Secondary prevention after coronary artery bypass graft surgery: a primer

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Purpose of review
Despite the benefits of surgical coronary revascularization, patients continue to be at risk for ischemic events in the years that follow coronary artery bypass graft surgery (CABG), mandating the role for postoperative secondary preventive therapy. The purpose of this review was to present a summary on the subject of secondary prevention after CABG, including an overview of a recently published scientific statement, and highlight the newest studies in the field.

Recent findings
Aspirin and statin therapy continue to be the mainstay of secondary prevention after CABG, although newer antiplatelet and lipid-lowering medicines are being actively studied for their potential benefits. Other important elements to secondary prevention after CABG include the aggressive management of hypertension, smoking cessation, and the initiation of cardiac rehabilitation.

Summary
Secondary prevention is an essential component of postoperative care after CABG. Instituting preventive therapies after surgery optimizes graft patency and helps patients achieve the highest level of physical health and quality of life following CABG.

Keywords
antiplatelet therapy, coronary artery bypass graft surgery, hypertension, lipid-lowering therapy, prevention

INTRODUCTION

Preventive medicine consists of measures taken for avoidance of disease [1,2]. Although 'primary prevention' aims to avert an illness before it ever occurs, the goals of 'secondary prevention' are to reduce the impact of a disease that is already in progress. This is achieved by initiating therapies to halt disease processes and avoid illness recurrence, as well as implementing programs to return people to their original health. Ultimately, secondary prevention prevents long-term disease-related sequelae [3].

Secondary prevention is an essential component of the management of patients recovering from coronary artery bypass graft surgery (CABG), a procedure that more than 400 000 Americans undergo each year [4]. CABG is the most complete and durable treatment of ischemic heart disease and has been an established therapy for nearly 50 years. Nevertheless, in the years that follow surgery, patients who have undergone CABG remain at risk for subsequent ischemic events, resulting from the progression of native coronary artery disease (CAD) and the development of vein graft atherosclerosis. Therefore, secondary therapies play a key role in the prevention of adverse cardiovascular outcomes. Postoperative antiplatelet agents and lipid-lowering therapies continue to be the mainstay of secondary prevention. Other opportunities that exist to improve the long-term clinical outcomes after CABG include the aggressive management of hypertension and diabetes mellitus, smoking cessation, weight loss, and cardiac rehabilitation. Secondary preventive therapies help maintain long-term graft patency and assist patients to obtain the highest level of physical health and quality of life following CABG.

Recently, the American Heart Association (AHA) issued a scientific statement specifically focused on

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secondary prevention after CABG. This statement thoroughly evaluated the evidence for preventive therapies following surgery and provided updated recommendations regarding their use [5▪▪]. Since the writing of this statement, several clinical trials in the cardiology and cardiac surgery community have been presented that have important implications for patients recovering from CABG surgery. The objective of the current study is to present a 'primer' on the subject of secondary prevention after CABG. Specifically, this will provide an overview of the recently published post-CABG AHA scientific statement, summarize some of the newest studies in the field, and highlight areas that are in need of further research.

ANTIPLATELET THERAPY

First discovered in 1897, aspirin irreversibly inhibits platelet cyclooxygenase-1 and decreases thromboxane-A2 production, ultimately preventing platelet aggregation. In patients with CAD, aspirin is well known to reduce the risk of stroke, myocardial infarction (MI), and vascular death [6–7]. Therefore, all patients undergoing CABG are candidates for long-term aspirin therapy [8]. Ideally, it should be initiated before surgery when CAD is first diagnosed [7,9,10]. Aspirin appears to be well tolerated when administered prior to surgery [11] and its preoperative use may lead to lower rates of morbidity and mortality after CABG [12,13]. In the postoperative period, aspirin helps prevent adverse cardiovascular events [14] and improves long-term survival [15,16].

Numerous clinical trials, some dating back to the 1970s, demonstrated that aspirin significantly improves vein graft patency rates after CABG, particularly during the first postoperative year [17–20]. In a meta-analysis of 17 randomized placebo-controlled trials, aspirin significantly reduces the odds of graft occlusion by 40% [aspirin versus placebo odds ratio: 0.60; 95% confidence interval (CI): 0.51, 0.71; $P < 0.0001$], with low

(100 mg) to medium (325 mg) daily doses being the most effective. The ideal time for postoperative initiation of aspirin appears to be within 6 h after CABG [21].

Nevertheless, even with routine aspirin-mediated platelet inhibition, saphenous vein graft disease continues to be a clinical challenge in the modern era. Early graft occlusion rates have been reported as high as 26% in recent clinical trials [22]. This may relate to the phenomenon of 'aspirin resistance,' whereby aspirin is unable to effectively inhibit platelet function early after CABG, especially at lower doses [23–26]. As such, several investigators have evaluated the role of other antiplatelet agents following surgery, including clopidogrel. Clopidogrel is a thienopyridine antiplatelet agent that irreversibly inhibits the platelet P2Y12 ADP receptor. When exposed to clopidogrel, platelets are inhibited from aggregating for the remainder of their 7–10-day lifespan [27,28]. Combining aspirin therapy with clopidogrel leads to potent synergistic antithrombotic effects [29] and substantial benefits have been demonstrated with dual antiplatelet therapy in several CAD and stent trials [30,31]. In the cardiac surgery literature, however, the results have been mixed. Two large observational studies suggested a clinical benefit associated with the use of clopidogrel after surgery [32,33]. On the other hand, a post-hoc analysis from the Randomized On and Off-Pump Bypass on and off-pump CABG trial found no improvement in graft patency among patients treated with received clopidogrel after surgery [34].

To date, five clinical trials have evaluated the use of clopidogrel after CABG, presenting mostly negative results, especially among patients undergoing on-pump surgery [35–39]. In the clopidogrel after surgery for coronary artery disease (CASCADE) trial, the combination of aspirin and clopidogrel did not significantly reduce the process of saphenous vein graft intimal hyperplasia 1 year after CABG as compared with aspirin alone [36]. However, in a post-hoc analysis, dual antiplatelet therapy was associated with a slowing in the angiographic progression of native CAD [40]. Summarizing the data on more than 25 000 patients published in both randomized and observational studies, Deo et al. [41] documented a lower risk of vein graft occlusion (relative risk: 0.59; 95% CI: 0.43, 0.82; $P = 0.02$) and 30-day mortality ($P < 0.0001$) with dual antiplatelet therapy, but at the cost of significantly more major bleeding events, compared with aspirin alone. Importantly, this benefit for dual antiplatelet therapy in terms of reducing vein graft occlusion was most applicable among patients undergoing off-pump CABG rather than on-pump surgery [39,41],

as off-pump patients have a relative hypercoagulable state and higher levels of postoperative platelet activity [42,43]. In light of these data, the recent AHA secondary prevention statement recommended aspirin alone for the majority of patients after CABG, whereas clopidogrel should be combined with aspirin specifically after off-pump surgery [5▪▪].

Less is known regarding the postoperative role of the newer P2Y12 inhibitors, prasugrel and ticagrelor, which have a more rapid onset of action and more consistent and pronounced platelet inhibition than clopidogrel [44–46]. Prasugrel was found to be superior to clopidogrel for patients with acute coronary syndrome (ACS) in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel -Thrombolysis in Myocardial Infarction 38 study [44], and in a post-hoc analysis of the patients who subsequently underwent CABG, prasugrel was associated with a lower rate of death after surgery, albeit with a greater amount of blood loss [47]. In the Platelet Inhibition and Patient Outcomes (PLATO) study, ticagrelor also significantly improved outcomes for patients with ACS as compared with clopidogrel [45]. In a subsequent post-hoc analysis of the 1261 patients who thereafter underwent CABG, ticagrelor led to a significant reduction in cardiovascular mortality (4.1 versus 7.9%, ticagrelor versus clopidogrel, $P < 0.01$), and no significant difference in CABG-related major bleeding [46]. Most recently, in Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis in Myocardial Infarction 54, a long-term prevention study, patients with CAD and a previous MI had a significantly lower risk of adverse cardiovascular outcomes when they received ticagrelor and aspirin as compared with aspirin alone, although the risks of major bleeding were slightly higher [48].

With the growing interest in the newer P2Y12 receptor inhibitors and the mixed results seen with clopidogrel after CABG [41], several trials have been initiated in the cardiac surgery community to investigate the role of ticagrelor and prasugrel after CABG. Approximately 1 year ago, we launched the Ticagrelor Antiplatelet Therapy to Reduce Graft Events and Thrombosis (TARGET) trial (ClinicalTrials.gov Identifier: NCT02053909) to evaluate the potential benefits of ticagrelor 90 mg twice daily as compared with aspirin 81 mg twice daily, on 1 and 2-year graft patency after CABG. Other studies are exploring the impact of combining aspirin with ticagrelor to reduce postoperative graft occlusion rates [The Effect Of Ticagrelor On Saphenous Vein Graft Patency In Patients Undergoing Coronary Artery Bypass Grafting Surgery, ClinicalTrials.gov Identifier: NCT02352402; Efficacy of Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery, ClinicalTrials.gov Identifier: NCT02201771], and ticagrelor's role in reducing postoperative clinical events [Ticagrelor With Aspirin for Prevention of Vascular Events in Patients Undergoing CABG, ClinicalTrials.gov Identifier: NCT01755520]. Finally, a Veteran Affairs study is currently examining the combination of prasugrel and aspirin versus aspirin alone on the prevalence of graft thrombus 1 year after CABG (ClinicalTrials.gov Identifier: NCT01560780).

LIPID MANAGEMENT

Extensive evidence exists supporting the use of statins to treat hyperlipidemia and reduce adverse cardiovascular events in patients with CAD, particularly for patients who have had CABG [49–52]. Statins have been shown to reduce the progression of native artery atherosclerosis, improve long-term survival, and reduce the risks of adverse cardiovascular events across a wide range of cholesterol levels [49,53–55]. Whereas elevated cholesterol levels are associated with faster progression of saphenous vein graft disease after CABG [56,57], statin treatment inhibits its development by reducing neointimal formation and smooth muscle proliferation [51,58–61].

The post-CABG Trial was the first major study to evaluate the role of statins after surgical revascularization. A total of 1351 patients who had previously undergone CABG 1–11 years earlier were randomized to receive lovastatin 40–80 mg daily or lovastatin 2.5–5 mg daily. Over the course of the study, patients who received the higher lovastatin doses achieved a reduction in low-density lipoprotein (LDL) levels to less than 100 mg/dl. This was associated with a lower incidence of new vein graft occlusions 4 years later, as well as a lower number of grafts with atherosclerosis progression [51]. Moreover, long-term follow-up demonstrated that higher lovastatin treatment led to a significant reduction in the need for repeat revascularization and new adverse cardiovascular events [62].

Thereafter, a number of surgical observational studies confirmed the importance of postoperative LDL reduction with statins [63–66]. In a cohort study of 7503 patients, statin treatment within 1 month of CABG was independently associated with a reduction in the risk of all-cause mortality and major adverse cardiovascular events late after surgery [50]. Several studies also demonstrated that statin treatment significantly reduces the risk of atrial fibrillation after CABG, both in the

perioperative period and long term after surgery [67,68]. This has been attributed to the nonlipid 'pleiotropic' properties of statins, leading to improvements in endothelial function and inhibition of inflammatory responses [69,70].

Recent attention in the cardiology community has turned toward the use of high-intensity statin therapy to achieve even further LDL reduction to 70 mg/dl or less [49,55,71]. Several studies, including the Treating to New Targets (TNT) trial [72], demonstrated significantly improved outcomes for CAD patients treated with high-dose statin therapy (i.e., atorvastatin or simvastatin 80 mg daily) as compared with usual medium or lower statin doses, findings that were subsequently confirmed in multiple meta-analyses [49,55,71]. Furthermore, in a subgroup analysis from the TNT trial that focused on patients who had CABG in the past (on average 4 years earlier), atorvastatin 80 mg was associated with a significantly lower risk for adverse cardiovascular events and a lower need for repeat revascularization during follow-up, as compared with patients who were randomized to atorvastatin 10 mg [73]. Given the data favoring more intensive statin treatment, the recent AHA guidelines and the CABG secondary prevention scientific statement recommended high-intensity statin therapy for the majority of patients who have previously undergone surgical revascularization [5▪▪,55].

Notwithstanding the new recommendations, it remains unclear whether high-intensity statins early after CABG will improve graft patency, and little experience has accrued with their use in the perioperative period. One observational study noted a reduction in the incidence of cardiovascular events among patients who received high-dose statin therapy prior to surgery [74]. However, two recent randomized controlled trials raised doubts regarding the perioperative benefits of high-dose statin therapy. No improvements were noted with high-dose statins in terms of reducing the risk of perioperative atrial fibrillation, myocardial damage, or kidney injury early after CABG [75▪,76▪]. On the subject of graft function, Hata et al. [77] noted yellow plaque and thrombus using intracoronary angioscopy in the vein grafts of patients with high LDL levels (>100 mg/dl) 1 year after surgery, whereas it was absent for those with low LDL levels (<80 mg/dl), suggesting that aggressive lipid-lowering therapy after CABG may prevent the development of saphenous vein graft disease. In a post-hoc analysis of the CASCADE trial, 1-year graft patency was significantly better for patients with LDL levels less than 100 mg/dl compared with those with LDL levels more than 100 mg/dl ($P = 0.03$), but there was no further improvement in graft patency when LDL levels were reduced to less than 70 mg/dl [58]. Soon, the Aggressive Cholesterol Therapy to Inhibit Vein Graft Events (ACTIVE) trial will be complete, which is evaluating the impact of high-dose atorvastatin on 1-year graft patency after CABG, as compared with conventional medium-dose atorvastatin (ClinicalTrials.gov NCT01528709).

In the absence of contraindications, essentially all patients undergoing CABG are candidates for long-term statin therapy, which should ideally be a high-intensity regimen such as atorvastatin 80 mg or rosuvastatin 20–40 mg [5▪▪,55]. Ezetimibe may also be considered, especially for patients who cannot tolerate high-dose statins, as it recently was shown to improve cardiovascular outcomes when added to simvastatin 40 mg for ACS patients in the IMProved Reduction of Outcomes: Vytorin Efficacy International Trial trial [78]. With regard to other lipid markers, observational studies have suggested an increased risk among patients with low high-density lipoprotein levels [79–83] or high triglyceride levels [79,81,84–90] after CABG. However, there is little data to support the use of niacin [91–94], fenofibrates [95–97], or gemfibrozil [82] following surgery, unless patients cannot tolerate statins [5▪▪,55,98]. Encouraging data continues to accumulate regarding the use of proprotein convertase subtilisin/kexin type 9 inhibitors [99,100], but to date, limited clinical information is available to recommend their use after CABG.

HYPERTENSION MANAGEMENT

Hypertension is a common condition prior to CABG, occurring in as many as 80% of patients [101]. The preoperative antihypertensive regimen for patients undergoing CABG can be quite varied, but in general, includes a β-blocker and an angiotensin-converting enzyme (ACE) inhibitor [102–103]. Despite the routine use of these medications, however, blood pressure (BP) control before and after CABG remains suboptimal [104]. For patients with CAD and those recovering from CABG, controversy exists regarding the ideal BP goals. Years ago, the AHA guidelines recommended a BP goal of less than 130/80 mmHg for patients with CAD [105], although more recent guideline statements proposed less aggressive BP target ranges of less than 140/85 [106] or less than 140/90 [107–108]. In the 2015 CABG secondary prevention scientific statement, a BP target of less than 140/85 was advised after surgery [5▪▪], but admittedly, no clinical trials have ever specifically assessed BP targets following CABG and their impact on clinical outcomes. Nevertheless, a BP goal of less than 140/85 seems broadly applicable to all patients who have undergone CABG, as these targets have been shown

in several trials to be well tolerated and to improve the clinical outcomes of patients with a history of hypertension, diabetes, and multiple cardiovascular risk factors [109–111].

Most recently, the results of the Systolic Blood Pressure Intervention (SPRINT) trial have become available. In this study, 9361 patients 50 years and older who had hypertension and increased cardiovascular risk (but not diabetes) were randomized to intensive BP reduction with a target SBP less than 120 mmHg or standard SBP reduction less than 140 mmHg. The SPRINT trial was stopped early, after a follow-up of only 3 years, because of a significantly lower rate of cardiovascular events in the intensive treatment group (hazard ratio: 0.75, 95% CI: 0.64, 0.89; $P < 0.001$), as well as a significantly lower rate of all-cause mortality ($P < 0.003$). Some adverse events (hypotension, syncope, and renal dysfunction) occurred at a higher rate in the intensive treatment group, but the rate of bradycardic events and injurious falls was similar [112■■]. Ultimately, it is difficult to extrapolate the results of SPRINT to the CABG population, as most patients undergoing CABG have numerous comorbidities, and many medical conditions were key exclusion criteria for the trial, such as a history of diabetes, previous stroke, heart failure, and chronic kidney disease. With the important benefits noted, however, the results from the SPRINT trial may lead to a modification in BP targets discussed in upcoming guideline statements.

In the post-CABG patient with hypertension, the choice of antihypertensive agents and the order of their introduction have not been methodically studied. Two major therapy groups, β-blockers and ACE inhibitors, are routinely given for their established cardioprotective features [102,103]. Although atrial fibrillation continues to occur at a high rate after CABG [113], β-blocker therapy remains a key preventive therapy [114]. A meta-analysis of contemporary clinical trials illustrated a 50% reduction in the risk of postoperative atrial fibrillation with prophylactic β-blocker therapy [115]. As such, β-blockers should be administered as soon as possible after CABG, in those patients without contraindications, to reduce the risk of atrial fibrillation [114,115] and to improve the outcomes of those patients with heart failure and left ventricular (LV) dysfunction [116]. Of note, only one randomized trial has ever evaluated the long-term use of metoprolol following CABG, and no clinical benefit was noted at 2 years, as compared with placebo [117,118]. Because of important side-effects associated with their prolonged use and their lower efficacy compared with other antihypertensive regimens (i.e., diuretics) [116], β-blockers should not be administered long term to all patients after

CABG. Instead, their use should be guided by the presence of other cardiovascular conditions (such as a history of previous MI, heart failure, and LV dysfunction).

ACE inhibitors should also be considered for CABG patients with a recent MI, LV dysfunction, diabetes mellitus, and chronic kidney disease. However, in the absence of these clinical conditions, the routine administration of ACE inhibitors after CABG may lead to more harm than benefit. In the Ischemia Management with Accupril post-bypass Graft via Inhibition of the coNverting Enzyme trial, 2253 stable CABG patients (without LV dysfunction, insulin-dependent diabetes, or renal dysfunction) were randomized to quinapril 40 mg daily or placebo within 7 days after surgery. Quinapril did not improve clinical outcomes over the 3-year follow-up of patients, and in fact led to a significant increase in cardiovascular complications and adverse events (such as hypotension) in the first 3 months after CABG [119].

In those patients who remain above the BP goal, despite a suitably titrated regimen including a β-blocker, and if appropriate an ACE inhibitor, then a calcium channel blocker or a diuretic can be considered as a next therapy choice. A long-acting dihydropyridine calcium channel blocker can effectively reduce BP and prevent graft spasm (radial artery conduit), and also may offer an antianginal effect. Diuretic therapy can be used in the CABG patient with hypertension, either for volume removal if the patient is edematous or to further reduce BP when given together with an ACE inhibitor or a β-blocker [120]. Selection of a diuretic class depends on the level of renal function, with thiazide-type drugs generally reserved for patients with a glomerular filtration rate more than 30 ml/min, and loop diuretics for patients with lower glomerular filtration rate values and the need for a diuretic of greater potency [121].

CARDIAC REHABILITATION

In addition to those discussed above, there are several other key principles of secondary prevention after CABG, including the management of concurrent medical conditions (such as obesity, diabetes mellitus, and metabolic syndrome) and the importance of smoking cessation, as detailed in the 2015 AHA scientific statement [5■■]. One approach available to help achieve many of these prevention goals is cardiac rehabilitation. Cardiac rehabilitation has been shown to improve a wide range of health factors, including medication adherence, risk factor management, functional capacity, and psychosocial wellbeing [122]. Focused weight loss in the cardiac

rehabilitation setting has been shown to improve the clinical outcomes of patients with CAD [123]. Moreover, cardiac rehabilitation can provide a supportive environment for patients who are struggling to quit smoking and achieve permanent abstinence. Importantly, smoking cessation has the greatest impact on reducing long-term mortality after CABG, more so than any other intervention or treatment [124].

Outpatient cardiac rehabilitation is a medically supervised, exercise-based program that is designed for patients with recent cardiovascular events to optimize overall health status and minimize the risks for future adverse outcomes [125–133]. The core components of contemporary cardiac rehabilitation programs include baseline patient assessments, nutritional counseling, risk factor management (lipids, BP, weight, diabetes mellitus, and smoking), psychosocial interventions, and physical activity with counseling and exercise training [122]. In the largest meta-analysis on the subject, cardiac rehabilitation was associated with a 26% risk reduction in the rate of cardiovascular mortality and a 20% risk reduction in overall mortality [129]. Moreover, a strong, inverse dose–response relationship has been observed between the number of cardiac rehabilitation sessions attended and long-term rates of MI and death [134]. Based on this compelling evidence, cardiac rehabilitation has been strongly recommended for patients with several different cardiovascular diseases [135], especially those recovering from recent CABG [125,136]. The benefits of cardiac rehabilitation, such as improved survival, have been reported for all types of CAD patients, including younger and older patients, as well as men and women [125–133].

Unfortunately, despite the wealth of evidence and the presence of insurance coverage, cardiac rehabilitation utilization patterns remain poor nationwide [122,137–140]. In a recent analysis of Medicare claims data, only 31% of CABG patients received a session of cardiac rehabilitation, and there was considerable geographic heterogeneity in cardiac rehabilitation utilization patterns [140]. One of the key barriers to cardiac rehabilitation utilization appears to be the cardiac rehabilitation referral process [135]. Even among hospitals using the AHA's Get with the Guidelines program, only 56% of eligible patients are referred to cardiac rehabilitation [139]. Clearly, improving referral patterns to cardiac rehabilitation programs is a key area in need of greater attention going forward [135,138].

CONCLUSION

Secondary prevention is an essential component to postoperative care after CABG, as patients remain at risk for future cardiovascular events despite successful revascularization. Aspirin and statin therapy continue to be the mainstay of secondary prevention, although newer antiplatelet and lipid-lowering medicines are being actively studied for their potential benefits. Other important elements of secondary prevention after CABG include the aggressive management of hypertension, smoking cessation, and the initiation of cardiac rehabilitation. Instituting these therapies after surgery optimizes graft patency and helps patients achieve the highest level of physical health and quality of life following CABG.

Conflicts of interest
There are no conflicts of interest.

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