Effect of Timing of Chronic Preoperative Aspirin Discontinuation on Morbidity and Mortality in Coronary Artery Bypass Surgery

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Background—Aspirin (ASA) has been shown to reduce postoperative coronary artery bypass grafting (CABG) mortality and ischemic events; however, the timing of chronic ASA discontinuation before surgery is controversial because of concern about postoperative bleeding. We evaluated the effect of the timing of ASA discontinuation before CABG on major adverse cardiovascular outcomes and postoperative bleeding using the Cleveland Clinic Cardiovascular Information Registry database.

Methods and Results—At the Cleveland Clinic between January 1, 2002, and January 31, 2008, 4143 patients undergoing CABG were taking preoperative chronic ASA. Of these, 2298 discontinued ASA 6 or more days before surgery (early discontinuation), and 1845 took ASA within 5 days of the surgery (late use). Because of substantial differences between these 2 groups, propensity score analysis, and matching based on 31 variables were used for fair comparison of outcomes. This resulted in 1519 well-matched pairs of patients (73%). There was no significant difference between those with early discontinuation and late ASA use with regard to the composite outcome of in-hospital mortality, myocardial infarction, and stroke (1.7% versus 1.8%, \( P=0.80 \)). Late use was associated with more intraoperative transfusions (23% versus 20%, \( P=0.03 \)) and postoperative transfusions (30% versus 26%, \( P=0.009 \)) but a similar number of reoperations for bleeding (3.4% versus 2.4% \( P=0.10 \)).

Conclusions—Among patients undergoing isolated CABG, late discontinuation of ASA resulted in no difference in postoperative cardiovascular outcomes; however, there was an increased transfusion requirement. Thus, we recommend weighing the risks and benefits of late ASA use in these patients. (Circulation. 2011;123:577-583.)

Key Words: aspirin ■ arteriosclerosis ■ bypass ■ coronary disease ■ surgery

Aspirin (acetylsalicylic acid [ASA]) is an integral chronic therapy for patients with coronary artery disease. It has been shown to reduce postoperative coronary artery bypass graft (CABG) surgery mortality and ischemic events. However, there has been controversy regarding the timing of ASA discontinuation before CABG surgery owing to concern about postoperative bleeding complications. The use of early postoperative aspirin is clear given its beneficial effect on vein graft patency and the decrease in adverse postoperative outcomes, including mortality, myocardial infarction (MI), stroke, renal failure, and bowel infarction.\(^1\)\(^2\) Prior retrospective studies of isolated CABG suggest that use of ASA in the preoperative period results in a significant reduction of in-hospital mortality ranging from 45% to 66% with use within 7 and 5 days of surgery, respectively.\(^2\)\(^3\)

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The recommendations regarding timing of ASA discontinuation differ between the cardiology and cardiovascular surgery societies. The American College of Cardiology and American Heart Association 2004 guideline update for CABG states that in stable patients, ASA should be discontinued 7 to 10 days before elective surgery\(^4\); in contrast, the Society of Thoracic Surgeons (STS) 2005 guidelines give a class IIa recommendation to the discontinuation of ASA 3 to 5 days before elective CABG.\(^5\) Thus, we sought to study the effect of ASA discontinuation earlier or later than 5 days before surgery on bleeding complications, postoperative complications, and mortality in patients undergoing isolated CABG in the current era.
Methods
We analyzed data obtained from the Cardiovascular Information Registry (CVIR), a database that contains clinical and laboratory information on consecutive patients undergoing cardiothoracic surgery at Cleveland Clinic. Data from this registry have been approved for use in research by the Institutional Review Board with patient consent waived. This registry is certified to provide data to the STS’s Adult Cardiac National Database. Beginning January 1, 2002, information on preoperative use of ASA and whether ASA was discontinued earlier than 5 days before surgery or within 5 days of surgery was collected prospectively. From that time until January 31, 2008, 4143 patients taking preoperative ASA underwent nonemergent isolated CABG at the Cleveland Clinic. Of these, 2298 (55%) discontinued ASA use 6 or more days before surgery (early-discontinuation group), and 1845 (45%) continued ASA use within 5 days of surgery (late-use group).

Clinical End Points
Our primary end point was a composite of in-hospital death, MI, and stroke. Standard STS definitions of MI and stroke were used.6 MI during the hospitalization had to fulfill 2 of the following 3 criteria: Ischemic symptoms in the presence or absence of chest discomfort, enzyme elevation, or at least 2 serial ECGs that showed ST–T–wave changes from baseline.

Secondary end points were bleeding complications. These included perioperative packed red blood cell (RBC) transfusion and return to the operating room for bleeding or tamponade. Tertiary end points were postoperative MI, postoperative stroke, and in-hospital mortality, individually.

Statistical Analysis
Because of substantial differences in characteristics between the 2 groups of patients, a propensity analysis was performed to reduce the bias when outcomes were compared.7 First, multivariable logistic regression was used to identify patient factors associated with continued ASA use within 5 days of surgery. Variables used for this analysis are categorized and listed in the Appendix in the online-only Data Supplement. Of note, the variables used in our modeling were only those collected prospectively from the CVIR database. Bagging was used for variable selection based on the median rule6 (variables or closely clustered variables that appeared with P<0.05 in 50% or more of 500 automated stepwise bootstrap models). This parsimonious model describes factors that predict continued aspirin use. Additional renal, coronary stenosis, and preoperative medication variables were added to the model to create the final propensity model. The preoperative medications included were β-blockers, angiotensin-converting enzyme inhibitors, intravenous nitrates, non-warfarin antiplatelet agents, warfarin, inotropes, steroids, and lipid-lowering agents. In all, 31 variables were included in the propensity model. The distribution of the propensity score in each group is shown in Figure 1 in the online-only Data Supplement. A standardized difference plot (online-only Data Supplement Figure II) demonstrates that the groups were well matched with regard to variables from the propensity model and additional demographic data.5

Using a greedy matching algorithm,10 patients from each group were matched on similar propensity scores, and 1519 well-matched pairs were obtained (73% of patients). These patients are shaded in Figure 1 in the online-only Data Supplement, which demonstrates that nearly all possible cases were matched, forming subsets of the original data that were more balanced on the basis of preoperative factors. Thereafter, primary, secondary, and tertiary outcomes were compared to evaluate group differences.

Statistical analyses were performed with SAS version 9.1. Descriptive summary data stratified by ASA use (earlier than 5 days or within 5 days before CABG) are presented for all variables listed in Table 1. Continuous data are expressed as mean±SD. Wilcoxon rank sum tests were used to analyze differences for the continuous data. Categorical data are displayed as frequencies and percentages, and comparisons were made with χ² tests (Fisher exact tests if appropriate). The confidence intervals used in Figure 1 were at the 68% level.

Results
Patient Demographics
Between January 1, 2002, and January 31, 2008, 4143 patients were taking ASA preoperatively and underwent elective CABG at the Cleveland Clinic. Of those, 2298 patients (55.5%) discontinued their ASA use more than 5 days before the day of surgery (early discontinuation), and 1845 (44.5%) continued ASA use within 5 days of surgery (late use). The demographic, clinical, and procedural data are included in Table 1.

The early-discontinuation and late-use groups were similar with regard to age, number of women, body mass index, history of smoking, and history of congestive heart failure. The early-discontinuation ASA group had higher preoperative creatinine (109±98.1 versus 96.4±61 µmol/L [1.23±1.11 versus 1.09±0.69 mg/dL], P<0.0001) and hematocrit levels (39.7±5.3 versus 38.8±5.48, P<0.0001). Comorbidities differed, with the early-discontinuation group having more patients with a history of hypertension (86% versus 83%, P=0.002), treated diabetes (37% versus 33%, P=0.003), peripheral arterial disease (56% versus 51%, P=0.002), and renal disease (6.4% versus 3.4%, P<0.0001) but fewer prior MIs (58% versus 61%, P=0.05). More early-discontinuation patients had prior drug-eluting stents placed (6% versus 2.7%, P<0.0001). The early-discontinuation patients were more likely to be taking preoperative angiotensin-converting enzyme inhibitors, lipid-lowering medications, and ADP inhibitors. The late-use group was more likely to be taking preoperative β-blockers and non-warfarin antiplatelet agents. Of note, the use of preoperative medications was collected as use within 24 hours of surgery (except non-warfarin antiplatelet agents and inotropes, which were used within 48 hours).

Patients with early discontinuation were more likely to have had prior cardiac surgery (21% versus 14%, P<0.0001), with most having had 1 prior cardiac surgery. The late-use group included more patients with at least 50% left main coronary artery stenosis. The groups were similar with regard to the number of coronary arteries with at least 50% stenosis and with regard to the use of 1 or 2 internal thoracic artery grafts. The duration of myocardial ischemia was similar, but cardiopulmonary bypass time was slightly longer for the early-discontinuation group (91.7±28.5 versus 90.2±27.4 minutes, P=0.04).

A multivariable logistic regression model was used to determine patient factors for late ASA use (Table 2). Patients with late ASA use were more likely to have a history of prior MI and more severe angina (higher Canadian angina class) and no history of hypertension. Late-use patients also were more likely to have had a later date of surgery, no history of prior cardiac surgery, and lower preoperative hematocrit and creatinine values.

Results of the matching are seen in Table 3 and the Figure. There were no statistical differences in outcomes between the matched groups. There was no difference in the composite
<table>
<thead>
<tr>
<th></th>
<th>Early Discontinuation of Aspirin Use (&gt;5 Days Before Surgery)</th>
<th>Late Use of Aspirin (≤5 Days Before Surgery)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number Available for Analysis</td>
<td>Value</td>
<td>Number Available for Analysis</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>2298</td>
<td>65.1 ± 10.3</td>
<td>1845</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2298</td>
<td>504 (22)</td>
<td>1845</td>
</tr>
<tr>
<td>Preoperative body mass index, kg/m², mean ± SD</td>
<td>2298</td>
<td>29.7 ± 5.7</td>
<td>1845</td>
</tr>
<tr>
<td>Preoperative creatinine, μmol/L (mg/dL), mean ± SD</td>
<td>2282</td>
<td>109.8 ± 98.1 (1.23 ± 1.11)</td>
<td>1832</td>
</tr>
<tr>
<td>Preoperative hematocrit, mean ± SD (%)</td>
<td>2255</td>
<td>39.7 ± 5.32</td>
<td>1818</td>
</tr>
<tr>
<td>History of MI, n (%)</td>
<td>2298</td>
<td>1325 (58)</td>
<td>1845</td>
</tr>
<tr>
<td>History of CVA, n (%)</td>
<td>2298</td>
<td>231 (10)</td>
<td>1845</td>
</tr>
<tr>
<td>History of hypertension, n (%)</td>
<td>2295</td>
<td>1978 (86)</td>
<td>1844</td>
</tr>
<tr>
<td>History of treated diabetes, n (%)</td>
<td>2296</td>
<td>855 (37)</td>
<td>1845</td>
</tr>
<tr>
<td>History of PVD, n (%)</td>
<td>2298</td>
<td>1290 (56)</td>
<td>1845</td>
</tr>
<tr>
<td>History of CHF, n (%)</td>
<td>2298</td>
<td>552 (24)</td>
<td>1845</td>
</tr>
<tr>
<td>History of smoking, n (%)</td>
<td>2295</td>
<td>1462 (64)</td>
<td>1844</td>
</tr>
<tr>
<td>History of renal disease,* n (%)</td>
<td>2298</td>
<td>147 (6.4)</td>
<td>1845</td>
</tr>
<tr>
<td>History of percutaneous intervention, n (%)</td>
<td>2298</td>
<td>665 (29)</td>
<td>1845</td>
</tr>
<tr>
<td>PTCA, n (%)</td>
<td>583 (25)</td>
<td>440 (24)</td>
<td>0.30</td>
</tr>
<tr>
<td>Drug-eluting stent,‡ n (%)</td>
<td>137 (6)</td>
<td>49 (2.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Bare-metal stent, ‡ n (%)</td>
<td>109 (4.7)</td>
<td>67 (3.6)</td>
<td>0.08</td>
</tr>
<tr>
<td>Stent (unknown type), n (%)</td>
<td>315 (14)</td>
<td>265 (14)</td>
<td>0.60</td>
</tr>
<tr>
<td>History of cardiac surgery, n (%)</td>
<td>478 (21)</td>
<td>262 (14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>No. of prior cardiac operations, n (%)</td>
<td>2298</td>
<td>1820 (79)</td>
<td>1583 (86)</td>
</tr>
<tr>
<td>No. of coronary arteries with ≥50% stenosis, n (%)</td>
<td>2272</td>
<td>27 (1.2)</td>
<td>20 (1.1)</td>
</tr>
<tr>
<td>Left main stenosis ≥50%, n (%)</td>
<td>2247</td>
<td>61 (27)</td>
<td>1810</td>
</tr>
<tr>
<td>No. of internal thoracic grafts, n (%)</td>
<td>2298</td>
<td>205 (8.9)</td>
<td>1845</td>
</tr>
<tr>
<td>β-blocker use, n (%)</td>
<td>2279</td>
<td>1842 (81)</td>
<td>1823</td>
</tr>
<tr>
<td>ACE inhibitor use, n (%)</td>
<td>2279</td>
<td>1442 (63)</td>
<td>1823</td>
</tr>
<tr>
<td>Lipid-lowering medication use, n (%)</td>
<td>2279</td>
<td>1022 (45)</td>
<td>1823</td>
</tr>
<tr>
<td>ADP inhibitor use, n (%)</td>
<td>2279</td>
<td>568 (25)</td>
<td>1823</td>
</tr>
<tr>
<td>Anticoagulant use (excluding warfarin), n (%)</td>
<td>2279</td>
<td>688 (30)</td>
<td>1823</td>
</tr>
<tr>
<td>Warfarin use, n (%)</td>
<td>2279</td>
<td>65 (2.9)</td>
<td>1823</td>
</tr>
</tbody>
</table>

CVA indicates cerebrovascular accident; PVD, peripheral vascular disease; CHF, congestive heart failure; PTCA, percutaneous transluminal coronary angioplasty; and ACE, angiotensin-converting enzyme.

Medication data refer to use within 24 hours of surgery, except for anticoagulants, which refers to use within 48 hours. Warfarin, specifically, refers to use within 24 hours.

*History of renal disease defined as documented history of renal failure and/or a history of creatinine ≥2.0 or on dialysis.

‡Data on whether patient had either a drug-eluting or a bare-metal stent was collected beginning in 2004.
end point, with 26 events (1.7%) in the early-discontinuation group versus 28 (1.8%) in the late-use group (P = 0.80). More intraoperative RBC transfusions (23% versus 20%, P = 0.03) and postoperative transfusions (30% versus 26%, P = 0.009) were used in the late-use group (Table 3). The rate of reoperation for bleeding was 2.4% versus 3.4% in the early-discontinuation and late-use groups, respectively (P = 0.10). There was no difference between early discontinuation and late use with regard to the individual outcomes of postoperative cerebrovascular accident (0.92% versus 0.79%, P = 0.70), postoperative MI (0.33% versus 0.39%, P = 0.80), or in-hospital death (0.66% versus 0.72%, P = 0.80; Figure). Postoperative length of stay was similar; the median length of stay was 6 days in both groups (P = 0.50).

### Table 2. Factors Associated With Late Aspirin Use (<5 Days) and CABG

<table>
<thead>
<tr>
<th>Factor</th>
<th>Coefficient±SE</th>
<th>P</th>
<th>R (%)</th>
<th>*Reliability *</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of MI</td>
<td>0.20±0.068</td>
<td>0.003</td>
<td>89</td>
<td>1000 bootstrap models</td>
</tr>
<tr>
<td>Canadian angina class (higher)</td>
<td>0.083±0.029</td>
<td>0.005</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Date of surgery (earlier)</td>
<td>−0.24±0.019</td>
<td>&lt;0.0001</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>History of cardiac surgery</td>
<td>−0.57±0.089</td>
<td>&lt;0.0001</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>History of hypertension</td>
<td>−0.22±0.089</td>
<td>0.01</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>History of COPD</td>
<td>−0.24±0.086</td>
<td>0.005</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>Preoperative creatinine (lower)</td>
<td>−0.13±0.047</td>
<td>0.007</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Preoperative hematocrit (lower)</td>
<td>−0.027±0.0064</td>
<td>&lt;0.0001</td>
<td>96</td>
<td></td>
</tr>
<tr>
<td>Preoperative BUN (lower)</td>
<td>−0.012±0.0040</td>
<td>0.004</td>
<td>64</td>
<td></td>
</tr>
</tbody>
</table>

SE indicates standard error; COPD, chronic obstructive pulmonary disease; and BUN, blood urea nitrogen.

*Reliability is percentage of 1000 bootstrap models that the variable entered.

### Table 3. Transfusion Use Based on Timing of Aspirin Discontinuation, Matched Groups

<table>
<thead>
<tr>
<th></th>
<th>Early Discontinuation of Aspirin Use (&lt;5 Days Before Surgery), n</th>
<th>Late Use of Aspirin (&gt;5 Days Before Surgery), n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count (%)</td>
<td>Count (%)</td>
<td>P</td>
</tr>
<tr>
<td>Patients who received an intraoperative RBC transfusion</td>
<td>1518 301 (20)</td>
<td>1516 351 (23) 0.03</td>
</tr>
<tr>
<td>No. of intraoperative RBC units used</td>
<td>1518</td>
<td>1516 0.10</td>
</tr>
<tr>
<td>0</td>
<td>1217 (80)</td>
<td>1165 (77)</td>
</tr>
<tr>
<td>1</td>
<td>83 (5.5)</td>
<td>86 (5.7)</td>
</tr>
<tr>
<td>2</td>
<td>124 (8.2)</td>
<td>163 (11)</td>
</tr>
<tr>
<td>3</td>
<td>45 (3)</td>
<td>45 (3)</td>
</tr>
<tr>
<td>4</td>
<td>27 (1.8)</td>
<td>37 (2.4)</td>
</tr>
<tr>
<td>≥5</td>
<td>22 (1.4)</td>
<td>20 (1.3)</td>
</tr>
<tr>
<td>Patients who received a postoperative RBC transfusion</td>
<td>1518 390 (26)</td>
<td>1516 454 (30) 0.009</td>
</tr>
<tr>
<td>No. of postoperative RBC units used</td>
<td>1518</td>
<td>1516 0.02</td>
</tr>
<tr>
<td>0</td>
<td>1128 (74)</td>
<td>1062 (70)</td>
</tr>
<tr>
<td>1</td>
<td>164 (11)</td>
<td>166 (11)</td>
</tr>
<tr>
<td>2</td>
<td>130 (8.6)</td>
<td>165 (11)</td>
</tr>
<tr>
<td>3</td>
<td>37 (2.4)</td>
<td>45 (3)</td>
</tr>
<tr>
<td>4</td>
<td>15 (0.99)</td>
<td>32 (2.1)</td>
</tr>
<tr>
<td>≥5</td>
<td>44 (2.9)</td>
<td>46 (3)</td>
</tr>
</tbody>
</table>

**Figure.** Adjusted analysis of ASA discontinuation and post-CABG outcomes. Outcomes shown with 68% confidence intervals. CVA indicates cerebrovascular accident; OR, operating room. Composite outcome includes in-hospital death, postoperative MI, and postoperative CVA.

**Discussion**

The guidelines regarding the timing of ASA discontinuation before CABG or whether it should be discontinued at all are varied. The American College of Cardiology/American Heart Association guidelines advocate discontinuation 7 to 10 days before surgery, whereas the STS advocates discontinuation 5 days before elective CABG. This is driven by concern about increased postoperative bleeding complications. Both guidelines quote a study by Kallis et al in 1994 in which 100 patients undergoing elective CABG randomly received 300 mg of ASA or placebo for 2 weeks before surgery. They found that patients taking ASA had increased blood loss...
(measured from mediastinal or chest tubes), received more RBC transfusions, and had more reoperations for bleeding. In addition, the STS found 4 more randomized controlled trials that suggested that preoperative use of ASA resulted in increased bleeding complications. Except for the study by Kallis et al, ASA was started within 48 hours of surgery, sometimes as late as the night before.\textsuperscript{11–14}

Both the American College of Cardiology/American Heart Association and the STS base the timing of ASA discontinuation on platelet physiology, because ASA is an irreversible cyclooxygenase inhibitor. New platelets need to be formed to overcome the effect of ASA. The lifespan of a platelet is approximately 7 to 10 days,\textsuperscript{15} which influenced the American College of Cardiology/American Heart Association recommendation. However, it takes 3 to 5 days for half of the platelet pool to be replenished, which may be enough to normalize bleeding time and thromboxane B\textsubscript{2} levels, and thus, the STS recommends 5 days as the cutoff.\textsuperscript{3}

In the present study of 4143 patients undergoing CABG, we found there was no significant difference with regard to timing of ASA discontinuation in the composite primary end point or the individual postoperative complications of MI, cerebrovascular accident, or in-hospital death. Late use was associated with increased use of RBC transfusions. Although there was no statistically significant difference in reoperation rate, there was a trend toward more reoperations in the late-use group that may correlate with increased use of RBC transfusion in this group. Ideally, a larger population would be used to study this effect. The patient group in the present study represents the largest group of patients studied with regard to bleeding and postoperative outcomes after CABG from a single center. There were no patients in either group who had reoperation for graft occlusion. Because of the significant difference in patient characteristics between groups, propensity analysis was performed, and patients were matched on the basis of their propensity score. The maximal number of patients was matched for each score, including those at both extremes. As seen in Figure II in the online-only Data Supplement, the groups were well matched with regard to standardized differences in certain variables. The distribution of scores was similar in both groups around a score of 50, without skew in either direction, which implies that there was equipoise with regard to timing of ASA discontinuation. To the best of our knowledge, this is the largest study to date to address the issue of early or late ASA use before CABG.

Many studies in recent years have advocated the restricted use of intraoperative and postoperative blood transfusion and the conservation of blood intraoperatively. This restricted use of RBC transfusions in particular is guided by concern about a possible increase in postoperative infection (bacteremia and superficial and deep sternal wound infections),\textsuperscript{16} acute lung injury,\textsuperscript{17} and all-cause mortality. In particular, Koch et al\textsuperscript{18} found that transfusion of RBCs was associated with increased mortality at 6 months, 5 years, and 10 years.

Some may argue that an increased rate of perioperative transfusion would support early discontinuation. Given the lack of difference in the incidence of reoperation for bleeding, we would support the late use of ASA in high-risk patients to reduce the rate of preoperative cardiovascular events. With our database, we were unable to account for those patients who were scheduled for CABG but may have had surgery cancelled or delayed owing to cardiac events. There is a possible risk of preoperative MI or death if ASA use is stopped before CABG is performed.

Two systematic reviews have observed the consequences of ASA withdrawal. One by Burger et al\textsuperscript{19} reported 3 retrospective studies that included patients undergoing chronic ASA therapy who presented with acute MI, acute coronary syndrome, and acute lower-limb ischemia. Among these patients, ASA withdrawal was associated with a 2.3% to 10.2% incidence of an acute coronary event and a 6.1% incidence of acute lower-limb ischemia. The mean time from ASA withdrawal to acute coronary syndrome was 8.5±3.6 days. Most of these patients (53.9%) discontinued ASA for upcoming noncardiac surgery. The other systematic review included 6 studies and 50 279 patients taking ASA for secondary prevention of coronary artery disease, acute coronary syndrome, CABG, and placement of a drug-eluting stent.\textsuperscript{20} There was an increased risk of major adverse cardiovascular events with ASA discontinuation (odds ratio 3.14, 95% confidence interval 1.75 to 5.61, \(P=0.0001\)). Specifically, for patients taking ASA for secondary prevention of acute coronary syndrome, the risk for major adverse cardiovascular events was increased (odds ratio 1.82, 95% confidence interval 1.52 to 2.18, \(P<0.00001\)). In the era of drug-eluting stents, with their increased incidence of late stent thrombosis, the issue of late ASA use has become more pertinent. Recent data suggest that patients are at highest risk of stent thrombosis if both antiplatelet agents (ASA and clopidogrel) are discontinued.\textsuperscript{21} Thus, keeping at least 1 antiplatelet agent “on board” may reduce this complication before surgery.

Currently, a randomized controlled trial is enrolling patients undergoing isolated, nonurgent CABG (on-pump and off-pump) to observe the effect of aspirin use (given just before surgery) and the operative use of tranexamic acid on all-cause mortality, ischemic complications, and bleeding outcomes at 30 days after surgery.\textsuperscript{22} The Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) Trial plans to include 4600 patients from several centers in Australia, New Zealand, Asia, and Europe and has already enrolled approximately 900 patients.\textsuperscript{22,23} It is hoped that ATACAS will yield data on the use of antiplatelet and antifibrinolytic agents immediately before surgery; however, it will not answer the question about the preoperative use of aspirin, because the late use of aspirin (within 5 days of surgery) is an exclusion criterion.

\textbf{Study Limitations}

One major limitation of the CVIR database is that it includes patients who have had surgery, but it does not include those who had CABG planned but did not undergo surgery owing to a preoperative illness that made surgery too much of a risk. If all patients who had planned CABG were included in the cohort, we might have found that early ASA discontinuation was associated with preoperative MI or stroke. Also, this was a single-center study. The CVIR database did not collect
information on ASA dose at the time of discontinuation or on exact ADP inhibitor use. The timing of ASA discontinuation was left to the discretion of individual surgeons. In 2008, we began to collect data regarding the dose of aspirin used as well as the actual day it was discontinued relative to the surgical date. These data were not available for the present study population (January 1, 2002, to January 31, 2008). We were unable to adjust for clopidogrel use; ideally, we would collect data on clopidogrel use within 5 days of surgery. Also, we do not have data on the effect of ASA dose on bleeding complications; presumably, there is no difference. We are currently collecting these data for patients undergoing open-heart surgery at our institution. In addition, the CVIR now collects data on medications used within 30 days before surgery and records the date of cessation as well. Antifibrinolytic use is not captured in the CVIR database. Except for an early study in the 1980s, aprotinin has not been used regularly at the Cleveland Clinic Foundation. Aminocaproic acid is used routinely for all CABG cases at the Cleveland Clinic Foundation as a loading dose, then given as an infusion during the case.

Past studies that argued for early discontinuation focused on several markers of increased bleeding. Here, we were able to report the number of transfusions used and the rate of reoperation for bleeding. We did not have data for the total amount of chest tube drainage or the rate of chest tube drainage. It is presumed that very high chest tube drainage or fast drainage would prompt reexploration in certain cases, transfusion of blood products, or both.

There are inherent limitations on the generalizability of a retrospective study regarding the discontinuation of ASA before CABG. A randomized, controlled trial would be ideal to control for unforeseen confounders. With the use of a propensity model to match the populations, we tried to come as close as possible to comparing groups similar in all ways except for their timing of ASA discontinuation.

Conclusions
The late use of ASA is associated with an increased use of transfusions but no statistically significant difference in reoperations for bleeding. There was no difference in post-operative MI or stroke or in-hospital all-cause mortality. Thus, on the basis of the present study, we recommend that clinicians weigh the risks and benefits of late ASA use on the basis of the patient’s risk profile before CABG.

Acknowledgment
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Disclosures
None.

References


CLINICAL PERSPECTIVE

The use of aspirin for patients with proven coronary artery disease is nearly ubiquitous, especially in those undergoing revascularization, whether percutaneous or surgical. The American Heart Association (AHA), American College of Cardiology (ACC), and Society of Thoracic Surgeons (STS) have given guidance as to the use of aspirin prior to coronary artery bypass grafting based on evidence mostly collected in the 1980s and 1990s. These guidelines are influenced by concerns of increased bleeding in the postoperative period and differ between societies. Thus, in the elective coronary artery bypass grafting population, aspirin is routinely discontinued up to 1 week prior to surgery. However, there is increasing concern that the discontinuation of aspirin, especially in patients with prior percutaneous coronary intervention, is linked to increased myocardial infarction, stroke, and death. More recently, there have been studies suggesting increased mortality in those who discontinue aspirin early before surgery. In our study of >4000 patients undergoing elective, isolated coronary artery bypass grafting, there was no significant difference between those with early discontinuation of aspirin (≥6 days before surgery) and late aspirin use (within 5 days) with regards to the composite outcome of in-hospital mortality, myocardial infarction, and stroke. Late use was associated with more intraoperative transfusion and postoperative transfusion but similar number of reoperations for bleeding. Thus, late use of aspirin results in no difference in the postoperative cardiovascular outcomes; however, there is an increased risk of bleeding and transfusion requirements.

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Effect of Timing of Chronic Preoperative Aspirin Discontinuation on Morbidity and Mortality in Coronary Artery Bypass Surgery
Miriam Jacob, Nicholas Smedira, Eugene Blackstone, Sarah Williams and Leslie Cho

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SUPPLEMENTAL MATERIAL

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eFigure Legend:

eFigure 1. Mirrored histogram of distribution of propensity scores for Aspirin Usage groups.

Mirrored histogram of distribution of propensity scores for Early Discontinuation (bars above zero line) and Late Use (bars below zero line). The darkened area represents matched patient pairs, showing that they cover the complete spectrum of cases.

eFigure 2. Covariate balance description before and after matching between Early Discontinuation versus Late Use groups.

Values in the x-axis represent the percent standardized difference between Early Discontinuation and Late Use groups.
eFigure 1

Aspirin Stopped Prior to 5 Days

Aspirin Within 5 Days

Number of Subjects

Propensity Score
Figure 2
Appendix 1: **Variables considered for multivariable logistic regression**

An asterisk denotes variables used in the final propensity model.

**Demographic:** Age (years)*, gender*, weight (kg), height (cm), body surface area (m$^2$), body mass index (kg•m$^{-2}$)*.

**Symptoms:** NYHA functional class (I-IV), Canadian Angina Class*.

**Ventricular dysfunction:** degree of left ventricular dysfunction (1=None, 2=mild, 3=moderate, 4=severe)*, Ejection fraction (%), Hypertension*.

**Valve Pathology:** Aortic valve: regurgitation*, stenosis,
Mitral valve: regurgitation*, stenosis,
Tricuspid valve: regurgitation.

**Coronary anatomy:** Left main trunk disease (maximum % stenosis)*, left anterior descending coronary artery system disease (maximum % stenosis)*, right coronary artery system disease (maximum % stenosis)*, left circumflex coronary artery system disease (maximum % stenosis)*.
**Other cardiac comorbidity:** Atrial fibrillation, history of MI*, history of cardiac disease, history of cardiac surgery*, complete heart block/Pacer*, ventricular arrhythmia.

**Noncardiac comorbidity:** History of diabetes*, history of peripheral vascular disease*, history of smoking, carotid disease, COPD*, popliteal disease, peripheral vascular disease, cholesterol values, triglycerides, BUN*, creatinine*, bilirubin*, hematocrit*.

**Experience:** Date of operation (years since 1/1/1997)*.

Influence du délai d'interruption préopératoire du traitement chronique par l'aspirine sur la morbidité et la mortalité chez les patients relevant d'un pontage aorto-coronaire

Miriam Jacob, MD ; Nicholas Smedira, MD ; Eugene Blackstone, MD ; Sarah Williams, MS ; Leslie Cho, MD

Contexte—Il a été établi que l’administration d’acide acétylsalicylique (AAS) diminue la mortalité et l’incidence des événements ischémiques après réalisation d’un pontage aorto-coronarien (PAC) ; les avis divergent toutefois quant à l’intervalle qu’il y a lieu de respecter entre l’interruption du traitement chronique par l’AAS et l’intervention chirurgicale pour prévenir les complications hémorragiques postopératoires. Nous avons donc utilisé la base de données du registre des informations cardiovasculaires de la Cleveland Clinic (Ohio, Etats-Unis) pour évaluer l’influence exercée par le délai d’arrêt de l’AAS avant la réalisation du PAC sur l’incidence des événements cardiovasculaires majeurs et des hémorragies postopératoires.

Méthodes et résultats—Entre le 1er janvier 2002 et le 31 janvier 2008, 4 143 patients ont fait l’objet d’un PAC à la Cleveland Clinic alors qu’ils avaient pris de l’AAS sur le long cours avant l’intervention. Parmi eux, 2 298 avaient arrêté l’AAS au moins 6 jours avant d’être opérés (interruption précocèe) et les 1 845 autres avaient continué à prendre le médicament au cours des 5 jours ayant précédé l’intervention (poursuite tardive). En raison des importantes différences existant entre ces deux groupes, nous avons procédé à une analyse du score de propension et à un apprentissage en fonction de 31 variables afin de pouvoir comparer les taux d’événements de façon équitable. Nous avons ainsi constitué 1 519 paires de patients parfaitement concordantes (représentant 73 % de la cohorte initiale). Aucune différence significative n’a été relevée entre les patients qui avaient interrompu précoce leur traitement par l’AAS et ceux qui l’avaient poursuivi tardivement en termes d’incidence du critère de jugement composite regroupant le décès pendant l’hospitalisation, l’infarctus du myocarde et l’accident vasculaire cérébral (1,7 % versus 1,8 % ; p = 0,80). La poursuite tardive du traitement a également diminué les taux de recours aux transfusions peropératoires (23 % versus 20 % ; p = 0,03) et postopératoires (30 % versus 26 % ; p = 0,009), mais le nombre de réinterventions motivées par des saignements a été comparable dans les deux groupes (3,4 % contre 2,4 % ; p = 0,10).


Mots clés : aspirine □ artériosclérose □ pontage □ maladie coronaire □ chirurgie

Le gène Notch1 exprimé par les cellules médullaires commande la réparation cardiaque après infarctus du myocarde

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Contexte—On connaît mal les voies de signalisation qui régulent le recrutement des cellules médullaires (CM) vers un territoire myocardique léssé. Les récepteurs Notch régissent la détermination binaire du destin cellulaire et pourraient également moduler la fonction des CM. On ignore toutefois si, par les signaux qu’il envoie à ces cellules, le gène Notch1 joue un rôle de commande de la régénération des tissus myocardiques léssés.

Méthodes et résultats—Les souris chez lesquelles une délétion cardiosélective de Notch1 a été pratiquée après leur naissance se montrent semblables aux animaux témoins en termes de taille d’infarctus et de fonction cardiaque après induction d’une lésion ischémique. En revanche, les souris porteuses d’une délétion hétézygote globale de Notch1 (N11) présentent des infarctus plus étendus et une fonction cardiaque plus fortement altérée. Après que la moelle osseuse (MO) de souris N11 a été transplantée chez des souris de type sauvage (TS), les infarctus développés par ces dernières ont été de plus grande taille, leur fonction cardiaque a présenté une dégradation plus marquée et la formation de néovaisseaux dans la zone bordant l’infarctus a été diminuée comparativement à ce qui a été observé chez des souris TS ayant reçu de la MO provenant d’homologues TS. En revanche, la greffe de MO de souris TS chez des animaux N11 a atténué les lésions myocardiques engendrées chez ces derniers. De fait, la délétion hétézygote du gène Notch1 au sein des CM contribue à diminuer le recrutement, la prolifération et la survie des cellules souches mésenchymateuses (CSM). Comparativement à celle de CSM de souris TS, l’injection de CSM provenant d’animaux N11 dans le territoire myocardique infarci a pour effet de majorer la lésion tissulaire, alors que l’injection de CSM suxprimant le domaine intracellulaire de Notch1 diminue la taille d’infarctus et améliore la fonction cardiaque.

Conclusions—Ces observations montrent que les signaux émis par Notch1 en direction des CM jouent un rôle majeur dans la réparation cardiaque et que, dès lors, l’approche consistant à intensifier ces signaux pourrait présenter un intérêt thérapeutique chez les patients atteints d’une affection cardiaque d’origine ischémique. (Traduit de l’anglais : Notch1 in Bone Marrow–Derived Cells Mediates Cardiac Repair After Myocardial Infarction. Circulation. 2011;123:866–876.)

Mots clés : cellules souches □ thérapie génique □ infarctus du myocarde □ angiogénèse

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