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Review

Antiplatelet Therapy and Coronary Artery Bypass Grafting: Analysis of Current Evidence With a Focus on Acute Coronary Syndrome

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ABSTRACT

This review was undertaken to summarize and discuss the current evidence around antiplatelet therapy and coronary artery bypass grafting (CABG). Aspirin (ASA) monotherapy remains the standard of care among patients before and after CABG. The role of more intense antiplatelet therapy—specifically, P2Y12 inhibitors—in improving clinical outcomes and graft patency is becoming increasingly apparent. As such, we provide an overview of a variety of antiplatelet regimens. The review discusses the evidence around preoperative management of antiplatelet therapies, with a particular focus on timing of cessation. It also evaluates the current literature to elucidate the best antiplatelet therapy regimen after CABG, focusing on acute coronary syndrome (ACS). Whenever possible, data are presented from randomized controlled trials (RCTs) and meta-analyses. Although guidelines recommend use of dual antiplatelet therapy (DAPT) after CABG for

RÉSUMÉ

La présente synthèse vise à résumer et à expliquer les données probantes actuelles concernant le traitement antiplaquettaire et le pontage aortocoronarien (PAC). La monothérapie par l'acide acétylsalicylique demeure le traitement de référence des patients avant et après un PAC. Le rôle d'un traitement antiplaquettaire plus intense (particulièrement par des inhibiteurs de la P2Y12) dans l'amélioration des résultats cliniques et de la perméabilité du greffon est de mieux en mieux connu. C'est pourquoi nous faisons également un survol de divers traitements antiplaquettaires. Notre synthèse présente les données probantes concernant la prise en charge périopératoire de traitements antiplaquettaires, en accordant une attention particulière au moment où ces traitements sont arrêtés. Nous évaluons également la littérature actuelle afin de trouver le meilleur traitement antiplaquettaire après un PAC, en mettant l'accent sur la présence d'un syndrome coronarien aigu

Coronary artery bypass grafting (CABG) is the gold standard for revascularization of coronary artery disease (CAD) for patients with left main or multivessel disease.[1-5] In CABG surgery, the most commonly used conduits are the left internal mammary artery (LIMA), saphenous vein grafts (SVG), right internal mammary artery (RIMA), and the radial artery (RA).[6] The long-term patency of arterial and SVG directly relates to clinical prognosis; an angiographic analysis of 5065 grafts in 1388 patients demonstrated SVG occlusion rates of 2.1% per year, worsening with time, and showed that graft occlusion was a significant determinant of reoperation rates and survival.[7] Although arterial grafts demonstrate significantly better long-term patency than SVG, only 10.6% of CABG surgeries in North America are performed with multiple arterial grafts, and SVG remains the most commonly used conduit in conventional CABG.[8] Treatment of SVG occlusion is challenging, and preventing their obstruction is of utmost importance to patient survival and reduction in reintervention. This is especially important among patients who have suffered acute coronary syndromes (ACS) and suffer from a prolonged prothrombotic state.[9,10]

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patients with ACS, available evidence is limited to small RCTs, and meta-analyses are of substudies of larger RCTs. There is also considerable heterogeneity in patient population of these studies; a significant number of patients underwent off-pump CABG (OPCAB) in trials that demonstrate graft-patency benefit with DAPT. With this limited evidence, DAPT remains underused in the CABG population, even among patients presenting after ACS.

(SCA). Dans la mesure du possible, les données présentées proviennent d'essais comparatifs avec répartition aléatoire (ECR) et de méta-analyses. Bien que les lignes directrices recommandent l'utilisation d'une bithérapie antiplaquettaire après un PAC chez les patients présentant un SCA, les données probantes proviennent uniquement d'ECR de petite envergure, tandis que les méta-analyses portent sur des sous-études d'ECR de plus grande envergure. La population de patients de ces études est très homogène; un nombre important de patients ont subi un PAC sans pompe dans le cadre d'études visant à démontrer les bienfaits de la bithérapie antiplaquettaire sur la perméabilité du greffon. La quantité de données probantes sur la bithérapie antiplaquettaire étant limitée, ce traitement demeure sous-utilisé chez les patients subissant un PAC, même ceux qui présentent un SCA.

The improvement in mortality and major adverse cardiovascular events (MACE) associated with antiplatelet agents after an ACS stems from their mechanism of platelet inhibition.[11,12] The heightened platelet reactivity after ACS can cause further MACE and worsen graft patency as well as native coronary disease. As such, secondary therapies—specifically, antiplatelet agents (Table 1)—are critical in maintaining patent grafts, reducing progression of native coronary disease, and preventing adverse clinical outcomes.[13,14] Herein, we present a comprehensive review of available evidence around the benefits of antiplatelet therapy after CABG surgery with a focus on DAPT therapy. Furthermore, we also comment on the risks associated with preoperative exposure to antiplatelet agents and review perioperative management of antiplatelet therapy.

Antiplatelet Agents

Antiplatelet agents are a mainstay of secondary prevention in patients with known CAD or ACS, resulting in a relative reduction—compared with controls—in mortality and myocardial infarction (MI).[15] Compared with placebo, use of antiplatelet therapy was shown to prevent late SVG occlusion (6% vs 14%, $P = 0.02$).[16,17] Dual antiplatelet therapy (DAPT) with acetylsalicylic acid (ASA) and a $P2Y_{12}$ antagonist (clopidogrel, prasugrel, or ticagrelor) provides more potent platelet inhibition than single antiplatelet therapy, leading to reduction of thrombotic risk.[18-21] Multiple randomized controlled trials (RCTs) have demonstrated the superiority of DAPT with ASA and a $P2Y_{12}$ over ASA monotherapy in reducing cardiovascular mortality, nonfatal MI, or stroke after an ACS[19-21] (Supplemental Appendix S1).

Acetylsalicylic Acid and CABG

ASA irreversibly inhibits platelet cyclooxygenase-1, decreasing thromboxane A2 production, preventing platelet aggregation, leading to a reduction in stroke, MI, and vascular death in patients with ischemic heart disease.[22] The half-life of ASA is 15 to 30 minutes, whereas its antiplatelet effect appears within 1 hour of ingestion and persists for approximately 4 days.[23]

Preoperative period

In a prospective cohort study of 1636 consecutive patients, Bybee et al. demonstrated that exposure to ASA within 5 to 7 days before CABG substantially decreases rates of mortality (1.7% with ASA vs 4.4% without ASA; adjusted odds ratio [aOR] 0.34; 95% confidence interval (CI) 0.15 to 0.75; $P = 0.007$), without increasing bleeding rates, transfusions, and further reduces nonfatal coronary events.[24] A double-blind, placebo-controlled RCT of 789 patients with stable CAD showed that preoperative ASA in patients with stable CAD significantly decreased long-term hazard of infarction or repeat revascularization (hazard ratio [HR] 0.58; 95% CI, 0.33-0.99).[25] In a case-control study of 8641 isolated patients with CABG, compared with nonusers, preoperative ASA users were at a significant less risk of in-hospital mortality in a univariate (OR 0.73; 95% CI, 0.54, 0.97) and multivariate (OR 0.55; 95% CI, 0.31, 0.98) analysis, without any difference in chest tube output, transfusion or re-exploration rates.[26] The largest RCT yet to evaluate perioperative use of ASA before CABG was the **A**ntithrombotic **T**herapy in **A**cute **C**oronary **Sy**ndromes (ATACAS) trial, which randomized 2100 patients to receive either ASA or placebo preoperatively. The primary outcome of death and thromboembolic events was not significant between the 2 treatment arms (risk ratio [RR] 0.94; 95% CI, 0.80, 1.12; $P = 0.55$), and also failed to demonstrate a significant difference in re-exploration for bleeding (RR 0.87; 95% CI, 0.47, 1.60; $P = 0.75$) or cardiac tamponade (RR 2.77; 95% CI, 0.88, 8.66; $P = 0.08$).[27] Most recently, a meta-analysis of 12 RCTs and 28 observational studies found that use of preoperative ASA decreased perioperative mortality (RR 0.71; 95% CI, 0.60, 0.84; $P = 0.0001$), and did not increase the incidence of reoperation for bleeding (RR 1.02; 95% CI, 0.86, 1.21; $P = 0.79$).[28] The current state of evidence suggests that it is reasonable to continue ASA until time of CABG. In fact, stopping ASA preoperatively may be harmful and should be avoided unless bleeding risks clearly outweigh the benefits.[29]

Postoperative period

Evidence that ASA improves graft patency and clinical prognosis after CABG has accumulated over the last 30 years; all patients should be on long-term ASA therapy after CABG.[30] Chesebro et al. conducted 1 of the first RCTs to

Table 1. Mechanism of action and administration for antiplatelets aspirin, clopidogrel, prasugrel, and ticagrelor

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Method of administration	Oral	Oral	Oral	Oral
Mechanism of inhibition	Cyclo-oxygenase-1 inhibition	$P2Y_{12}$ receptor inhibition	$P2Y_{12}$ receptor inhibition	$P2Y_{12}$ receptor inhibition
Reversibility potential	Irreversible	Irreversible	Irreversible	Reversible
Action onset	30-40 min	2-6 hours	30 min	30 min
Action duration	4-5 days	3-7 days	5-9 days	1-2 days
Plasma half-life	2-3 hours	30-60 min	30-60 min	6-12 hours
Chemical classification	Acetylsalicylic acid	Thienopyridine	Thienopyridine	Cyclopentyl-triazolo-pyrimidine
Initial dose	150-300 mg (80-150 mg intravenously)	300-600 mg	60 mg	180 mg
Maintenance dose	75-150 mg daily	75 mg daily	10 (5) mg daily	90 mg twice daily
Activation mechanism	Prodrug: hydrolysis by an esterase	Prodrug: hepatic metabolism	Prodrug: hepatic metabolism	Active drug with additional active metabolite
How long to hold prior to surgery	No interruption when possible	5 days	7 days	5 days

demonstrate a significantly higher vein-graft patency at 1 year with antiplatelet therapy (ASA and dipyridamole within 7 hours of CABG) compared with placebo (89% vs 77%, $P < 0.0001$).[31] To date, the largest trial comparing ASA with placebo in CABG patients is the Veterans Administration Cooperative Study.[32] At 1 year after surgery, 1315 grafts were angiographically reviewed; 22.6% of grafts in the placebo group vs 15.8% of grafts in the ASA group ($P = 0.03$) were occluded. Beyond improved graft patency, several studies have demonstrated better clinical outcomes with ASA after CABG. In 2002, Mangano et al. prospectively evaluated the impact of ASA given within 48 hours after CABG in 5065 patients; postoperative ASA was associated with a 68% reduction in the incidence of death (1.3% vs 4.0%, $P < 0.001$), a 48% reduction in the incidence of MI (2.8% vs 5.4%, $P < 0.001$), and a 50% reduction in the incidence of stroke (1.3% vs 2.6%, $P = 0.01$) during index hospitalization.[33] A long-term analysis of the CABG cohort within the **Syn**ergy between Percutaneous Coronary Intervention with **Tax**us and Cardiac Surgery (SYNTAX) trial reported that lack of ASA prescription at hospital discharge was the strongest predictor of death at 4 years (HR 3.56; 95% CI, 2.04-6.21; $P < 0.001$).[34] In a meta-analysis of 10 studies evaluating ASA vs control, Alghamdi et al. reported that ASA significantly reduced graft occlusion (OR 0.60; 95% CI, 0.51-0.71; $P < 0.0001$).[35] The Antithrombotic Trialists' Collaboration carried out a collaborative meta-analysis, evaluating antiplatelet therapy in nearly 200,000 patients and found that, in patients with CAD, ASA significantly reduced combined endpoints of nonfatal MI, nonfatal stroke, or vascular death by 37%. Among patients requiring CABG, use of ASA postoperatively was associated with improved graft patency at 1 year; the odds of graft closure were reduced by 44%. With regard to ASA dosage, the Antithrombotic Trialists' Collaboration demonstrated a pooled OR for graft occlusion of 44% comparing low-dose ASA (<325 mg per day) and of 50% comparing high-dose ASA (>500 mg per day) with placebo or control group. They failed to demonstrate a difference in graft occlusion rates between low-dose and high-dose ASA.[36] Despite the proven benefits of ASA, progressive neointimal hyperplasia continues to pose a problem and cause SVG failure; more potent antiplatelet inhibition may hold the answer.[37-39]

Clopidogrel and CABG

Clopidogrel is a thienopyridine, with a half-life for circulating drug of approximately 8 hours. Its irreversible antiplatelet effects can last for up to 10 days.

Preoperative period

Despite its clear benefit in patients presenting with ACS, preoperative exposure to clopidogrel within 5 to 7 days before CABG is associated with significant morbidity. In a systematic review of 23 studies, exposure to clopidogrel within 7 days before CABG increased risk of re-exploration for bleeding and blood transfusions.[40] In a matched-pair by propensity-scored analysis of CABG patients with exposure to clopidogrel before surgery, compared with those without, the clopidogrel group was at a significantly higher risk for re-exploration because of bleeding (OR 4.9; 95% CI, 2.63-8.97; $P = 0.01$), increase in blood transfusions (OR 1.9; 95% CI, 1.33-2.75; $P = 0.01$).[41] Given its pharmacology and strong observational evidence, guidelines strongly recommend cessation of clopidogrel at least 5 to 7 days before CABG to reduce hemorrhage-related morbidity.[42-45]

Postoperative period for patients with ACS

Clopidogrel is synergistic with ASA for antithrombotic effects and, as such, was evaluated after ACS in the **C**lopidogrel in **U**nstable Angina to Prevent **R**ecurrent **E**vents (CURE) trial.[21,46] The CURE trial randomized 12,562 patients with ACS to either ASA only or DAPT with ASA and clopidogrel for 3 to 12 months. The primary composite outcome of cardiovascular death, nonfatal MI, or stroke occurred significantly less frequently in the DAPT arm compared with the ASA-only arm (9.3% vs 11.4%; $P < 0.001$).[21] The postoperative benefit of DAPT with clopidogrel and ASA was analyzed in subgroup of CURE patients who underwent CABG within 25.5 days (interquartile range: 12 to 70.5 days) from randomization; 1061 patients were randomized to ASA and 1011 to ASA and clopidogrel. Although the benefits of DAPT with ASA and clopidogrel were consistent among the groups undergoing CABG, PCI, or medical therapy (test for interaction, $P = 0.53$), the impact of DAPT among CABG patients did not reach significance for the primary composite outcome (RR 0.89; 95% CI, 0.71-1.11).[46]

Postoperative period for all CABG Patients

In a study evaluating graft patency, Gao et al. randomized 249 patients undergoing CABG (58% without cardiopulmonary bypass [OPCAB]) to DAPT with ASA 100 mg and clopidogrel 75 mg daily or ASA 100 mg monotherapy. At 3 months, computed tomography (CT) angiography demonstrated significantly better SVG patency with DAPT compared with ASA monotherapy (91.6% vs 85.7%, $P = 0.04$).[47] The **C**lopidogrel **A**fter **S**urgery for **C**oronary **A**rtery **D**isease (CASCADE) trial randomized 113 patients comparing ASA 162 mg daily to ASA 162 mg and clopidogrel 75 mg daily. After 8 years of follow-up, the investigators found that DAPT did not significantly reduce SVG intimal hyperplasia. The overall graft patency rates were not significantly different either (89.1% with DAPT vs 91.2% with ASA only, $P = 0.79$).[48] Sun et al. further randomized 100 CABG patients to postoperative DAPT with clopidogrel 75 mg and ASA 81-mg daily to ASA 81-mg alone and assessed graft patency by CT angiography (CTA). They found no significant difference in graft patency among all grafts (92.9% vs 95%, $P = 0.43$) or SVG alone (93.2% vs 93.5%, $P = 0.92$).[49] Meanwhile, the Prevention of **C**oronary Arte**ry** Bypa**ss** Occlusion **A**fter Off-Pump Procedure (CRYSSA) trial randomized 300 patients undergoing OPCAB CABG and showed that DAPT with ASA and clopidogrel was associated with significantly lower SVG occlusion rates (7.4% vs 13.1%; $P = 0.04$) compared with ASA monotherapy. The CRYSSA trial found no difference in major bleeding between the 2 arms (1.3% vs 1.3%; $P = 1$).[50] Kim et al. compared clinical outcomes in 3268 patients who received DAPT with ASA and clopidogrel after CABG to 11,799 patients who received ASA only. In this propensity-scored observational study, DAPT was associated with lower in-hospital mortality (aOR 0.50; 95% CI, 0.25-0.99, $P = 0.048$) but no significant difference in ischemic events (aOR 0.99; 95% CI, 0.59-1.64, $P = 0.960$).[51] A multivariate analysis of 3545 Danish CABG patients receiving DAPT with ASA and clopidogrel vs ASA reported lower mortality with the former (adjusted HR 0.34; 95% CI, 0.20-0.61, log-rank $P = 0.002$), with no reduction in recurrent MI or need for repeat revascularization between discharge and maximum follow-up (mean follow-up was 466 days).[52] A meta-analysis of 5 RCTs and 6 observational studies summarizing the available data on DAPT with clopidogrel and ASA reported that DAPT reduced vein-graft occlusion (RR 0.59; 95% CI, 0.43-0.82, $P = 0.02$) and 30-day mortality (0.8% vs 1.9%, $P < 0.0001$) compared with ASA alone, with a possible increase in major bleeding (RR 1.17, 95% CI, 1.00-1.37, $P = 0.05$).[53] Apart from improving graft patency, Une et al.—in a secondary analysis of CASCADE—demonstrated that DAPT was superior to ASA monotherapy in reducing the incidence of new occlusions within native coronary arteries (7% vs 22%; $P = 0.02$).[14] Current data demonstrate a benefit of DAPT with clopidogrel and ASA for clinical outcomes, but mixed results with graft patency, suggesting a systemic—rather than cardiac-only—benefit.

Prasugrel and CABG

Two other $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, have a more rapid onset of action and more consistent and pronounced platelet inhibition than clopidogrel.[54,55] Prasugrel is also a thienopyridine agent and, like clopidogrel, its antiplatelet effects last for 5 to 7 days.

Preoperative period

Among patients with ACS undergoing isolated CABG, exposure to prasugrel within 5 days of surgery, when compared with clopidogrel, resulted in a significant increase in chest tube output at 12 hours (mean +/− SD; 655 ± 580 mL vs 503 ± 378 mL, $P = 0.050$), platelet transfusions (mean +/− SD; 0.95 +/− 2.84 vs 0.25 +/− 1/14 units; $P = 0.018$), and a trend toward increased red blood cell transfusions and surgical re-explorations for bleeding. Meanwhile, if prasugrel was stopped more than 7 days before CABG, postoperative blood loss and blood transfusions were not significantly different from the clopidogrel arm.[56] Given its pharmacology, available evidence around other thienopyridine agents, and the retrospective analysis of prasugrel compared with clopidogrel, it is strongly recommended to stop prasugrel at least 7 days before elective CABG.[42,44,45]

Postoperative period for patients with ACS

The benefit of prasugrel among the ACS population was evaluated in Prasugrel vs Clopidogrel in Patients with Acute Coronary Syndrome (TRITON-TIMI 38) RCT. The investigators randomized 13,608 patients with ACS to DAPT with ASA (dose) plus clopidogrel 75 mg daily or ASA (dose) plus prasugrel 10 mg daily for 6 to 15 months. The primary composite outcome of cardiovascular death, nonfatal MI, or stroke was significantly lower among patients in the prasugrel arm (9.9% vs 12.1%, $P < 0.001$), but major bleeding complications were significantly higher (2.4% vs 1.8%, $P = 0.03$).[20] In a subgroup analysis of patients with ACS undergoing CABG (n = 346), all-cause mortality within 30 days was significantly reduced among patients receiving DAPT with prasugrel (2.3% vs 8.7%, aOR 0.26, $P = 0.025$).[57] Despite an increase in bleeding, platelet transfusion, and surgical re-exploration for bleeding, prasugrel was associated with improved mortality after CABG when compared with clopidogrel.

Ticagrelor and CABG

Ticagrelor is a direct-acting, reversibly binding, $P2Y_{12}$ inhibitor that exhibits a rapid onset and offset of antiplatelet effect. Its chemical structure is quite different from that of thienopyridines and does not require hepatic activation. Because the reversible receptor inhibition of ticagrelor is noncompetitive, it inhibits platelet aggregation despite increasing concentrations of ADP. As such, despite increased ADP concentrations or platelet transfusions, one would expect to see no reduction in level of platelet inhibition.[58] Although the half-life of ticagrelor is approximately 7 hours, its residual antiplatelet effect decreases to 30% after approximately 2.5 days.[23]

Preoperative period

The mechanism of action of ticagrelor presents quite a challenge around management of intraoperative bleeding when patients are exposed to it preoperatively.[58] In a small, propensity-scored, matched-pair analysis of patients who have

undergone CABG and exposed to ticagrelor vs clopidogrel up until surgery, the former was associated with a significantly higher incidence of re-exploration for bleeding (21% vs 0%, $P = 0.02$), total blood loss (mean +/− SD; 1028.8 +/− 735.5 vs 436.8 +/− 289.4; $P < 0.01$), and red blood cell transfusions (mean +/− SD; 3.6 +/− 4.4 vs 0.2 +/− 0.8; $P < 0.01$).[59] In another retrospective analysis, the continuation of ticagrelor until CABG, when compared with clopidogrel, was associated with a significantly higher median blood loss at 24 hours (800 mL [780 mL to 1600 mL] vs 680 mL [400 mL to 860 mL]; $P = 0.0006$), as well as significantly higher red blood cell, platelet, and prothrombin concentrate transfusions.[60] Finally, in the largest registry evaluating preoperative exposure to ticagrelor, the **E**uropean Multicenter Study on **C**oronary **A**rtery **B**ypass **G**rafting (E-CABG) evaluated 786 patients with ACS, carrying out a 1-to-1 propensity-scored analysis comparing preoperative ticagrelor with ASA. In patients receiving the former up until surgery, compared with ASA, ticagrelor was associated with a significantly higher rate of platelet transfusion (13.5% vs 6%,$P = 0.009$). With regard to severe bleeding, continuing ticagrelor up until the time of CABG or discontinuing it less than 2 days before CABG demonstrated significantly higher risk of E-CABG bleeding grades 2 and 3 (18.2% vs 5.9%, $P = 0.03$). The risk of severe bleeding was similar in patients for whom ticagrelor and ASA were discontinued 2 to 3 days before CABG.[61] The Society of Thoracic Surgeons (STS) recommends stopping DAPT for 5 to 7 days (no matter the P2Y12 inhibitor) among elective patients. However, in patients with coronary stents implanted less than a year before, or presenting with ACS, they recommend stopping DAPT for less than 5 days and proceeding with CABG.[62] Meanwhile, given the pharmacotherapy of ticagrelor, and available evidence, all other guidelines strongly recommend stopping ticagrelor for a minimum of 48 to 72 hours before cardiac surgery.[42,44,45]

Postoperative period for patients with ACS

The **Pl**atelet Inhibition **a**nd Patien**t** **O**utcomes (PLATO) trial investigators randomized 18,624 patients with ACS to DAPT with either ASA plus ticagrelor 90 mg twice daily or ASA plus clopidogrel 75 mg daily. It should be noted that patients randomized in PLATO received ticagrelor and ASA at presentation to the emergency department, regardless of their eventual treatment modality. The composite primary end point of cardiovascular death, MI, or stroke was significantly reduced in the ticagrelor arm (9.8% vs 11.7%, $P < 0.001$), with significant reductions in all-cause mortality (4.5% vs 5.9%, $P < 0.001$), vascular mortality (4.0% vs 5.1%, $P < 0.001$), and MI (5.8% vs 6.9%, $P < 0.005$). However, ticagrelor was associated with a higher rate of major bleeding (4.5% vs 3.8%, $P = 0.03$).[19] In the 1261-patient subgroup who underwent CABG within 7 days of taking ticagrelor or clopidogrel, the direction of effect on the primary outcome at 1 year was again consistent but did not reach significance (10.6% vs 13.1%, $P = 0.29$). Although cardiovascular mortality (4.1% vs 7.9%, $P < 0.01$) and all-cause mortality (4.7% vs 9.7%, $P < 0.01$) were significantly lower with ticagrelor, MI and stroke failed to demonstrate a statistically significant benefit with ticagrelor, which drove the composite to nonsignificance. The interaction between treatment modalities was not significant. CABG-related major bleeding did not differ significantly between the 2 arms. Although the investigators noted that ticagrelor had a faster offset, the timing of preoperative drug cessation did not demonstrate a difference in major/fatal/life-threatening CABG-related bleeding or **G**lobal **U**tilization of **S**treptokinase and **T**issue-Plasminogen Activator for **O**ccluded Coronary Arteries (GUSTO) study severe bleeds between ticagrelor and clopidogrel, not even if it were stopped 1 day before surgery ($P = 0.76$ for interaction).[63] To further address the benefit of DAPT among patients suffering with ACS, a meta-analysis of 9 RCTs with a total population of 4887 who had undergone CABG showed a significant reduction in all-cause mortality at 1 year with DAPT with ticagrelor or prasugrel compared with DAPT with clopidogrel (RR 0.49, 95% CI, 0.33-0.71, $P = 0.0002$; n = 1695) and concluded that more potent P2Y12 inhibitors reduced mortality by approximately 50%.[18] Given the improved cardiovascular survival among patients receiving DAPT with ticagrelor, without an increased risk of major bleeding when compared with DAPT with clopidogrel, ticagrelor is increasingly studied among patients who have undergone CABG in hopes of improved graft patency and survival.

Postoperative period for all CABG patients

Most recently, Zhao et al. randomized 500 CABG patients (regardless of if they had an ACS or not) 1:1:1 to ASA 100 mg or ticagrelor 90 mg twice daily or DAPT with ASA and ticagrelor; the drugs were started within 24 hours post-CABG. Vein-graft patency at 1 year after surgery for ASA monotherapy vs ticagrelor monotherapy vs DAPT was 76.5% vs 82.8% vs 89.9% (P for DAPT vs ASA = 0.0006). At 1 year after surgery, the trial failed to show a statistically significant difference in event rates of MACE, MI, and stroke among the 3 arms. There was also no statistically significant increase in major bleeding in the DAPT arm. Of note, only 23.2% of patients in the ticagrelor + ASA arm, 21.7% of patients in the ticagrelor arm, and 27.7% of patients in the ASA arm underwent CABG with use cardiopulmonary bypass.[64] Most recently, the **Ti**cagrelor **C**ompared with **A**spirin for Prevention of Vascular Events in Patients Undergoing Coronary Artery **B**ypass Grafting (TiCAB) trial randomized 1893 CABG patients in a 1:1 fashion to either ticagrelor 90 mg twice daily or aspirin 100 mg once daily. Although the study planned to randomize 3760 patients, recruitment was halted owing to funding issues. The primary outcome of MACE at 12 months did not differ significantly between the 2 arms (9.7% in ticagrelor arm vs 8.2% in the ASA arm, $P = 0.27$). Unfortunately, this study did not evaluate DAPT.[65]

Limitations of Evidence

The existing evidence for use of DAPT after CABG has limitations. The RCTs are of small sample size or are substudies of larger RCTs. Direct-comparison meta-analyses, unfortunately, combine RCT and observational data to reach statistical significance.[66] Furthermore, those meta-analyses are limited by lack of direct comparisons of various P2Y12 inhibitors on top of ASA.[18] There is also considerable heterogeneity within the RCTs on whether patients underwent OPCAB or CABG with cardiopulmonary bypass. In fact, a large majority of patients randomized in the 2 trials demonstrating DAPT superiority

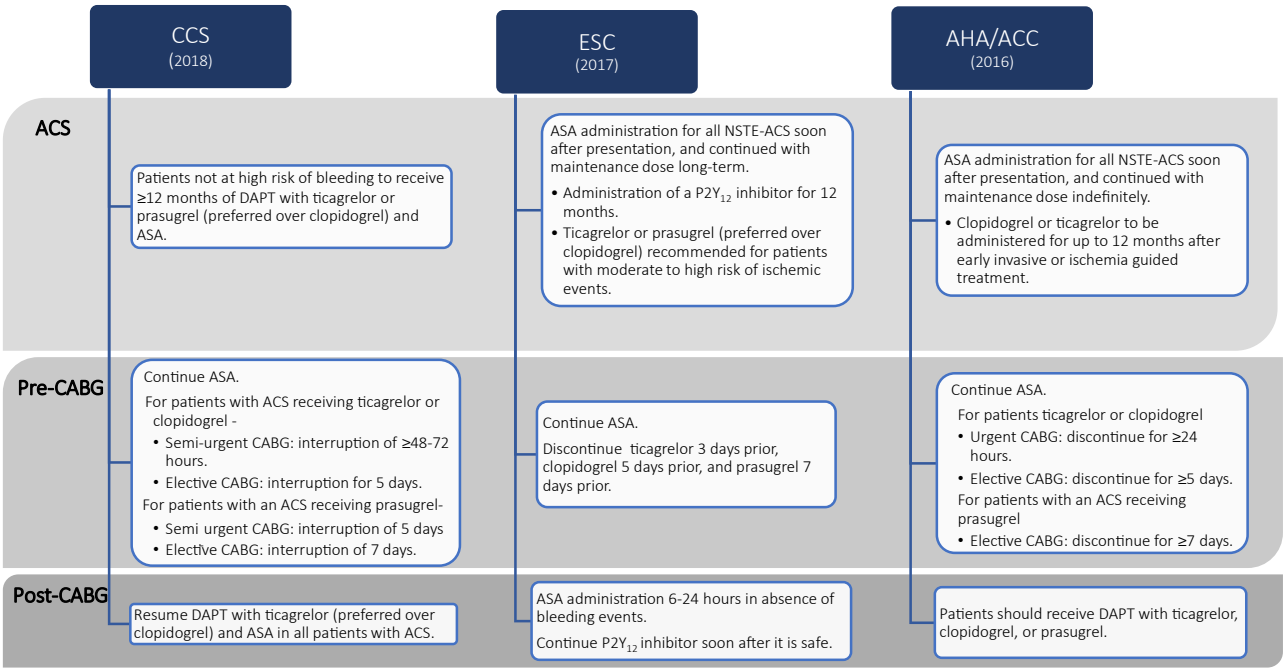

Figure 1. Summary of CCS, ESC, and AHA/ACC guidelines for antiplatelet management before and after CABG surgery. ACS, acute coronary syndrome; AHA/ACC, American Heart Association/American College of Cardiology; ASA, acetylsalicylic acid; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; DAPT, dual antiplatelet therapy; ESC, European Society of Cardiology; NSTE-ACS, non-ST elevation ACS.

over ASA monotherapy underwent OPCAB.[50,64] The available evidence does not evaluate the use of DAPT in patients undergoing multiple arterial grafting. Arterial grafts are associated with significantly better long-term patency rates and clinical outcomes compared with SVG, and the effect DAPT has on SVG may not apply to arterial grafts.[67] Cardiac surgery with cardiopulmonary bypass is known to result in increased fibrinolysis. Classically, this phenomenon is reversed by use of lysine analogues such as tranexamic acid (TXA) or epsilon amino caproic acid (EACA). Unfortunately, RCTs evaluating DAPT do not make note of which antifibrinolytic agents were used intraoperatively or the doses administered, all of which can affect blood loss, re-exploration rates, and transfusion rates.[68] Finally, more recently, results of the **C**ardiovascular **O**utcom**e**s for **P**eople Using **A**nticoagulation **S**trategie**s** (COMPASS) trial, demonstrated the superiority of dual antithrombotic therapy with ASA and rivaroxaban among patients with peripheral vascular disease (PVD).[69] In a subgroup analysis of their study, it was noted that the combination of ASA and very low-dose rivaroxaban significantly reduced MACE in patients presenting with ACS, without a significant increase in major bleeding.[70] However, this did not hold true for patients with stable CAD and PVD undergoing CABG, who were at a significant risk for major bleeding, without any MACE benefit.[71] The COMPASS substudy highlights again the systemic benefit derived from dual antithrombotic therapy after an ACS, a benefit that may not hold for all patients who undergo CABG.

Guidelines and Evidence-Practice Gap

The Canadian Cardiovascular Society (CCS), European Society of Cardiology (ESC), and American Heart Association/American College of Cardiology (AHA/ACC) recommend DAPT with ticagrelor or prasugrel for 12 months after an ACS, regardless of management strategy (medical therapy, PCI, or CABG) (Fig. 1).[45,72,73] Similarly, as per the STS, guideline-directed DAPT reinitiation is a class I (level A) recommendation among patients requiring CABG after ACS to reduce MACE outcomes as well as improve SVG patency.[62] Among patients who have patent coronary stents implanted within the year leading to their CABG, DAPT should be stopped for as few days as possible and resumed postoperatively.[62] Despite guidelines, considerable variability remains as to when and whether cardiac surgeons resume DAPT after surgery, and DAPT is underused in patients undergoing CABG.[74] In a cohort study of patients with ACS by Anastasius et al., CABG was an independent predictor for DAPT underuse (defined as discharge with prescription for single antiplatelet alone or no antiplatelet prescription): OR 0.09, 95% CI, 0.05-0.14. The **A**rterial **R**evascularization **T**rial (ART) demonstrated that only 21% of patients with ACS undergoing CABG were discharged on DAPT.[74-76] Yanagawa et al. surveyed 75 Canadian cardiac surgeons and found that only 44.6% restart DAPT in patients who suffered recent ACS because a majority of them—81%—were more concerned with major bleeding than reduction of ischemic events. Surgeons were more likely to initiate DAPT if patients had previous stents to vessels that were not bypassed, required endarterectomy, suffered perioperative MIs, or underwent OPCAB, practice patterns for which there is no available evidence.[77] The discordance between guidelines and practice can be attributed to a number of factors: lack of knowledge about recent guidelines on P2Y12 inhibitors, perceived issues with drug coverage and costs, and lack of robust evidence supporting the use of DAPT after CABG for all patients.[78]

Conclusion

This article presents a comprehensive review of evidence and guidelines around antiplatelet management before and after CABG. Our summary demonstrates that the evidence for DAPT after CABG is limited by small RCTs and subgroup analyses of large RCTs. Guidelines, despite limitations of available data, support the use of DAPT with ASA and ticagrelor for patients with ACS after CABG, and we believe that surgeons should consider initiating DAPT in these patients. Give the guideline-practice gaps, barriers to optimal use of DAPT post-CABG in ACS need to be identified and addressed to improve guidelines and adherence to guideline-recommended antiplatelet therapies. Next steps should focus on evaluating the strength of the evidence, clarifying gaps in prescription patterns, outline barriers to guideline implementation, and develop strategies to address these issues.

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Supplementary Material

To access the supplementary material accompanying this article, visit the online version of the *Canadian Journal of Cardiology* at www.onlinecjc.ca and at https://doi.org/10.1016/j.cjca.2019.06.003.