REVIEW

Antiplatelet therapy for patients undergoing coronary artery bypass surgery

Christine M. DeStephan, David J. Schneider

Department of Medicine, Cardiovascular Research Institute, The University of Vermont, Burlington, Vermont, United States

Abstract

Considerable variation in the use and duration of antiplatelet medications during the perioperative and postoperative care of patients undergoing coronary artery bypass grafting (CABG) reflects the limited number of studies focused directly on these patients as well as the variation in the results reported. In this review we highlight the incidence and mechanisms of graft closure as well as the evidence in support of antiplatelet therapy that is balanced by the impact of antiplatelet therapy on the risk of bleeding to provide recommendations for the use of this therapy in patients undergoing CABG. Low-dose acetylsalicylic acid (ASA; ≤ 160 mg daily) reduces the incidence of perioperative myocardial infarction, acute renal injury, and mortality without increasing the risk of bleeding and so is recommended both before and after CABG. The use of dual antiplatelet therapy with ASA plus a $P2Y_{12}$ antagonist adds a greater risk of bleeding. While additional studies are required, we can make the following recommendations: because of increased bleeding and mortality when patients are treated with clopidogrel preoperatively, CABG should be delayed for five days. Because of increased bleeding when patients are treated with ticagrelor preoperatively, CABG should be delayed for three days. Because of increased bleeding when patients are treated with prasugrel preoperatively, CABG should be delayed for seven days. For patients who had a coronary stent placed preoperatively or had an acute coronary syndrome preoperatively, resumption of therapy with their $P2Y_{12}$ antagonist postoperatively for 12 months reduces the subsequent incidence of cardiovascular events.

Key words: coronary artery bypass grafting, antiplatelet therapy, acetylsalicylic acid, clopidogrel

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INTRODUCTION

Despite increased usage of percutaneous coronary intervention (PCI) for the treatment of coronary artery disease (CAD), coronary artery bypass grafting (CABG) remains an effective and durable treatment for multi-vessel CAD. Current guidelines recommend at least 12 months of dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and $P2Y_{12}$ antagonist for patients with acute coronary syndrome (ACS) and at least six months of DAPT for patients with stable CAD, who undergo percutaneous revascularisation. The perioperative and postoperative treatment with antiplatelet agents in patients undergoing surgical revascularisation has been less extensively studied, with varying results reported. Furthermore, there is considerable variation in the use and duration of antiplatelet medications after CABG. In this review we highlight the incidence and mechanisms of graft closure as well as the evidence in support of antiplatelet therapy that is balanced by the impact of antiplatelet therapy on the risk of bleeding to provide recommendations for the use of this therapy in patients undergoing CABG.

MECHANISMS OF BYPASS GRAFT FAILURE

An important limitation of CABG is saphenous vein graft (SVG) failure that is associated with recurrent angina, the need for repeated coronary revascularisation, myocardial infarction (MI), and death [1, 2]. The use of an internal thoracic artery graft has been associated with improved outcomes because of greater long-term patency [3]. At 10 years internal thoracic artery patency ranges from 85% to 91% [3, 4]. By contrast, failure of SVGs one year after surgery ranges from 10% to 25% [4, 5]. Between one to five years after CABG an additional 5% to 10% of SVGs will close, and from six to 10 years after CABG an additional 20% to 25% of SVGs will fail [6]. Thus, at 10 years SVG patency rates are approximately 50%, and only half of these are free of atherosclerosis [7]. SVG failure

Address for correspondence:
David J. Schneider, MD, Cardiovascular Research Institute, The University of Vermont, 308 S. Park Drive, Colchester, VT 05446, USA, tel: 802-656-8955, fax: 802-656-8932, e-mail: David.Schneider@med.uvm.edu

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can be considered as occurring early (within one month after CABG), intermediate (within the first year), or late [8].

Early graft failure that occurs within one month is primarily due to technical failure or thrombosis, most commonly at the site of anastomosis. Endothelial injury is a key trigger for early graft failure because exposure of blood to the sub-endothelium promotes platelet adhesion and thrombosis. Initial harvesting of the vein disrupts the vasa vasorum and adventitia and can cause endothelial injury because of hypoxia [9]. In addition, intraoperative assessment of graft integrity by high-pressure distension can induce endothelial injury [10, 11] and thereby expose the sub-endothelium to pro-inflammatory and pro-coagulant reactions, even before aortocoronary graft implantation. Implantation exposes the vein to arterial pressure increasing the venous diameter, causing turbulent blood flow and shear stress that can damage the endothelium layer [12].

Intermediate graft failure that occurs between one month and one year after CABG is caused primarily by progressive neointimal thickening that is both cellular and acellular. A primary inciting factor is the exposure of veins to arterial pressure, which is likely to affect all SVGs to some extent [13, 14]. Arterial blood flow damages the endothelium, leading to the release of growth factors and cytokines as well as initiating adhesion and activation of platelets and macrophages. Smooth muscle cells migrate from the media and proliferate. The migrated smooth muscle cells release extracellular matrix that contributes to neointimal thickening [15]. Factors that contribute to smooth muscle cell proliferation include reduction in nitric oxide produced by the endothelium as well as release of prostaglandins and adenosine [15, 16]. Migration and proliferation of smooth muscle cells and fibroblasts as well as extracellular matrix deposition contribute to neointimal hyperplasia, which encroaches on the lumen and promotes late graft failure from atherosclerosis [17].

Late graft failure that occurs more than one year after CABG is primarily caused by progressive atherosclerosis. Endothelial injury and neointimal hyperplasia initiate this process. SVG atherosclerosis differs from native coronary artery atheroma in that it tends to be more diffuse and concentric but less calcified [18]. SVG atherosclerosis occurs at two main sites: at the aortic anastomosis and in the main shaft of the graft. Shaft lesions have been associated with increased rates of death and MI because they exhibit a greater incidence of plaque rupture and no-reflow [18, 19].

In summary, SVG failure is an important limitation of CABG. Platelets play a key role in this process [20], which is initiated by endothelial injury. Techniques that limit endothelial injury are pivotal to long-term SVG patency. In light of the central role of platelets to SVG failure, antiplatelet therapy would be expected to limit SVG failure.

ANTIPLATELET AGENTS IN CABG

Early small studies with ASA, dipyridamole, and warfarin did not demonstrate clear benefits of these agents in the prevention of SVG failure. Chesebro et al. [21] compared the combination of ASA and dipyridamole with placebo in 407 patients undergoing CABG. Treatment was begun as early as 7 h after surgery. Coronary angiography performed at one-month follow-up showed that SVG patency was significantly greater in the antiplatelet therapy cohort (98% vs. 90%, $p < 0.001$). Longer-term follow-up in the same study showed a significant difference in patency favouring antiplatelet therapy (89% vs. 77%, $p < 0.001$), suggesting that ASA plus dipyridamole prevented late as well as early SVG failure [12]. The Veterans Administration Cooperative Study compared the use of different antiplatelet regimens for one year in 772 patients undergoing CABG [22]. Regimens tested included ASA 325 mg daily, ASA 325 mg three times daily, ASA plus dipyridamole (325 mg and 75 mg, three times daily), sulfinpyrazone (267 mg three times daily), and placebo (three times daily). At 60 days post-surgery, 555 patients (1781 grafts) had coronary angiography. Graft patency was as follows: ASA once daily 93.5%, ASA three times daily 92.3%, ASA and dipyridamole three times daily 91.9%, sulfinpyrazone 90.2%, and placebo 85.2% (all ASA regimens were superior to placebo, $p < 0.05$). These results established the role of ASA as beneficial in the prevention of SVG failure during the first year after CABG. In addition to its effect on graft patency, ASA reduces in-hospital mortality [22–24]. Recent meta-analyses have demonstrated that preoperative ASA reduces the risk of perioperative MI by 21% to 44% [25, 26]. In addition, mortality was reduced by 29% and acute kidney injury was reduced by 32% [26]. Accordingly, ASA is recommended before CABG in both European and American guidelines [27, 28].

DAPT with a $P2Y_{12}$ antagonist plus ASA prevents cardiovascular events after ACS and PCI. The most extensively studied agent is clopidogrel. Clopidogrel is a thienopyridine pro-drug that requires metabolism to its active form that binds irreversibly to the platelet $P2Y_{12}$ receptor [29]. Treatment of patients with ACS with the combination of ASA plus clopidogrel reduces the incidence of subsequent cardiovascular events [30]. In patients who had CABG, there was a trend favouring ASA plus clopidogrel with a reduction in the primary outcome (14.5% vs. 16.2%, ASA plus clopidogrel vs. ASA alone). The benefit in patients treated with ASA plus clopidogrel was seen before CABG while patients were waiting for surgery, and no benefit was demonstrated for clopidogrel after CABG [31].

No large randomised controlled trials have assessed the effect of DAPT on SVG patency. Gao et al. [32] randomised 249 patients to either clopidogrel 75 mg plus ASA 100 mg daily or ASA 100 mg alone starting within 48 h of surgery. SVG patency that was assessed by computed tomography angiography (CTA) in 90% of patients at three months demonstrated

a higher patency in the ASA plus clopidogrel group compared to ASA alone (91.6% vs. 85.7%, p = 0.04). The Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) trial was a randomised, double-blind, placebo-controlled trial comparing ASA 162 mg alone with ASA 162 mg plus clopidogrel 75 mg [33]. Graft patency was assessed in 113 patients at one year by coronary angiography combined with intravascular ultrasound. The combination of ASA plus clopidogrel did not significantly decrease the development of intimal hyperplasia or affect SVG patency (94.3% vs. 93.2%). Rafiq et al. [34] reported a randomised trial comparing ASA plus clopidogrel with ASA alone in patients undergoing CABG, who were deemed hypercoagulable by thromboelastography. They found no difference in SVG patency rates at three months. Mannacio et al. [35] assessed the impact of ASA 100 mg plus clopidogrel compared with ASA alone in 300 patients undergoing off-pump CABG and found that SVG failure assessed by CTA was reduced (7.4% vs. 13.1%, p = 0.04) by the combination of ASA plus clopidogrel. Based on these results, current guidelines recommend one year of DAPT after CABG in patients presenting with ACS or undergoing off-pump surgery [36].

Ticagrelor, a non-thienopyridine $P2Y_{12}$ antagonist that binds reversibly to the $P2Y_{12}$ receptor prevented cardiovascular events better than clopidogrel when combined with ASA in patients with ACS [37]. Among patients who were treated with CABG in the Platelet Inhibition and Patients Outcomes (PLATO) trial, the use of ticagrelor compared to clopidogrel was associated with better clinical outcomes both in ACS patients with prior CABG and in those who underwent a redo CABG [38, 39]. The primary and unexpected finding of reduced cardiovascular and total mortality among patients who had CABG was directionally consistent but substantially greater (more than twofold) compared with that of the parent study [37, 38]. Notably, the mortality benefits with ticagrelor were confined to patients in whom their $P2Y_{12}$ antagonist (ticagrelor or clopidogrel) was discontinued two to four days before surgery [38]. These results support the notion that a reversible $P2Y_{12}$ antagonist may have beneficial effects related to the redistribution of ticagrelor to young platelets released after surgery [40, 41]. CABG is associated with the release of young platelets that are pro-thrombotic [41]. Outcomes in patients undergoing CABG in the PLATO trial suggest that modest $P2Y_{12}$ antagonism with ticagrelor discontinued two to four days before surgery will decrease mortality. A retrospective analysis of the TRITON-TIMI 38 trial, in which a risk-adjusted assessment of patients who underwent CABG after presenting with ACS, demonstrated a significantly reduced all-cause mortality with prasugrel compared with clopidogrel (2.31% vs. 8.67%, p = 0.025) [42].

A small hypothesis-generating study demonstrated that initiation of ticagrelor after CABG may improve SVG patency [43]. A total of 70 patients were enrolled in the study and randomised to ASA alone or ASA plus ticagrelor 90 mg twice daily. Graft occlusion occurred in 7/25 (28.0%) patients on ASA plus ticagrelor and in 17/31 (48.3%) on ASA alone (p = 0.044). A recently published study from six tertiary hospitals in China compared ticagrelor plus ASA, ticagrelor alone, or ASA alone in 500 randomised patients undergoing elective CABG. Patients and physicians were not blinded to treatment allocation. The primary outcome was SVG patency assessed one year after CABG by either CTA or coronary angiography. Among the 500 randomised patients (mean age 63.6 years; 91 women [18.2%]), 461 (92.2%) completed the trial. SVG patency rates one year post-CABG were 88.7% (432 of 487 vein grafts) with ticagrelor plus ASA, 82.8% (404 of 488 vein grafts) with ticagrelor alone, and 76.5% (371 of 485 vein grafts) with ASA alone. The difference between ticagrelor plus ASA compared with ASA alone was significant (12.2%, 95% confidence interval [CI] 5.2%–19.2%, p < 0.001), whereas the difference between ticagrelor alone compared with ASA alone was not significant (6.3%, 95% CI 1.1%–13.7%, p = 0.10). Five major bleeding episodes occurred during one year of follow-up (three with ticagrelor + ASA; two with ticagrelor alone). This evidence suggests that the combination of ticagrelor and ASA increased graft patency after one year [44]. In summary, a series of smaller trials suggest that the use of ticagrelor may reduce the incidence of SVG failure. Fortunately, two larger trials are actively recruiting patients to assess the impact of ticagrelor on SVG patency [45, 46].

BLEEDING, TRANSFUSION, AND ANTIPLATELET AGENTS IN CABG

Bleeding and the transfusion of blood products in patients undergoing CABG have been independently associated with an incrementally greater risk of death in direct proportion to the number of units transfused [47–50]. The adverse consequences of bleeding that contribute to mortality include end-organ hypoperfusion that can lead to multiple organ dysfunction syndrome [50]. Transfusion of blood products is associated with haemolytic and non-haemolytic reactions, transmission of infectious diseases, transfusion-related acute lung injury, and transfusion-associated circulatory overload [48]. Because any antiplatelet therapy can be expected to increase the risk of bleeding, the choice to administer antiplatelet therapy before surgery needs to balance the risks of bleeding with potential benefits.

A recent meta-analysis demonstrated that preoperative use of ASA was associated with an increased transfusion of blood products that was confined to higher doses of ASA because the use of low-dose ASA (≤ 160 mg/day) was not associated with an increase in transfusion [26]. Reoperation for bleeding was not increased by the preoperative use of ASA, but chest tube output was greater in patients receiving ASA preoperatively. Thus, the beneficial effects of ASA in the reduction of perioperative MI and the reduction in acute kidney injury are not offset by greater transfusion of blood

products or reoperation for bleeding when low-dose ASA is used. Consistent with these observations, mortality is reduced when low-dose ASA is used preoperatively.

While low-dose ASA does not appear to increase substantially the risk of bleeding, DAPT has been consistently associated with a greater risk of bleeding. Because the newer agents, ticagrelor and prasugrel, are more powerful $P2Y_{12}$ antagonists, and because ticagrelor binds reversibly to the $P2Y_{12}$ receptor while clopidogrel and prasugrel bind irreversibly, each of these agents must be considered individually. Furthermore, the antiplatelet effects of these agents will be affected substantially by the duration of time between the last dose of $P2Y_{12}$ and the performance of CABG.

Among patients treated preoperatively with ASA plus clopidogrel, 5% had reoperation for bleeding, compared with 1.9% reoperation rate in patients not treated with clopidogrel [51]. A report from a single-centre study as well as a national registry report from Sweden demonstrated that transfusion of blood products was greater in patients whose last dose of clopidogrel was < 120 h before surgery [52, 53]. Consistent with the greater incidence of bleeding, mortality was greater in patients treated with clopidogrel (3.9% vs. 2.5%, $p < 0.001$) [53]. Based on these results CABG should be performed more than 120 h after the last dose of clopidogrel unless there is a compelling clinical indication for earlier surgery.

Ticagrelor is indicated for the treatment of ACS, and an analysis of results in patients undergoing CABG noted a similar incidence of bleeding in patients randomised to either clopidogrel or ticagrelor [38]. The offset of effects of ticagrelor are more rapid than those of clopidogrel [54]. The antiplatelet effects seen three days after discontinuation of ticagrelor are comparable with those seen five days after discontinuation of clopidogrel. Consistent with these observations, both a single-centre study as well as a national registry report from Sweden did not identify an increased risk of bleeding when ticagrelor was stopped 72 h before surgery [52, 53]. These results are consistent with the timing of mortality benefit seen in patients undergoing CABG and enrolled in the PLATO trial [38], and support a recommendation that CABG should be performed three to four days after the last dose of ticagrelor.

There are limited trial data available for the preoperative use of prasugrel in patients undergoing CABG. Registry data suggest that patients treated with prasugrel have a longer delay from performance of catheterisation to CABG (median time 114 h) and still exhibit a greater risk of bleeding [55]. A small (n = 143) single-centre registry study demonstrated that treatment with prasugrel was associated with more frequent surgical re-exploration for bleeding complications (8% vs. 1%, $p = 0.03$). Prasugrel is a thienopyridine $P2Y_{12}$ antagonist that binds irreversibly to the receptor. The limited clinical data available suggest that discontinuation of prasugrel seven days before surgery is appropriate to limit the risk of bleeding.

ANTIPLATELET THERAPY AFTER CABG IN PATIENTS WITH CORONARY STENTS

Among patients who undergo CABG after placement of a coronary stent, consensus guidelines recommend that DAPT should be continued for the entire duration of therapy based on the type of stent, a class I recommendation [56]. The risk of stent thrombosis is influenced by the clinical syndrome as well as the type of stent. After ACS, one year of DAPT is recommended regardless of stent type. By contrast, a shorter duration of DAPT is acceptable when a bare metal stent is used for patients with stable CAD.

Stent thrombosis in bare metal stents is most likely to occur in the first few days to weeks after stent placement, and so the minimum duration of DAPT after PCI with a bare metal stent is one month. The risk of stent thrombosis in stable CAD after placement of a drug eluting stent is greatest in the first three to six months after implantation. Recent randomised controlled trials support a shorter duration of DAPT in patients with stable CAD [57, 58].

Palmerini et al. [59] identified 10 trials published between December 2011 and November 2014 that included 31,666 randomly assigned patients. By frequentist pairwise meta-analysis, shorter DAPT was associated with significantly lower all-cause mortality compared with longer DAPT (hazard ratio [HR] 0.82, 95% CI 0.69–0.98, $p = 0.02$), with no significant heterogeneity apparent across trials. The reduced mortality with shorter compared with longer DAPT was attributable to lower non-cardiac mortality (HR 0.67, 95% CI 0.51–0.89, $p = 0.006$), with similar cardiac mortality (HR 0.93, 95% CI 0.73–1.17, $p = 0.52$). Shorter DAPT was associated with a lower risk of major bleeding, but a higher risk of MI and stent thrombosis [59]. This analysis is consistent with other such analyses that demonstrate decreased rates of bleeding with shorter DAPT duration that is offset by higher rates of stent thrombosis. Unfortunately, an important confounding variable is the continued evolution of technology with drug eluting stents. Fortunately, newer generation stents are associated with a lower rate of stent thrombosis and MI [60]. Nevertheless, a consistent finding is an increase in all-cause mortality and bleeding events associated with longer duration of DAPT [60, 61].

The balance between stent thrombosis and risk of bleeding has particular relevance when emergent CABG is performed in patients who were treated with coronary stent prior to surgery. Verma et al. [62] examined the effect of antiplatelet therapy on outcomes in patients after CABG. Their meta-analysis included nine randomised clinical trials (n = 4887) with up to one year of follow-up. Of these nine trials, seven compared clopidogrel plus ASA to ASA alone. Two of the trials reported on ACS patients who were treated with either ticagrelor (n = 1261) or prasugrel (n = 485) plus ASA compared with clopidogrel plus ASA. Post-operative

Table 1. Recommendations for antiplatelet therapy in patients undergoing CABG

Antiplatelet agent	Days between last dose and CABG	Duration of treatment after CABG when preoperative ACS	Duration of treatment after CABG when preoperative stent for stable CAD
Acetylsalicylic acid	0	Long-term	Long-term
Clopidogrel	5	1 year	6 months
Ticagrelor	3	1 year	6 months
Prasugrel	7	1 year	6 months

ACS — acute coronary syndrome; CABG — coronary artery bypass grafting; CAD — coronary artery disease

antiplatelet therapy was generally started when chest tube bleeding was no longer significant, typically within 24 to 48 h of surgery. There were no differences in all-cause mortality in clopidogrel plus ASA compared with ASA alone. By contrast, all-cause mortality was significantly lower when treatment with ticagrelor or prasugrel was compared with clopidogrel (risk ratio 0.49, 95% CI 0.33–0.71, $p = 0.002$; $n = 1695$; interaction $p < 0.01$ compared to clopidogrel plus ASA vs. ASA trials). Although major bleeding was not significantly increased (relative risk 1.31, 95% CI 0.81–2.10, $p = 0.27$; seven trials, $n = 4500$), heterogeneity was apparently related predominantly to greater bleeding associated with prasugrel attributable to CABG-related major bleeding (relative risk 3.15, 95% CI 1.45–6.87, $p = 0.004$; one trial, $n = 437$).

The authors concluded that the benefit of treatment with DAPT after CABG is derived primarily from patients with ACS. Heterogeneity of trial design and medium sample sizes limit the analyses. Nevertheless, their results suggest that higher-intensity $P2Y_{12}$ antagonist (prasugrel or ticagrelor) but not lower-intensity (clopidogrel) therapy was associated with a reduction in mortality among ACS patients treated with CABG [62].

SUMMARY/CLINICAL RECOMMENDATIONS (TABLE 1)

Because antiplatelet therapy reduces the risk of cardiovascular events in patients with CAD, it is not surprising that antiplatelet therapy reduces the risk of cardiovascular events in patients after CABG. Treatment with low-dose ASA reduces saphenous vein graft failure in the first year after CABG. Moreover, it reduces MI and acute kidney injury without a meaningful increase in bleeding. These benefits combined with a reduction in mortality associated with low-dose ASA have led to consensus recommendation for the use of ASA both perioperatively and long-term after CABG.

The use of DAPT both perioperatively and long-term is less clearly defined. Based on available information we will provide clinical recommendations for each agent for both perioperative and long-term treatment.

Clopidogrel is a thienopyridine $P2Y_{12}$ antagonist that binds irreversibly to the platelet. Attenuation of antiplatelet effects is mediated by the production and release of new platelets. Patients who have been treated with clopidogrel before CABG have a greater risk of bleeding and greater mortality when surgery is performed less than five days (120 h) after the last dose. Based on these results, CABG should be delayed for five days after the last dose of clopidogrel unless earlier surgery is clinically indicated. In patients who have been treated preoperatively with a coronary stent and in patients who have had recent ACS, clopidogrel should be restarted after CABG and continued for one year to reduce the incidence of stent thrombosis and to reduce the risk of cardiovascular events.

Ticagrelor is a direct-acting $P2Y_{12}$ antagonist that binds reversibly to platelets. Antiplatelet effects decline as the concentration of ticagrelor and its active metabolite decrease. Patients who have been treated preoperatively with ticagrelor exhibit greater bleeding when CABG is performed less than 72 h after the last dose. Because clinical trial results demonstrated a mortality benefit when CABG was performed three to four days after the last dose of ticagrelor, CABG should be performed more than three days (72 h) after the last dose of ticagrelor and consideration should be given to performing CABG from three to four days after the last dose of ticagrelor unless earlier surgery is clinically indicated. For patients who had a coronary stent placed preoperatively and those who had recent ACS, ticagrelor should be resumed postoperatively and continued for 12 months.

Prasugrel is a thienopyridine $P2Y_{12}$ antagonist that binds irreversibly to the platelet. Antiplatelet effects decrease as new platelets are produced. Prasugrel is a powerful $P2Y_{12}$ antagonist that has been associated with a substantially greater risk of bleeding. The limited clinical information available supports a seven-day delay of CABG after the last dose of prasugrel unless earlier surgery is clinically indicated. Similar to the other agents, preoperative placement of coronary stents and recent ACS should prompt re-initiation of therapy postoperatively to complete a one-year course.

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