Use of Antiplatelet Drugs After Cardiac Operations

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Unfortunately, venous bypass grafts still have a prominent role in operative coronary revascularization (coronary artery bypass graft [CABG]). Venous grafts develop pathologically occlusive disease that limits the effectiveness of CABG, and antiplatelet drugs following operation may limit this problem. The types and indications of antiplatelet drugs following CABG generate some controversy in the recent literature. This review surveys relevant evidence about the use of antiplatelet drugs following CABG to identify the controversial issues, define appropriate questions, and attempt to provide evidence-based interventions that may be helpful in limiting graft occlusion after CABG. Evidence suggests that, in most CABG patients, dual antiplatelet drugs (aspirin and clopidogrel), given after operation, minimizes early (within 1 year) graft failure and improves intermediate-term outcomes, better than single antiplatelet therapy with aspirin alone. There are gaps in the knowledge base that supports this contention, and future clinical trials will likely augment or alter this recommendation.

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QUESTIONS ABOUND ABOUT DUAL ANTIPLATELET THERAPY

The Bleeding Risk of Dual Antiplatelet Therapy and the Effect on Vein Graft Patency

Patients with acute coronary syndromes (ACS) derive long-term event-free benefit from dual antiplatelet therapy. A minority of patients with ACS (10%-20%) require urgent or emergent operation after initial treatment of ACS. Inevitably, some patients on dual antiplatelet drugs will have coronary artery bypass graft (CABG), while on therapeutic doses of these drugs. The effect of stopping dual antiplatelet therapy before operation on vein graft patency is uncertain. This uncertainty is reflected in the diversity of surgeons’ preferences about dealing with preoperative antiplatelet drugs.1

In the modern era, preoperative clopidogrel is an essential risk factor for blood transfusion, for re-exploration due to bleeding, and for life-threatening bleeding.2 One study found that, aside from preoperative medications like clopidogrel, there are no strong preoperative multivariate clinical risk factors that predict postoperative bleeding. Contrary to the findings of the post hoc analyses of randomized trials, observational studies showed that recent exposure to clopidogrel before CABG translates to increased risk of postoperative death, reoperations for bleeding, blood loss, and need of blood transfusions.3 Clopidogrel plus aspirin treatment within 5 days before surgery increased the risk of bleeding and reoperation in all CABG patients, irrespective of whether surgery was performed on- or off-pump.4 Importantly, stopping clopidogrel for even a few days reduces the bleeding risk in CABG patients.5 There is an approximate 20% decrease in bleeding risk with each day that clopidogrel is stopped before CABG. However, evidence-based guidelines continue to recommend stopping clopidogrel at least 5 days before CABG and that performing CABG on aspirin alone is associated with postoperative increased bleeding (usually mild) but likely decreases the long-term hazard of coronary events.6 Figure 1 is a summary of management principles in patients taking clopidogrel and aspirin before operation. Importantly, there is almost no evidence that addresses the effect of preoperative antiplatelet therapy on postoperative vein graft patency. Traditional
dogma suggests that vein graft patency is independent of the presence of antiplatelet drugs before or during operation. This dogma allowed surgeons to stop antiplatelet drugs before operation without fear of progression of postoperative graft thrombosis as long as antiplatelet drugs were started shortly after operation. Given our current understanding of the pathophysiology of vein graft disease, the optimal time to have an antiplatelet effect for limiting vein graft disease is when the vein graft is harvested. Intimal injury-inducing platelet activation and deposition is the inciting event for the progression of vein graft disease. It makes sense to have an antiplatelet effect while harvesting venous conduit as most platelet-related intimal injuries occur at the time of harvest. Adding antiplatelet therapy after intimal injury is a little like “closing the barn door after the horse has been stolen.” It is possible that the best way to minimize vein graft disease is to have an antiplatelet effect on board at the time of vein graft harvest. Of course, the bleeding risk of antiplatelet drugs produces other concerns that argue in favor of stopping antiplatelet drugs before operation. Newer strategies are needed that provide a local antiplatelet effect that minimizes intimal injury to harvested vein grafts while limiting the systemic bleeding risk associated with these drugs.

Postoperative Antiplatelet Drugs and Bypass Graft Patency

Thrombosis of vein grafts limits the benefits of coronary artery operations. There is a continuous annual risk of graft loss, mainly vein grafts, following operative coronary revascularization (CABG). Graft loss is greatest in the first year after operation due to conduit trauma, intimal disruption, and reactive inflammation associated with harvest and implantation into arterial pressure. The re-endothelialization of venous conduits is particularly sensitive to platelet deposition in endothelial-traumatized surfaces with development of neointimal hyperplasia and ultimately atherosclerosis. Based on this pathophysiology, antiplatelet regimens aimed at limiting harmful re-endothelialization make intuitive sense.

Nearly all of the evidence that antiplatelet drugs minimize vein bypass graft disease is limited to 2 drugs: aspirin and clopidogrel. These 2 drugs alter platelet function at 2 different sites in the platelet activation mechanism. Aspirin inhibits the cyclooxygenase
pathway activated by arachidonic acid, and clopidogrel inhibits the P2Y12 adenosine diphosphate surface receptor. It is not reasonable to lump all drugs that inhibit platelet P2Y12 adenosine diphosphate receptors into a single category. Virtually no evidence exists regarding the effect of newer antiplatelet drugs, like prasugrel, ticagrelor, and cangrelor on vein graft patency. Until more evidence dealing with the effect of nonclopidogrel antiplatelet drugs on graft patency appears in the literature, rational recommendations by necessity apply only to aspirin and clopidogrel in postoperative CABG patients.

There is very little evidence that antiplatelet therapy after operation affects arterial bypass graft patency (particularly internal mammary artery grafts).9,9 For the most part, concerns about perioperative antiplatelet regimens relate to saphenous vein graft patency. Beginning in the 1980s, the use of antiplatelet drugs, mainly aspirin, following CABG gained acceptance for limiting postoperative vein graft occlusion.10,11 Despite these older randomized trials, the use of antiplatelet drugs following CABG continues to generate interest and controversy, so much so, that at least 2 recent meta-analyses and systematic reviews appeared in the literature about this subject.8,12 In these analyses, dual antiplatelet therapy, with clopidogrel and aspirin, led to improved early vein graft patency compared with aspirin alone. This benefit of dual antiplatelet therapy following CABG did not extend to arterial graft patency,16 and once a vein graft is occluded, percutaneous approaches to graft occlusion are fraught with risk and have limited success.13 Patients with prior CABG who develop ACS have a poor prognosis, substantially worse than for those without prior CABG.14

Contrary evidence, although limited, suggests no or minimal benefit of dual antiplatelet therapy on graft patency. Two publications reviewed available evidence dealing with the effect of dual antiplatelet drug therapy after CABG on vein graft patency.15,16 Although these studies suggested modest, if any, benefit from dual antiplatelet therapy after CABG, both of these studies identified knowledge gaps in the available evidence. Study data were limited to subgroup analyses, observational studies, and trials with surrogate end points. The authors uniformly concluded that more evidence from randomized trials assessing hard end points is necessary to sort out the benefits of dual antiplatelet therapy in limiting vein graft disease after CABG.

The benefit of antiplatelet drugs for limiting vein graft thrombosis is offset by the risk of perioperative bleeding if dual antiplatelet drugs are given shortly before, or early after, operation. Evidence-based guidelines and current studies recommend discontinuing clopidogrel and other P2Y12 inhibitors before CABG.17-19 The most serious risk of taking dual antiplatelet therapy up until the time of CABG is life-threatening bleeding,20 but reports indicate that surgeons are unwilling to limit dual antiplatelet therapy before operation,1 despite guideline-recommended warnings against this practice. Although it is possible that therapeutic dual antiplatelet drug effect at the time of vein graft harvest may lessen vein graft disease, the exact effect of discontinuing dual antiplatelet drugs before operation on graft patency is uncertain and individual variability in drug responsiveness compounds this uncertainty.

Evidence-Based Indications for Dual Antiplatelet Drugs After CABG (Drug-Eluting Stents, ACS, and Recent Myocardial Infarction)

The current guidelines favor the use of aspirin in combination with clopidogrel (dual antiplatelet therapy) to reduce atherothrombotic risks based on the results of a number of large clinical trials. These large randomized trials (CURE, CREDO, ACUITY, CHARISMA, etc) found that dual antiplatelet therapy reduces death, myocardial infarction (MI), and stroke at 1 year in patients with ACS or with recent drug-eluting stents, compared with aspirin alone. These studies suggest benefit from dual antiplatelet therapy, regardless of whether CABG is part of the treatment for patients with ACS.21 A logical extension of these observations is that patients having CABG for ACS should be on dual antiplatelet therapy after operation independent on their effect on graft patency for at least 1 year after operation. Several studies suggest that the combination of aspirin and clopidogrel given in the early postoperative period translates into improved short- and longer-term outcomes up to 1 year after operation.22-24 In a study, among patients with MI revascularized by CABG, only 27% received clopidogrel after discharge.25 These authors found that clopidogrel-treated patients had a lower risk of the combined end point of death or recurrent MI. They concluded that increased focus on discharge clopidogrel treatment of these patients should be made.

Very little evidence supports use of dual antiplatelet therapy for more than a year following a coronary event, regardless of whether the treatment regimen included CABG. A meta-analysis of randomized trials found that extension of dual antiplatelet therapy beyond a year increases the risk of bleeding without reducing ischemic events.25 In particular, Sanon et al26 found that dual antiplatelet therapy did
not provide survival benefit compared with aspirin alone at an average of 4 years after CABG. Nonetheless, because of the large population represented in trials like the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) and others, the weight of evidence supports use of dual antiplatelet drugs for a year in patients with ACS undergoing CABG.

Point-of-Care Platelet Function Testing and Aspirin “Resistance”

There is well-recognized variability in the efficacy of antiplatelet drugs to limit platelet reactivity. New evidence addresses the adequacy of platelet inhibition caused by single and dual antiplatelet drugs. Point-of-care testing allows nearly immediate assessment of platelet reactivity in the perioperative period and allows identification of nonresponders to antiplatelet drugs. For example, a study found that aspirin did not inhibit platelet reactivity in more than 40% of patients immediately after CABG. Aspirin nonresponders may benefit from addition of clopidogrel or other P2Y12 inhibitors in the postoperative period. Point-of-care testing allows identification of those patients with drug resistance who may benefit from dual antiplatelet therapy after CABG, but without more clinical evidence this assertion is speculative.

THE EVIDENCE AND PROBLEMS WITH UNANSWERED QUESTIONS

Platelet Inhibition by Antiplatelet Drugs Started After Operation: Drug Resistance

Variability in individual responsiveness, including “resistance,” risks thrombotic events in patients despite receiving apparently appropriate antiplatelet therapy. This is particularly true of patients after cardiac operations. The antiplatelet effect of aspirin immediately after CABG is limited. Aspirin inhibition of thromboxane B2 production and arachidonic acid–induced platelet aggregation are markers of platelet inhibition early after CABG. The median thromboxane B2 inhibition >90% (the value required for full platelet inhibition) was not achieved until postoperative day 5 in most patients. Further, postoperatively administered acetylsalicylic acid (300 mg) did not sufficiently inhibit platelet aggregation in 46.5% of post-CABG patients. In this group of patients either an increase in aspirin dose or a switch to dual antiplatelet therapy should be considered (Fig. 2).

Adequate antiplatelet effect is a balance. Very low platelet reactivity in patients on dual antiplatelet drugs risks bleeding, whereas high platelet reactivity risks enhanced aggregation, thrombosis, and acceleration of vein graft disease. Consensus statements and practice guidelines propose a “therapeutic index” for dual antiplatelet therapy that minimizes

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**Figure 2.** Flowchart describing recommended postoperative management of dual antiplatelet drugs. (Color version of figure is available online at [http://www.semthorcardiovascsurg.com](http://www.semthorcardiovascsurg.com).)
bleeding risk and optimizes antithrombotic effect. Careful monitoring of antiplatelet effect optimizes this “therapeutic index.”

**Point-of-Care Testing to Manage Antiplatelet Drug Use Before and After CABG**

Recent prospective randomized trials using point-of-care platelet function tests to guide therapy in medically managed patients did not demonstrate clinical benefit of these tests, thus questioning whether treatment modification based on the results of these tests can actually influence outcomes. These trials had major limitations. Point-of-care tests vary widely and measure different aspects of platelet function. Arguably, the most important feature of point-of-care testing from a surgical perspective is the value of finding on-treatment normal platelet reactivity before CABG. Approximately 30% of patients taking dual antiplatelet drugs have normal platelet reactivity and reduced bleeding risk from CABG. The finding of normal platelet reactivity while on dual antiplatelet therapy minimizes waiting times in patients who need urgent CABG. Various point-of-care platelet function tests predict perioperative CABG bleeding in patients on dual antiplatelet drugs. As a generalization, residual platelet reactivity between 30% and 40% of baseline predicts excessive bleeding and blood transfusion. Levels of platelet reactivity greater than these values provide adequate platelet reactivity. A strategy based on preoperative platelet function testing to determine the timing of CABG in clopidogrel-treated patients translated to the same amount of bleeding observed in clopidogrel-naive patients and allowed approximately 50% shorter waiting time than recommended in the current guidelines. Figure 1 provides an algorithm that addresses the management of patients requiring CABG who are treated with dual antiplatelet drugs before operation. This algorithm not only approximates multiple levels of evidence in a field that is changing, but also provides a safe approach to patients taking dual antiplatelet therapy before CABG.

**Antiplatelet Therapy Following Off-Pump Coronary Artery Bypass?**

Antiplatelet drug resistance is a problem especially in patients having off-pump CABG (OPCAB). Mannacio et al found that, for patients having OPCAB, combined clopidogrel and aspirin treatment overcomes single-drug resistances and improves venous graft patency, without risking increased bleeding. Platelet function testing, especially point-of-care tests, helps to estimate thrombotic and bleeding risk in OPCAB patients.

**Bridging Strategies**

Available evidence, both clinical and theoretical, suggests that bridging strategies that substitute short-acting antiplatelet drugs for longer acting dual antiplatelet agents before CABG reduces ischemic events in patients with recent drug-eluting stents who require urgent CABG. Among patients who discontinue clopidogrel therapy before cardiac surgery, the use of one short-acting antiplatelet agent (cangrelor) compared with placebo resulted in a higher rate of maintenance of platelet inhibition and potentially safe CABG without major bleeding.

**THE BALANCE—A RECOMMENDATION**

Figure 1 summarizes evidence-based management options in patients taking preoperative dual antiplatelet drugs. The effects of preoperative antiplatelet drugs on postoperative vein graft patency are largely unknown, but consideration of the pathophysiology of vein graft disease suggests that early antiplatelet effects at the time of vein graft harvest may limit vein graft disease but risk bleeding. A better understanding of the effect of perioperative antiplatelet drugs on vein graft harvest and subsequent vein graft disease is needed.

The bulk of available evidence about the effect of antiplatelet drugs on vein graft disease deals with antiplatelet drugs administered after operation. Figure 2 provides a synthesis of evidence about indications for dual antiplatelet drugs in patients after CABG. Figure 2 and the Table summarize clinical situations where either aspirin or aspirin plus clopidogrel have efficacy in limiting vein graft occlusions while minimizing bleeding and providing longer-term freedom from adverse events. Based on the features in the Table, it is possible to construct a treatment algorithm (Fig. 2) that facilitates decision making about use of dual antiplatelet therapy (ie, aspirin and clopidogrel) after CABG. The Table and Figure 2 do not meet rigorous Class I evidence-based guideline standards, but rather, for the most part, reflect available information from observational studies. The summaries reflected in the Table and Figure 2 are the best we can do, given the lack of more comprehensive evidence. To simplify and summarize the information in Figure 2, it is clear that most patients having CABG benefit from postoperative dual antiplatelet therapy for at least a year after operation.
THE FUTURE HOLDS HOPE

Perioperative Anti-fibrinolytic Drugs Combined With Preoperative Dual Antiplatelet Drugs

Clopidogrel exposure immediately before operation increases bleeding risk and transfusion requirements in patients having CABG. Tranexamic acid reduced this risk and provided extra protection in the patients with clopidogrel exposure before operation. Other anti-fibrinolytic drugs like aminocaproic acid and aprotinin could reduce the amount of transfusion during the perioperative period especially in patients with preoperative anemia taking dual antiplatelet drugs. A study suggests that aprotinin attenuated this blood loss in OPCAB patients. These observations are intriguing and suggest that dual antiplatelet drugs may provide counterbalance to anti-fibrinolytic drug-induced clotting in certain patients. Further study to determine optimal balance and patient selection for management of anti-fibrinolytic drugs combined with dual antiplatelet drugs is warranted. An important side effect of combining dual antiplatelet therapy with anti-fibrinolytics may be the availability of an antiplatelet drug effect during and after the intraoperative harvest of vein grafts. The effect of anti-fibrinolytic drugs on vein graft patency is uncertain, but likely to be minimal as vein graft disease initiates by a platelet-specific mechanism, not a mechanism that involves fibrinolysis. The combination of anti-fibrinolytic therapy and dual antiplatelet therapy provides an intriguing possibility to limit vein graft disease while minimizing perioperative bleeding risk.

Pathophysiology of Graft Failure After CABG

Understanding the pathophysiology of saphenous vein graft failure suggests diverse approaches that may limit this problem in the future. A recent review speculates that modification of surgical technique, enhanced conventional pharmacology, use of external sheaths, introduction of cytostatic drugs, and gene transfer offer possible interventions that may limit vein graft disease and prolong graft patency. The current data available show that there are promising experimental approaches (in vitro models and animal in vivo models) for pharmacological and gene therapeutic treatment to limit vein graft failure.

Certain drugs may limit graft disease. The results indicate that the antispasmodic and antiaggregatory effects of levosimendan are most active in vascular tissue and in platelets. The storage of radial artery with levosimendan before implantation may help to prevent the intraoperative spasm of the graft and subsequent thrombotic occlusion during CABG. Hyperhomocysteineemia may be a novel risk factor for the suppressed blood platelet response to ace-tysalicylic acid, and homocysteine may act as a
specific sensitizer of blood platelets to some agonists. Acetylated homocysteine reverses this effect. Acetylated homocysteine and allow aspirin to limit postoperative vein graft disease. These findings suggest a new beneficial effect of the acetylation properties of high-dose aspirin therapy. 40

Reducing Noncardiac Postoperative Complications With Dual Antiplatelet Therapy

Percutaneous interventions for coronary artery disease when compared with CABG have increased repeat interventions but reduced cerebrovascular event rates. An observational study suggests that addition of dual antiplatelet therapy to patients after CABG lessens the stroke risk. 40 Future studies evaluating the use of perioperative dual antiplatelet drugs in CABG patients to lessen stroke risk in high-risk patients are worth pursuing. Perioperative dual antiplatelet therapy may lessen thrombotic complications in certain high-risk individuals and future studies to address this possibility are worthy targets for research.

SUMMARY

We summarized the relevant evidence about the use of antiplatelet therapy after CABG. Synthesis of available, but less than optimal, evidence suggests that most patients having CABG could benefit from dual antiplatelet therapy started after operation. Gaps in the knowledge base exist, and these gaps are worth addressing in future studies.

POSTOPERATIVE ANTIPLATELET DRUGS


