for aggressive antiplatelet therapy with a combination of aspirin and an ADP receptor inhibitor has been well established for coronary stent thrombosis prevention (5,6,19–24). Historically, because ticlopidine has a delayed onset of activity (25,26) and has been shown to enhance efficacy when started several days before coronary stenting (27), antiplatelet therapy was initiated before the diagnostic coronary angiography whenever there was a possibility of subsequent ad hoc stent implantation. This practice has continued in most centers even as clopidogrel has effectively replaced ticlopidine.

Clopidogrel, however, has a significantly more rapid onset of activity when compared with ticlopidine that may make premedication with clopidogrel unnecessary. After a 300 mg loading dose, clopidogrel displays 30% antiplatelet

Table 4. Patients With Clopidogrel Exposure

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n = 51)</th>
<th>No Aspirin (n = 81)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest tube output (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-h</td>
<td>817 ± 761</td>
<td>509 ± 395</td>
<td>0.320</td>
</tr>
<tr>
<td>24-h</td>
<td>1274 ± 1165</td>
<td>800 ± 480</td>
<td>0.270</td>
</tr>
<tr>
<td>Transfusions (U)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red blood cells</td>
<td>2.59 ± 2.53</td>
<td>2.00 ± 1.41</td>
<td>1.000</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.94 ± 1.26</td>
<td>0.38 ± 0.52</td>
<td>0.360</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>0.78 ± 1.29</td>
<td>0</td>
<td>0.355</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>0.22 ± 1.40</td>
<td>0</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD.

Table 5. Patients Without Clopidogrel Exposure

<table>
<thead>
<tr>
<th></th>
<th>Aspirin (n = 78)</th>
<th>No Aspirin (n = 87)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest tube output (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-h</td>
<td>501 ± 427</td>
<td>530 ± 616</td>
<td>1.000</td>
</tr>
<tr>
<td>24-h</td>
<td>809 ± 545</td>
<td>869 ± 687</td>
<td>1.000</td>
</tr>
<tr>
<td>Transfusions (U)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red blood cells</td>
<td>1.84 ± 2.15</td>
<td>1.64 ± 2.17</td>
<td>1.000</td>
</tr>
<tr>
<td>Platelets</td>
<td>0.25 ± 0.54</td>
<td>0.23 ± 0.65</td>
<td>1.000</td>
</tr>
<tr>
<td>Fresh frozen plasma</td>
<td>0.22 ± 0.84</td>
<td>0.26 ± 0.86</td>
<td>1.000</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>0.14 ± 1.14</td>
<td>0.19 ± 1.25</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Data are shown as mean ± SD.
activity in 5 h, nearly approximating the 40% steady-state antiplatelet activity achieved with a 75 mg daily dose (9). The main circulating metabolite, an inactive carboxylic acid derivative, has a peak plasma concentration in 1 h (28). In the CURE study, survival benefit was seen in 2 h (18).

Clopidogrel loading has been administered after stent implantation in two randomized studies. The Clopidogrel Aspirin Stent International Cooperative Study (CLASSICS) demonstrated superior safety of clopidogrel over ticlopidine with an overall low incidence of cardiac events when given after intracoronary stenting (14). The trial, however, was designed as a safety study and had insufficient power to assess the efficacy of therapy. The trial also excluded patients with increased risk for stent thrombosis, a group thought to benefit most from combination aspirin and ADP inhibitor therapy (29). Taniuchi et al. (11) studied a population that included higher risk patients and found a similar 30-day stent thrombosis rate between patients receiving clopidogrel and patients receiving ticlopidine, both administered after stent implantation (2.02% vs. 1.92%, p = 0.901).

Managing patients with clopidogrel exposure. In this new era of aggressive platelet inhibition in coronary disease, the optimal management of patients presenting for CABG receiving clopidogrel is still evolving. The findings from this study suggest that these patients should have surgery delayed, when possible, to allow platelet function to recover. The optimal duration of this delay, however, is still unclear and further evaluation is needed. In the CURE study (18), patients that stopped taking clopidogrel within five days of CABG had a trend towards more major bleeding than those on placebo (9.6% vs. 6.3%, p = 0.06). There was no excess of major bleeding reported, however, in patients that had CABG more than five days after the last clopidogrel dose (4.4% vs. 5.3%). In this study, there was poor correlation between 24-h chest tube output and duration of delay to surgery. Although all reoperations occurred in patients with a delay of three days or less, there were very few patients with more than a three-day delay.

If CABG cannot be safely delayed, platelet transfusions can be considered when rapid reversal of clopidogrel is needed. In the setting of abciximab exposure before CABG, however, prophylactic platelet transfusions have been cautioned against because of the possibility of acute reversal of the clinical benefits of platelet inhibition (30,31). With abciximab exposure, it has been recommended to reserve platelet transfusions for patients that display clinical bleeding after discontinuation of extracorporeal circulation and neutralization of heparin with protamine (32,33). Whether the same recommendations are applicable to clopidogrel is still to be seen.

Aprotinin, an antifibrinolytic agent, has been successfully used in cardiac surgery to reduce overall bleeding and transfusion requirements in patients exposed to aspirin (34–36). Aprotinin is appealing because whereas it reduces overall bleeding, it appears to preserve platelet function during cardiopulmonary bypass (37,38). Its use has been shown to reduce bleeding time prolongation from clopidogrel in animals (39). The efficacy of aprotinin in patients receiving clopidogrel, however, has not yet been evaluated.

Preoperative antplatelet therapy and CABG. Aorto-coronary grafts have a significant rate of acute thrombotic occlusion. Within the first few months after CABG, the
cumulative vein graft patency rate is between 77% and 90% (40). Aspirin therapy started immediately after CABG not only improves early graft patency but also improves survival (41–44). Although preoperative aspirin was initially found to increase rates of reoperation for bleeding, transfusions and hospital stay with CABG (45–49), subsequent studies have not found the same increase in bleeding (50–52). In fact, preoperative aspirin is now suggested to decrease mortality in CABG patients (53).

Even though excessive bleeding with preoperative clopidogrel was found in this study, the safety of aggressive platelet inhibition in the setting of cardiac surgery has been reported in patients with preoperative abciximab (32). In fact, it has been suggested that platelet inhibition with GP IIb/IIIa inhibitors, or “platelet anesthesia,” may allow platelets to escape the hemostatic effects of cardiopulmonary bypass and may improve postoperative hemostasis (54). Decreased platelet loss has been seen with GP IIb/IIIa inhibition during simulated cardiopulmonary bypass (55), and animal studies have shown a reduction in postoperative bleeding (56,57).

The potential benefit of preoperative antiplatelet therapy in CABG, beyond aspirin, is still poorly defined, however. Even so, the use of clopidogrel before CABG is intriguing. Clopidogrel may be uniquely effective in preventing acute thrombotic graft closure, not simply because of its potency in comparison to aspirin, but also because of its mechanism of action. The shear-induced platelet activation seen with cardiopulmonary bypass is inhibited by clopidogrel within hours (58,59). Clopidogrel has also been found to be superior to aspirin for secondary prevention of ischemic events after CABG (60). If the bleeding with preoperative clopidogrel can be minimized while preserving its antiplatelet effect, a role for preoperative clopidogrel in CABG may emerge in the future.

Study limitations. The imbalance of class III to IV angina (71.1% vs. 47.9%, p = 0.002) raises concern that there may be differences in the use of antithrombotic and other antiplatelet agents between the groups that may be influencing outcomes. Patients receiving either GP IIb/IIIa inhibitors or coumadin were excluded from the study. Any difference in preoperative heparin exposure is felt unlikely to affect postoperative bleeding because of the extensive use of heparin during CABG and its reversal with protamine. Nonetheless, because patients were not randomized to clopidogrel exposure, unrecognized confounding factors may exist. In addition, the nurses measuring and recording chest tube drainage were not actively blinded to clopidogrel or aspirin exposure, thus allowing possible bias.

We were unable to fully evaluate the effect of aspirin in this study. There was no increase in bleeding or transfusions when aspirin alone was compared with no antiplatelet therapy. Within the clopidogrel group, more bleeding and transfusions were seen in patients that also received aspirin, but these increases were not found to be statistically significant. Although synergy of clopidogrel and aspirin has been described (61,62), this could not be adequately assessed in this study because the number of patients that received only clopidogrel was limited. The results of this study essentially reflect the effects of the combination of clopidogrel and aspirin and cannot be generalized to patients that are receiving clopidogrel alone.

Clinical implications. In this study, the use of clopidogrel in combination with aspirin before nonemergent first-time CABG was associated with higher postoperative bleeding and morbidity. These findings raise concern regarding the routine administration of clopidogrel before anticipated but undecided coronary stent implantation. Further studies will be needed, however, to better define the role of clopidogrel before CABG. For now, it may be sensible to delay surgery, when possible, in patients recently exposed to the combination of clopidogrel and aspirin.

Acknowledgment
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Reprint requests and correspondence: Dr. Rupsa R. Yee, Division of Cardiology, California Pacific Medical Center, 2333 Buchanan Street, San Francisco, California 94115. E-mail: phillinx@sutterhealth.org.

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