# Perioperative Management of Antiplatelet Agents in Patients Undergoing Cardiac Surgery

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SURGICAL REVASCULARIZATION for coronary artery disease is one of the most common surgeries performed. With constant aging of the world's population and the increase in the number and complexity of percutaneous coronary interventions (PCIs), there is a shift toward performing coronary artery bypass graft (CABG) surgery among an elderly and sicker patient population. To reduce the risk of cardiovascular events in these higher-risk patients, there is a need for more intensive medical therapy, including the use of antiplatelet agents. The caveat is that these patients are also at an increased risk for adverse events and complications related to medical therapy.

Antiplatelet medications are the most important drug therapy for patients with acute and chronic cardiovascular disease.[1,2] Although their use has proven to be beneficial in reducing cardiovascular events, the administration of these medications also is associated with an increased risk of bleeding, which is an important factor in cardiovascular outcome.[3,4] Because antiplatelet agents commonly are used in patients undergoing cardiovascular surgery, bleeding often occurs in these patients during the perioperative period, which significantly affects morbidity and mortality, reoperation rates, blood transfusions, intensive unit and in-hospital length of stay, and the incidence of associated complications. With the recent introduction of newer and more potent antiplatelet agents, it is particularly important to have clear guidelines for the use of these medications in patients undergoing cardiac surgery during the perioperative period.

## A REVIEW OF CURRENT ORAL ANTIPLATELET AGENTS

### Aspirin

Aspirin targets cyclooxygenase-1 and inhibits the formation of thromboxane A2. This results in the functional permanent inhibition of platelet activity. Aspirin is the most commonly prescribed drug for patients with cardiovascular disease, and most patients with acute coronary syndrome (ACS) who are referred for CABG surgery will be treated with aspirin. There is variability among surgeons and among guidelines on the perioperative use of aspirin for cardiac and noncardiac surgery because of concerns about bleeding on one hand and the increased tendency for a hypercoagulopathic state during the perioperative period on the other hand. Many cardiac surgeons feel comfortable to continue aspirin therapy up to the day of surgery, whereas others prefer early discontinuation of the drug and readministration after the surgery.[5]

#### *Beneficial Effects of Aspirin in Patients Undergoing CABG Surgery*

*Effect of Aspirin on Graft Patency.* Saphenous vein graft harvesting, and the subsequent exposure of grafts to arterial pressure, cause endothelial damage that may lead to platelet aggregation and graft thrombosis. The administration of aspirin and dipyridamole during the perioperative period improves saphenous vein graft patency both early (<1 month) and at 1 year and is associated with a decrease in lipid accumulation in the graft.[6] Further support for the use of aspirin postoperatively comes from a systematic review of studies by the Antiplatelet Trialists' Collaboration. This review showed that early initiation of aspirin was associated with improved graft patency during the first year after surgery. According to this report, restarting aspirin before surgery or within 24 hours after surgery had a similar effect.[7] It is important to note that aspirin was effective for improving graft patency when administered in doses of 75 to 325 mg/d. Higher doses had no additive benefit and were associated with an increased risk of side effects.[7] Therefore, the lower doses are preferable for this indication (Table 1).

*Effect of Aspirin on Mortality.* Aspirin is effective in reducing mortality in patients undergoing CABG surgery, whether related to graft patency or simply to the existence of cardiovascular disease in these patients. In a study from the Mayo Clinic that included 1,636 patients undergoing their first isolated CABG surgery, patients receiving preoperative aspirin had significantly lower postoperative in-hospital mortality compared with those not receiving preoperative aspirin (1.7% *v* 4.4%, $p = 0.007$). There were no differences in bleeding or cerebrovascular events between groups in this study.[8] In a large case control study in New England that included 8,641 consecutive isolated CABG procedures, preoperative aspirin use by patients was associated with a 27% reduction in in-hospital mortality.[9]

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**Table 1. Antiplatelet Agent Recommendations for Patients Undergoing CABG Surgery**

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| Aspirin (100-325 mg daily) should be administered to CABG patients preoperatively |
| Clopidogrel and ticagrelor should be discontinued for at least 5 days before elective CABG surgery |
| Prasugrel should be discontinued for at least 7 days before elective CABG surgery |
| In patients referred for urgent CABG surgery, clopidogrel and ticagrelor should be discontinued for at least 24 hours to reduce major bleeding complications |
| Short-acting intravenous glycoprotein IIb/IIIa inhibitors (eptifibatide or tirofiban) should be discontinued for at least 2 to 4 hours before CABG surgery |
| The GP IIbIIIa inhibitor abciximab should be discontinued for at least 12 hours before CABG |

Adapted from the 2011 American College of Cardiology Foundation, American Heart Association Task Force on Practice Guidelines guidelines.[11]

*Risk of Using Aspirin During the Perioperative Period*

Today, more cardiac surgeons feel comfortable with the perioperative use of aspirin. However, the concern regarding bleeding risk remains. A recent study from the Cleveland Clinic showed no difference in the cardiovascular outcome, but it did show an increased bleeding rate when aspirin was continued.[10] The recommended aspirin dose ranges between 75 and 325 mg/d.[11,12] The current joint guidelines recommend that aspirin should be given preoperatively, and if aspirin is not given preoperatively, it should be given within 6 hours postoperatively and continued indefinitely (Table 1).[11] If postoperative bleeding prevents the early administration of aspirin, it is recommended that aspirin be started as soon as possible. For patients allergic to aspirin, it is recommended that clopidogrel, 300 mg, be administered as a loading dose 6 hours after surgery followed by 75 mg daily.[12]

## Thienopyridines

Thienopyridines are prodrugs that are biotransformed into molecules that bind irreversibly to the P2Y12 receptor. Three thienopyridines are available: ticlopidine, clopidogrel, and prasugrel. Ticlopidine rarely is used today because of its side effects. Thienopyridines usually are prescribed as part of a treatment regimen for patients with recent ACS or after PCI. The indications for their use and discontinuation differ accordingly.

## Clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi Pharmaceuticals)

Clopidogrel is a prodrug that is metabolized to its active metabolite by the hepatic cytochrome CYP2C19 and CYP3A4 enzymes. The active metabolites bind to the platelet P2Y12 receptor irreversibly and thus inhibit the binding of adenosine diphosphate (ADP) to the platelet P2Y12 receptor for the entire lifespan of these platelets.[13,14]

*Beneficial Effects of Clopidogrel in Patients Undergoing CABG Surgery*

Treatment with dual antiplatelet agents is recommended for patients with recent ACS. In the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial, patients with ACS received aspirin and clopidogrel (300-mg loading dose followed by 75-mg daily dose) or placebo for 9 to 12 months.[15] Clopidogrel was associated with reduced cardiovascular death, myocardial infarction, or stroke in patients with ACS regardless of whether they underwent revascularization or not and the type of revascularization.[15,16] In patients with ACS who were treated with CABG surgery, clopidogrel administration before CABG surgery was associated with an 11% relative risk reduction.[15] The median time to CABG surgery in the CURE trial was 26 days. The benefit of clopidogrel in reducing the risk of ischemic events compared with placebo was observed mainly before CABG surgery compared with after surgery. Therefore, it is recommended that patients with ACS be treated with clopidogrel as soon as the diagnosis of ACS is made and that clopidogrel, 75 mg/d, be continued for 9 to 12 months after the procedure in addition to treatment with aspirin.[12] In the ACUITY (Acute Catheterization and Urgent Intervention Triage strategY) trial, 13,819 patients with moderate- or high-risk non–ST-elevation ACS underwent early invasive management. The timing of clopidogrel initiation was per investigator discretion; 1,539 patients underwent CABG surgery, 50.9% of whom received clopidogrel before surgery. The patients who received clopidogrel before surgery had fewer ischemic events but prolonged hospitalization. There was no difference in CABG-related bleeding (about 50%) in both groups.[17] There are less data regarding the effect of clopidogrel on graft patency. The results of a small randomized trial suggested that adding clopidogrel to aspirin improved radial artery graft patency.[18]

*Risk of Using Clopidogrel During the Perioperative Period*

The use of clopidogrel is associated with an increase in the incidence of bleeding and the need for transfusions after surgery.[15,17,19] The highest bleeding risk exists if surgery is performed soon after treatment with clopidogrel. When clopidogrel is withheld for a longer duration, the risk is lower.[20,21] In fact, when clopidogrel is withheld more than 5 days before CABG surgery, the bleeding risk is not increased.[17] Therefore, it is recommended that clopidogrel be discontinued for at least 5 days before elective CABG surgery.[11] When surgery is more urgent, it is recommended to wait at least 24 hours after the last dose of clopidogrel to avoid major bleeding risk. Performing CABG surgery earlier than 5 days after clopidogrel discontinuation may be reasonable for patients with ACS. The decision about the timing of surgery depends on the urgency of the procedure, which is reflected by the anatomic findings on coronary angiography and the clinical status of the patient.

Results from the ACUITY trial showed that most patients with ACS who received clopidogrel and are treated by CABG surgery, undergo surgery within <5 days from clopi-