Secondary Prevention After Coronary Artery Bypass Graft Surgery

A Scientific Statement From the American Heart Association

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Nearly 400 000 coronary artery bypass graft surgery (CABG) procedures are performed annually in the United States.[1] A proven therapy for nearly 50 years, CABG is the most durable and complete treatment of ischemic heart disease. However, in the months and years that follow surgery, patients who have undergone CABG remain at risk for subsequent ischemic events as a result of native coronary artery disease (CAD) progression and the development of vein graft atherosclerosis. Secondary therapies therefore play a key role in the maintenance of native and graft vessel patency and in the prevention of adverse cardiovascular outcomes. Postoperative antiplatelet agents and lipid-lowering therapy continue to be the mainstay of secondary prevention after coronary surgical revascularization. Other opportunities for improving long-term clinical outcomes after CABG include the aggressive management of hypertension and diabetes mellitus, smoking cessation, weight loss, and cardiac rehabilitation (CR). Secondary preventive therapies help maintain long-term graft patency and help patients obtain the highest level of physical health and quality of life after CABG.

This scientific statement seeks to expand on two 2011 American Heart Association (AHA) and American College of Cardiology Foundation (ACCF) documents that provided a general overview of secondary prevention[2] and briefly summarized the use of medical therapy after surgical coronary revascularization.[3] Since the writing of these 2 statements, important evidence from clinical and observational trials has emerged that further supports and broadens the merits of intensive risk-reduction therapies for CABG patients. The purpose of this scientific statement, specifically focused on the CABG population, is to thoroughly evaluate the current state of evidence on preventive therapies after surgery. In addition to providing revised and updated recommendations on the use of secondary preventive therapies after CABG, this statement highlights areas in need of prospectively collected clinical trial data.

Comprehensive risk factor management reduces risk as assessed by a variety of outcomes, including improved survival, reduced recurrent events, the need for revascularization procedures, and improved quality of life. It is important not only that the healthcare providers implement these recommendations in appropriate CABG patients but also that healthcare systems support this implementation to maximize the benefit to the patient. In this scientific statement, classifications of recommendations and levels of evidence are expressed in AHA/ACCF format, as detailed in the Table. Recommendations made herein are based largely on recent clinical and observational trials and major practice guidelines previously published by the AHA/ACCF and the National Institutes of Health. Thus, the development of the present statement involved a process of partial adaptation of other guideline statements and reports and supplemental literature searches.

Table. Applying Classification of Recommendation and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT			
	CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	**CLASS IIa** *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	**CLASS IIb** *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	**CLASS III** *No Benefit* or **CLASS III** *Harm* Procedure/ Test / Treatment COR III: No benefit / Not Helpful / No Proven Benefit COR III: Harm / Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit is not recommended is not indicated should not be performed/ administered/ other is not useful/ beneficial/ effective COR III: Harm potentially harmful causes harm associated with excess morbidity/mortality should not be performed/ administered/ other
Comparative effectiveness phrases†	treatment/strategy A is recommended/indicated in preference to treatment B treatment A should be chosen over treatment B	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials.

Although randomized trials are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

†For comparative effectiveness recommendations (Class I and IIa; Level of Evidence A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

The recommendations listed in this document are, whenever possible, evidence based. Writing group members performed these relevant supplemental literature searches with key search phrases, including but not limited to coronary artery bypass graft surgery; tobacco, smoking, and smoking cessation; blood pressure control and hypertension; cholesterol, hypercholesterolemia, lipids, lipoproteins, and dyslipidemia; physical activity, exercise, and exercise training; weight management, overweight, and obesity; type 2 diabetes mellitus management; antiplatelet agents and anticoagulants; renin, angiotensin, and aldosterone system blockers; β-blockers; influenza vaccination; clinical depression and depression screening; and cardiac rehabilitation. These searches were limited to studies, reviews, and other evidence conducted in human subjects and published since 1979. In addition, writing group members reviewed documents related to the subject matter previously published by the AHA, the ACCF, and the National Institutes of Health.

Antiplatelet Therapy

Aspirin

First discovered in 1897, aspirin irreversibly inhibits platelet cyclooxygenase-1. By decreasing thromboxane A2 production, aspirin prevents platelet aggregation, reducing the risk of stroke, myocardial infarction (MI), and vascular death

in patients with ischemic heart disease.[4,5] Over 30 years of experience has accrued with the use of aspirin after cardiac surgery, and essentially all patients undergoing CABG are candidates for long-term aspirin therapy.[6] Aspirin inhibition of platelet function after CABG helps maintain graft patency and prevent major adverse cardiovascular events. Aspirin significantly improves vein graft patency rates, particularly during the first postoperative year. Preoperative aspirin use is safe and appears to reduce CABG operative morbidity and mortality rates.[7,8] Therefore, aspirin should ideally be initiated before surgery at the time of hospital admission (with acute coronary syndrome or MI) or when CAD is first diagnosed.[5,9,10]

Considerable research has been performed to evaluate the impact of different dosing regimens and initiation times on post-CABG graft patency. The first randomized trials on the subject were conducted in the late 1970s, demonstrating that aspirin was safe for use in the postoperative period. However, no benefit was seen in terms of graft patency in these early studies because of limited trial enrollment and late administration, typically ≥3 days after surgery.[11–13] In one of the first studies assessing aspirin administration within the early hours after surgery, Chesebro et al[14] conducted a controlled trial comparing graft patency in 407 patients randomized to placebo or the combination of aspirin and dipyridamole beginning as early as 7 hours after surgery. Within 1 month of surgery, vein graft patency was significantly higher in patients treated with antiplatelet therapy (98% versus 90%, aspirin and dipyridamole versus placebo; $P<0.0001$). In a subsequent report, the authors noted an improvement in vein graft patency with antiplatelet therapy 1 year after surgery (89% versus 77%, aspirin and dipyridamole versus placebo; $P<0.0001$). Antiplatelet therapy was also shown to prevent the development of late vein graft occlusions in those patients whose grafts were documented as patent at the 1-month time point (6% versus 14% late occlusion rate, aspirin and dipyridamole versus placebo; $P=0.02$).[15]

The largest placebo-controlled trial to date, the Veterans Administration Cooperative Study, randomized 772 CABG patients to several postoperative aspirin regimens administered for 1 year. Within 60 days of surgery, 555 patients (1781 grafts) underwent angiographic graft assessment, revealing the following graft patency rates: aspirin 325 mg daily, 93.5%; aspirin 325 mg 3 times daily, 92.3%; and aspirin 325 mg and dipyridamole 75 mg 3 times daily, 91.9%. Compared with the patency rate of placebo (85.2%), aspirin regimens significantly improved graft patency ($P<0.05$).[16] In a subsequent report of 1-year graft patency assessed in 406 patients (1315 grafts), the graft occlusion rate was 15.8% in all of the aspirin groups combined compared with 22.6% for the placebo group ($P=0.03$). Thus, early postoperative aspirin administered for 1 year, regardless of dose, improved 60-day and 1-year graft patency.[17]

In addition to its graft patency benefits, several observational studies have shown that aspirin use is associated with improved clinical outcomes after CABG. In 2002, Mangano et al[18] evaluated the impact of aspirin administration within 48 hours after surgery. Among 5022 patients who survived the first 48 hours after surgery, aspirin (up to 650 mg daily) was administered to 59.7%. In their analysis, the authors reported that postoperative aspirin therapy within 48 hours of surgery was associated with a 68% reduction in the incidence of postoperative death (1.3% versus 4.0%, aspirin versus no aspirin; $P<0.001$). Aspirin was also associated with a 48% reduction in the incidence of MI (2.8% versus 5.4%; $P<0.001$), a 50% reduction in the incidence of stroke (1.3% versus 2.6%; $P=0.01$), a 74% reduction in the incidence of renal failure (0.9% versus 3.4%; $P<0.001$), and a 62% reduction in the incidence of bowel infarction (0.3% versus 0.8%; $P=0.01$). Moreover, the authors reported that aspirin administration within 48 hours of surgery was safe, without an increase in the risk of hemorrhage, gastritis, infection, or impaired wound healing (odds ratio [OR] for adverse events, 0.63; 95% confidence interval [CI], 0.54–0.74).[18] In a study assessing the impact of long-term postoperative aspirin therapy, Johnson et al[19] found that CABG patients who consistently took aspirin over a 4-year period after surgery had significantly better long-term survival compared with those who did not (relative risk [RR] of death, 0.58; 95% CI, 0.47–0.70). Similar findings were noted in a long-term analysis of the CABG cohort of the Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial, in which a lack of aspirin prescription at hospital discharge was identified as the strongest predictor of death at 4 years (hazard ratio [HR], 3.56; 95% CI, 2.04–6.21; $P<0.001$).[20]

With several trials featuring varied treatment protocols having been published in the literature, Fremes et al[21] reviewed the impact of antiplatelet and anticoagulant therapy on vein graft patency in a meta-analysis of 17 randomized trials. Summarizing the data, the authors reported that aspirin significantly reduced the odds of graft occlusion compared with placebo (aspirin with or without dipyridamole versus placebo: OR, 0.60; 95% CI, 0.51–0.71; $P<0.0001$). Combining dipyridamole with aspirin provided no additional benefit compared with aspirin alone (aspirin plus dipyridamole versus aspirin alone: OR, 0.94; 95% CI, 0.72–1.24; $P=0.71$). The authors further noted that a low (100 mg) to medium (325 mg) dose of daily aspirin was more effective and safer than a high dose (975 mg). Although preoperative administration provided no additional benefit, the ideal time for initiation of aspirin appeared to be within 6 hours after CABG. All together, the authors recommended indefinite aspirin use postoperatively in doses of 100 to 325 mg daily. Subsequently, Lim et al[22] performed a meta-analysis of 5 randomized, controlled trials to compare the efficacy of low-dose (50–100 mg daily) and medium-dose (300–325 mg daily) aspirin therapy after CABG. Compared with low-dose aspirin, there was a trend toward an improvement in graft patency in favor of medium-dose aspirin (RR, 0.74; 95% CI, 0.52–1.06; $P=0.10$). Although statistical significance was not achieved, the authors advocated for the use of aspirin at a medium dose of 325 mg daily because of its excellent safety profile and minimal increase in cost. This finding is in agreement with the results of previous studies that demonstrated that lower doses of aspirin (100–200 mg) may be insufficient to effectively inhibit platelet function early after CABG as a result of resistance to the antiplatelet effect of aspirin in the postoperative period.[23,24] A phenomenon called aspirin resistance, this factor may adversely affect postoperative vein graft patency.[23,25,26]

$P2Y_{12}$ Receptor Inhibitors

Clopidogrel is a thienopyridine antiplatelet agent that irreversibly inhibits the platelet $P2Y_{12}$ adenosine diphosphate receptor. When exposed to clopidogrel, platelets are inhibited from aggregating for the remainder of their 7- to 10-day life span.[27,28] In contrast to ticlopidine, a thienopyridine that had been shown to improve graft patency,[29,30] clopidogrel is 7-fold more potent and free of the unfavorable side effect profile of ticlopidine, which includes neutropenia and rash.[28] Combining aspirin therapy with clopidogrel leads to potent synergistic antithrombotic effects,[31] and substantial benefits have been demonstrated in several CAD trials studying the impact of dual antiplatelet therapy.[32,33]

The potential clinical benefits of clopidogrel administration after CABG were first evaluated in subgroup analyses from the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) and Clopidogrel for the Reduction of Events During Observation (CREDO) multicenter trials. In the CURE study, 12 562 patients presenting with acute coronary syndromes without ST-segment elevation were randomized to aspirin alone or aspirin plus clopidogrel for 3 to 12 months. The primary outcome (cardiovascular death, nonfatal MI, or stroke) occurred in 9.3% of patients treated with aspirin plus clopidogrel compared with 11.4% in patients treated with aspirin alone ($P<0.001$).[32] In the subgroup of patients who ultimately underwent CABG after enrollment in the trial, there was a trend favoring aspirin plus clopidogrel with a reduction of the primary outcome (14.5% versus 16.2%, aspirin plus clopidogrel versus aspirin alone; RR, 0.89; 95% CI, 0.71–1.11). However, that benefit was entirely preoperative while the patients were awaiting surgery, and no benefit for clopidogrel was demonstrated for CURE patients after CABG.[34]

In response to a suggestion that dual antiplatelet therapy may be beneficial after CABG, Kim et al[35] evaluated a large administrative database to compare the early clinical outcomes of 3268 patients who received both clopidogrel and aspirin early after CABG (with or without cardiopulmonary bypass) with those of 11 799 patients who were treated with aspirin alone. Using propensity-score analysis, the authors found that compared with aspirin alone, dual antiplatelet therapy was associated with lower in-hospital mortality (1.0% versus 1.8%; adjusted OR, 0.50; 95% CI, 0.25–0.99). However, there was no difference in the rate of ischemic events (1.3% versus 1.5%; adjusted OR, 0.99; 95% CI, 0.59–1.64), and surprisingly, bleeding events were significantly lower in the group who received both aspirin and clopidogrel (4.2% versus 5.2%; adjusted OR, 0.70; 95% CI, 0.51–0.97), raising concerns about selection bias. Similar findings were reported by Sørensen et al,[36] who evaluated the efficacy of clopidogrel after CABG using administrative data from 3545 patients in Denmark. Using multivariate analysis, the authors reported a lower risk of death (adjusted HR, 0.34; 95% CI, 0.20–0.61) in patients who received clopidogrel after surgery. However, clopidogrel did not significantly reduce the incidence of recurrent MI, cardiovascular death, or the need for repeat revascularization in this study.

To date, 4 clinical trials have evaluated the impact of clopidogrel on the process of vein graft disease and graft occlusion after on-pump CABG, although most studies have enrolled a mix of both on-pump and off-pump patients. In the first study published in 2009, Gao and colleagues[37] performed a nonrandomized trial involving 197 CABG patients, 37% of whom underwent off-pump surgery. Patients were assigned postoperatively to either isolated clopidogrel 75 mg daily (n=102) or clopidogrel 75 mg plus aspirin 100 mg daily (n=95) on the basis of a weekly alternating treatment scheme. The trial was neither blinded nor placebo controlled. No significant difference in graft patency was seen when isolated clopidogrel treatment was compared with dual antiplatelet therapy after CABG through the use of computed tomography angiography at 1 month or 1 year (1 month: 98.1% versus 98.2%, $P=0.73$; 1 year: 93.5% versus 96.3%, $P=0.25$, clopidogrel versus clopidogrel plus aspirin). Although no differences were noted in this trial, other studies have suggested that clopidogrel on its own may be insufficient as a sole antiplatelet agent early after CABG. Unlike aspirin, clopidogrel does not appreciably inhibit platelet aggregation during the first 5 postoperative days after coronary surgery,[38] and it is not until days 9 to 28 after CABG that the antiplatelet effects of clopidogrel (at daily doses of 75 mg) become apparent.[39]

In a subsequent placebo-controlled trial, Sun et al[40] used partial blinding to compare the combination of postoperative clopidogrel 75 mg and aspirin 81 mg daily with aspirin 81 mg alone among 100 patients undergoing on-pump CABG. Graft patency was assessed with computed tomography angiography, which was performed for 79 patients at 1 month. No difference was seen in terms of graft patency between the 2 groups, either among all grafts (92.9% versus 95%, aspirin versus aspirin and clopidogrel; $P=0.43$) or vein grafts alone (93.2% versus 93.5%, aspirin versus aspirin and clopidogrel; $P=0.92$).

In the first trial to demonstrate a statistical impact of clopidogrel on graft patency, Gao et al[41] randomized 249 patients undergoing CABG (58% off-pump) to receive either clopidogrel 75 mg plus aspirin 100 mg daily or aspirin 100 mg alone starting within 48 hours of surgery. No blinding or placebo control was used in this trial. At 3 months, graft patency was assessed in 90% of patients with computed tomography angiography. Overall graft patency was not significantly different between the 2 groups (89.7% versus 93.5%, aspirin versus aspirin and clopidogrel; $P=0.07$). However, vein graft patency was significantly improved in the combined treatment group compared with the isolated aspirin treatment group (85.7% versus 91.6%, aspirin versus aspirin and clopidogrel; $P=0.04$). Although dual antiplatelet therapy improved vein graft patency in this study, providing low-dose aspirin (100 mg) to the control subjects may have resulted in undertreatment of these patients, biasing the results in favor of those who received combination therapy.

Using a higher dose of aspirin, the Clopidogrel After Surgery For Coronary Artery Disease (CASCADE) trial was a randomized, double-blind, placebo-controlled trial of 113 patients comparing aspirin 162 mg daily with aspirin 162 mg plus clopidogrel 75 mg daily. The majority of patients (96%) underwent on-pump CABG in this study. Patients underwent conventional coronary angiography 1 year after surgery, and each patient underwent intravascular ultrasound assessment of

1 randomly selected vein graft to evaluate the extent of graft intimal hyperplasia. The combination of aspirin plus clopidogrel did not significantly reduce the development of vein graft intimal hyperplasia as indicated by intravascular ultrasound 1 year after CABG compared with aspirin. Overall graft patency (95.2% versus 95.5%, aspirin and clopidogrel versus aspirin; *P*=0.90) and vein graft patency (94.3% versus 93.2%, aspirin and clopidogrel versus aspirin; *P*=0.69) were not different between the groups at 1 year.[42]

Most recently, investigators from the Randomized On/Off Bypass (ROOBY) on-pump and off-pump CABG trial performed an observational study to evaluate the impact of clopidogrel use on graft patency 1 year after surgery. The authors noted similar graft patency between patients who received clopidogrel after surgery (86.5%) and those who did not (85.3%; *P*=0.43).[43] To summarize the published data, 3 meta-analyses have assessed the potential benefits of dual antiplatelet therapy after CABG, presenting mixed results. In the largest meta-analysis on the subject involving 5 randomized trials and 6 observational studies including >25 000 patients, dual antiplatelet therapy was found to reduce vein graft occlusion (RR, 0.59; 95% CI, 0.43–0.82; *P*=0.02) and 30-day mortality (*P*<0.0001) compared with aspirin alone.[44] On the other hand, another review came to the opposite conclusion, stating that combination antiplatelet therapy has not been demonstrated to improve graft patency.[45] Although there is some suggestion that adding clopidogrel to aspirin may improve postoperative vein graft patency, that effect appears to be most pronounced after off-pump CABG.[44–46] Dual antiplatelet therapy was also found to significantly increase the risk of major bleeding after surgery.[44]

Whereas controversy remains concerning clopidogrel use after CABG, 2 new agents have recently been introduced, increasing the number of therapeutic options available for postoperative platelet inhibition. Like clopidogrel, both prasugrel and ticagrelor inhibit the platelet $P2Y_{12}$ adenosine diphosphate receptor, but they have a more rapid onset of action and more consistent and pronounced platelet inhibition than clopidogrel.[47–49] Prasugrel was first evaluated in the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) study, in which 13 608 patients presenting with acute coronary syndromes were randomized to receive aspirin plus clopidogrel 75 mg daily or aspirin plus prasugrel 10 mg daily for 6 to 15 months. The primary outcome (cardiovascular death, nonfatal MI, or stroke) was significantly reduced for patients who received prasugrel (9.9% versus 12.1%, prasugrel versus clopidogrel; *P*<0.001), although major bleeding complications were observed more frequently with prasugrel (2.4% versus 1.8%, prasugrel versus clopidogrel; *P*=0.03).[47] In a post hoc analysis of the 346 randomized patients in the TRITON-TIMI 38 study who underwent CABG, prasugrel was associated with a lower rate of death after CABG compared with clopidogrel (adjusted OR, 0.26; *P*=0.025). However, prasugrel led to more blood loss after surgery (*P*=0.05).[50]

The use of ticagrelor for the treatment of acute coronary syndrome was assessed in the Platelet Inhibition and Patient Outcomes (PLATO) study, a randomized trial comparing 1-year treatment with aspirin plus ticagrelor 90 mg twice daily with aspirin plus clopidogrel 75 mg daily in 18 624 patients. The primary end point of the study (cardiovascular death, MI, or stroke) was significantly reduced by ticagrelor (9.8% versus 11.7%, ticagrelor versus clopidogrel; *P*<0.001), but ticagrelor was associated with a higher rate of major bleeding (4.5% versus 3.8%, ticagrelor versus clopidogrel; *P*=0.03). The trial investigators thereafter performed a post hoc analysis of the 1261 patients who underwent CABG within 7 days of receiving study drug treatment in PLATO. In this CABG subgroup, ticagrelor led to a nonsignificant reduction in the primary end point at 1 year (10.6% versus 13.1%, ticagrelor versus clopidogrel; *P*=0.29) and a significant reduction in cardiovascular mortality (4.1% versus 7.9%, ticagrelor versus clopidogrel; *P*<0.01). There was no significant difference in CABG-related major bleeding between the randomized treatments.[49] On further review of the causes of death in the CABG subgroup, the mortality reduction with ticagrelor appeared to be related to fewer deaths as a result of cardiovascular, bleeding, and infection complications compared with clopidogrel.[51]

Although the post hoc analyses of prasugrel and ticagrelor after surgery are provocative, no prospective, randomized data have yet to become available on their use specifically in the CABG population. This area remains the subject of active research, with ongoing antiplatelet trials evaluating graft patency and clinical events compared with standard isolated aspirin therapy.

Off-Pump CABG

By avoiding cardiopulmonary bypass, off-pump surgery (off-pump coronary artery bypass [OPCAB]) reduces the systemic inflammatory response after CABG and improves hemostasis by averting the activation and consumption of clotting factors and platelets associated with bypass. However, the clotting disorders and platelet dysfunction induced by cardiopulmonary bypass may actually have desirable effects by protecting anastomosis patency and preventing graft thrombosis. Several reports have documented the existence of a relative hypercoagulable state after off-pump surgery, associated with higher levels of postoperative platelet activity and a decrease in platelet sensitivity to aspirin after OPCAB.[52–60] Moreover, in some early studies of graft patency after OPCAB, vein graft occlusion was noticeably higher both early and late after OPCAB compared with conventional CABG.[53,61] Questions were therefore raised about whether antiplatelet therapy with aspirin alone would be sufficient for patients after OPCAB, and as early as 2003, leading off-pump centers instituted policy changes to treat all OPCAB patients with both clopidogrel and aspirin after surgery for a duration of 3 months.[62]

Although dual antiplatelet therapy developed into the standard of care after OPCAB, data confirming the merits of combined aspirin and clopidogrel after off-pump surgery have been fairly limited. Some benefits were noted in terms of improved graft patency[63] and clinical outcomes[64] in single-center observational studies. In a small, randomized trial comparing the combination of clopidogrel 75 mg and aspirin 150 mg daily with aspirin 150 mg alone, Nielsen et al[65] noted that patients who received dual antiplatelet therapy achieved greater platelet inhibition as determined by thromboelastography studies 30

days after OPCAB. Most recently, Mannacio et al[66] performed a single-center, prospective, randomized trial to evaluate the impact of clopidogrel on graft patency after off-pump surgery. Three hundred OPCAB patients without a history of diabetes mellitus were randomized to receive either aspirin 100 mg plus clopidogrel 75 mg daily or aspirin 100 mg daily for 1 year after surgery. The authors noted that combined therapy with aspirin and clopidogrel was associated with a significant reduction in the rate of vein graft occlusion as assessed by computed tomography angiography at 1 year (7.4% versus 13.1%, aspirin and clopidogrel versus aspirin alone; P=0.04). Similar findings were reported in a meta-analysis evaluating the role of dual antiplatelet therapy after CABG surgery in which the benefit of combined clopidogrel and aspirin treatment was most pronounced after off-pump CABG, reducing vein graft occlusion by 55% compared with aspirin alone.[44]

Antiplatelet Therapy Recommendations

1. **Aspirin should be administered preoperatively and within 6 hours after CABG in doses of 81 to 325 mg daily. It should then be continued indefinitely to reduce graft occlusion and adverse cardiac events (*Class I; Level of Evidence A*).**
2. **After off-pump CABG, dual antiplatelet should be administered for 1 year with combined aspirin (81–162 mg daily) and clopidogrel 75 mg daily to reduce graft occlusion (*Class I; Level of Evidence A*).**
3. **Clopidogrel 75 mg daily is a reasonable alternative after CABG for patients who are intolerant of or allergic to aspirin. It is reasonable to continue it indefinitely (*Class IIa; Level of Evidence C*).**
4. **In patients who present with acute coronary syndrome, it is reasonable to administer combination antiplatelet therapy after CABG with aspirin and either prasugrel or ticagrelor (preferred over clopidogrel), although prospective clinical trial data from CABG populations are not yet available (*Class IIa; Level of Evidence B*).**
5. **As sole antiplatelet therapy after CABG, it is reasonable to consider a higher aspirin dose (325 mg daily) rather than a lower aspirin dose (81 mg daily), presumably to prevent aspirin resistance, but the benefits are not well established (*Class IIa; Level of Evidence A*).**
6. **Combination therapy with both aspirin and clopidogrel for 1 year after on-pump CABG may be considered in patients without recent acute coronary syndrome, but the benefits are not well established (*Class IIb; Level of Evidence Level A*).**

Antithrombotic Therapy

In the early years of coronary bypass graft surgery, before the introduction of routine aspirin use in the 1980s, a need was recognized for adjunctive pharmacotherapy to improve patency and to prevent thrombosis of bypass grafts after CABG. With the hypothesis that anticoagulation could reduce the likelihood of graft occlusion, several trials were performed to evaluate the role of anticoagulation with warfarin, a vitamin K antagonist. In 1979, in one of the first trials on the subject, Pantely et al[11] found no improvement in graft patency among CABG patients treated with warfarin. Two subsequent studies suggested some benefit associated with warfarin treatment, but aspirin treatment had yet to be incorporated into everyday practice at that time.[12,67] In the largest trial in the field, the Post-Coronary Artery Bypass Graft (Post-CABG) trial randomized 1351 patients to low-dose warfarin anticoagulation (mean international normalized ratio, 1.4) or placebo, with all patients receiving aspirin 81 mg daily. The authors noted no significant differences in angiographic outcome between the patients who were randomized to warfarin or placebo, and warfarin did not slow the process of vein graft disease.[68] With inconsistent results reported from clinical trials and increased bleeding risks associated with warfarin, Fremes et al[21] summarized the literature with a meta-analysis of 17 trials on antithrombotic and antiplatelet therapy after CABG. This analysis illustrated that both aspirin (OR, 0.60; 95% CI, 0.51–0.71; P<0.0001) and anticoagulation (OR, 0.56; 95% CI, 0.33–0.93; P=0.025) reduced the odds of graft occlusion compared with placebo. However, anticoagulation did not improve graft patency compared with aspirin alone (OR, 0.95; 95% CI, 0.62–1.44; P=0.87).

Overall, the data do not support the use of warfarin antithrombotic therapy to prevent graft occlusion after CABG or to slow the process of vein graft disease. Outside the scope of this statement and covered in detail elsewhere, postoperative antithrombotic therapy should continue to be reserved for patients recovering from CABG who have other indications for warfarin, including those with atrial fibrillation (AF),[69] patients with a history of venous thromboembolism,[70] and those who undergo concurrent valve replacement at the time of surgery.[71] When warfarin is prescribed after CABG, aspirin is typically administered at lower doses (75–162 mg daily) to reduce the risk of bleeding complications.[69–71] Although newer antithrombotic agents (dabigatran, apixaban, rivaroxaban) have recently become available, their efficacy in the CABG population has yet to be prospectively evaluated. Moreover, safety concerns have been raised about their use early after surgery and in those with mechanical prosthetic valves.[72–74]

Antithrombotic Therapy Recommendations

1. **Warfarin should not be routinely prescribed after CABG for graft patency unless patients have other indications for long-term antithrombotic therapy (such as AF, venous thromboembolism, or a mechanical prosthetic valve) (*Class III; Level of Evidence A*).**
2. **Antithrombotic alternatives to warfarin (dabigatran, apixaban, rivaroxaban) should not be routinely administered early after CABG until additional safety data have accrued (*Class III; Level of Evidence C*).**

Lipid Management

Statins and Low-Density Lipoprotein Management

Elevated low-density lipoprotein (LDL) cholesterol levels strongly influence the process of saphenous vein graft disease after CABG, including the development of intimal hyperplasia

and atheromatous plaques.[75,76] Through lifestyle changes and medications, the treatment of hyperlipidemia reduces adverse cardiovascular events in patients with CAD, and among CABG patients in particular.[68,77–79] Statins, the most commonly prescribed agents for hyperlipidemia, have been shown to improve survival and to reduce the risks of adverse cardiovascular events across a wide range of cholesterol levels. Statins also reduce the progression of native artery atherosclerosis.[77,80–82] Of importance to the CABG population, statins have been demonstrated to inhibit the development of saphenous vein graft disease[68,83] by reducing neointimal formation and smooth muscle proliferation.[84–86]

A number of studies have investigated the role of statins for postoperative cholesterol reduction after CABG. In the landmark Post-CABG Trial, 1351 patients who had previously undergone CABG 1 to 11 years earlier and who had LDL levels between 130 and 175 mg/dL were randomized to aggressive cholesterol reduction with lovastatin 40 to 80 mg daily or moderate cholesterol reduction with lovastatin 2.5 to 5 mg daily. As measured annually during the study period, mean LDL levels of patients who received aggressive treatment ranged from 93 to 97 mg/dL compared with 132 to 136 mg/dL for patients who received moderate treatment (P<0.001). Angiography ≈4 years after study initiation demonstrated that aggressive cholesterol reduction lowered the incidence of new vein graft occlusions (10% versus 21%, aggressive reduction versus moderate reduction; P<0.0001) and the number of grafts with progression of atherosclerosis (27% versus 39%, aggressive reduction versus moderate reduction; P<0.001).[68] In a follow-up study of trial participants 3 years later, the aggressive treatment approach was associated with a 30% reduction in the need for repeat revascularization and a 24% reduction in adverse cardiovascular events (both P=0.001).[87] Overall, the Post-CABG trial noted that aggressive lowering of LDL to <100 mg/dL reduced both cardiovascular events and the progression of atherosclerosis in native coronary arteries and saphenous vein grafts.[68,87]

The importance of postoperative LDL reduction with statins has been confirmed in several other randomized and observational studies in the cardiac surgery literature. A small, controlled trial published in 1999 noted that statin treatment started 4 weeks preoperatively and continued for 1 year after CABG reduced the risk of MI both in the perioperative period (0% versus 14%, preoperative statin versus regular care; P=0.02)[88] and during the first year after CABG (0% versus 19%, preoperative statin versus regular care; P=0.03).[89] 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 (adjusted HR, 0.82; 95% CI, 0.72–0.94; P=0.004) and major adverse cardiovascular events (adjusted HR, 0.89; 95% CI, 0.81–0.98; P=0.02) late after surgery.[78] Nearly identical findings were reported in 2 observational studies that followed, with significant associations demonstrated between postoperative statin therapy and lower all-cause mortality and cardiac events long term after CABG.[90,91] Of interest, the survival benefits associated with statins after CABG appear to be similar in magnitude to that associated with the use of 2 internal mammary artery grafts compared with the use of only 1 graft.[92]

In addition to their lipid-lowering effects, statins appear have important non–lipid-related actions that may contribute to their beneficial effect.[93,94] These cholesterol-independent or "pleiotropic" properties include improvements in endothelial function, nitric oxide levels, and antioxidant activity, as well as the inhibition of inflammatory responses, vasoconstriction, thrombosis, and platelet aggregation.[94–98] Administering statins before surgery has been shown to diminish the systemic inflammatory response associated with the use of cardiopulmonary bypass during CABG.[99–102] Through antisympathetic activity and the stabilization of ion channels,[103] both randomized and observational studies have illustrated that statin treatment significantly reduces the risk of AF after CABG both in the perioperative period and long term after surgery.[104–110] Although selection bias cannot be excluded, several nonrandomized, retrospective studies have noted significant associations between perioperative statin use and a lower risk of postoperative renal dysfunction,[111,112] infection,[113] stroke,[114–116] and mortality,[111,116–118] even among patients without elevated lipid profiles before surgery.[119] Some investigators have suggested that preoperative statin treatment may reduce the risk of mortality late after surgery,[117,120–122] but it is also possible that preoperative statin administration simply predicts those who will receive statins after surgery,[123] ultimately leading to improved long-term outcomes.[78]

Recently, attention in the cardiology community has turned toward the use of high-intensity statin therapy to achieve an LDL reduction to ≤70 mg/dL to further improve cardiovascular outcomes in patients with CAD.[77,82,124] In the Treating to New Targets (TNT) Trial, 10 001 patients with CAD were randomized to receive either atorvastatin 80 mg/d or atorvastatin 10 mg/d.[125] In a subgroup analysis that focused on the 4654 patients with a history of previous CABG, atorvastatin 80 mg was associated with a significantly lower risk for adverse cardiovascular events (HR, 0.73; 95% CI, 0.62–0.87; P=0.0004) and a lower need for repeat revascularization (HR, 0.70; 95% CI, 0.60–0.82; P<0.0001) during follow-up compared with atorvastatin 10 mg.[126] Similar findings, albeit nonsignificant, were also reported in the comparison of intensive statin therapy with standard statin therapy among patients with a history of previous CABG in the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction (PROVE-IT TIMI 22) and the Aggrastat to Zocor (A to Z) trials.[127] Although a potential benefit with high-intensity statin therapy was suggested, these subgroup analyses were limited by the lack of graft patency data and the lengthy time span between surgery and study recruitment.

More recently, several studies have evaluated the impact of intensive lipid reduction early after CABG. In a cohort study of 418 CABG patients, Ouattara et al[128] noted a significant reduction in the incidence of perioperative cardiovascular events (heart failure, malignant arrhythmia, or cardiac death) in patients who received high-dose statin therapy before surgery compared with those who were treated with low-dose statins (OR, 0.62; 95% CI, 0.41–0.93; P<0.05). Applying intracoronary angioscopy 12 to 16 months after CABG, Hata et al[129] noted yellow plaque and thrombus in the vein grafts of all 11 studied patients who had LDL levels >100 mg/dL (mean, 130 mg/dL). In contrast, in the 10 patients who had

LDL levels <80 mg/dL (mean, 64 mg/dL), no yellow plaque or thrombus was seen, suggesting that aggressive lipid-lowering therapy after CABG may prevent the development of saphenous vein graft disease. In a recent post hoc analysis of the CASCADE trial, 1-year graft patency was notably higher for patients with LDL levels <100 mg/dL (96.5%) compared with those with LDL levels >100 mg/dL (83.3%; *P*=0.03). However, no improvement in graft patency was noted with further LDL reduction to <70 mg/dL (*P*=1.00).[83]

Extensive evidence exists supporting the use of high-intensity statin therapy for secondary prevention among patients with clinical atherosclerotic cardiovascular disease.[82] Although the data are sparse in the CABG literature, the recent ACC/AHA cholesterol guideline statement recommended high-intensity statin therapy for the majority of patients who have clinical atherosclerotic cardiovascular disease, which would include nearly all patients who have previously undergone CABG.[82] The only exception to this recommendation relates to patients >75 years of age, given the potential for drug-drug interactions in this population and because few patients of this age were included in the high-intensity statin trials.[82] Notwithstanding the new recommendations, little experience has accrued with the use of high-intensity statin therapy early after CABG as it relates to patient compliance and side effects. Moreover, it remains unclear whether high-intensity statin therapy early after CABG will improve graft patency or slow the process of vein graft disease compared with usual moderate statin doses, highlighting the need for further research on the subject.

Statins are generally well tolerated and appear to be one of the safest classes of drugs ever developed.[130,131] Although concerns had previously been raised about the safety of statins early after CABG,[132] more recently, it has become clear that the perioperative risks associated with statin use are markedly less than originally anticipated.[133,134] Furthermore, delaying statin reinitiation early after surgery may lead to greater harm.[122] Postoperative statin withdrawal may worsen endothelial function and result in a greater risk of postoperative complications.[133,135] Several studies in the cardiac and vascular surgery literature have reported a significantly greater risk of postoperative morbidity and mortality among patients whose statins are discontinued after surgery.[122,136,137]

Despite their benefits and low risk profile,[134] statins remain underused after CABG,[123,138] and long-term patient adherence to these medications remains a challenge.[139] To maximize the benefits associated with their use and to potentially improve perioperative outcomes, statins should be administered preoperatively when CAD is first documented and restarted early after CABG surgery. Postoperatively, statin use should be resumed when the patient is able to take oral medications and should be continued indefinitely. There is no evidence to support the use of one statin over another, either before or after CABG, although the administration of generic statins is appealing from a cost point of view because this may improve patient compliance.[140] Essentially all patients undergoing CABG are candidates for long-term statin therapy in the absence of contraindications such as liver disease. For the occasional subject who cannot take statins, alternative lipid treatments such as bile acid sequestrants, niacin, and fibrates should be considered, as described elsewhere.[82,141]

High-Density Lipoprotein Management

Many patients remain at high risk for adverse cardiovascular events even when their LDL levels have been aggressively reduced by statins.[142] Thus, increasing attention has recently been directed to the evaluation of therapies to raise high-density lipoprotein (HDL) levels to further improve cardiovascular outcomes.[143–147] Frequently seen in patients with CAD, a low HDL level has been well described as an independent risk factor for adverse cardiovascular outcomes in several studies.[142,148–152] Some of the earliest data on the subject became available from the Framingham Heart Study, in which low HDL was found to be a more potent CAD risk factor than high LDL.[148,150] Recent studies from the current era have shown that HDL levels are inversely related to cardiovascular events, even among patients receiving statin therapy[152] and those with LDL levels aggressively treated to <70 mg/dL.[151] In addition, moderate increases in HDL appear to be associated with regression of coronary atherosclerosis in statin-treated patients.[153]

Smoking cessation, weight loss, exercise, and moderate alcohol intake all modestly increase HDL. Fibrate therapy can raise HDL levels by 5% to 10%, and niacin increases HDL by 15% to 25%. Statins, on the other hand, have little effect on HDL. Given the risk for adverse cardiovascular events that remains despite statin treatment,[142,151] several research groups have focused their attention on the evaluation of therapies to increase HDL and to possibly improve clinical outcomes in patents already treated with preventative medications.[143–147] Many clinical trials have confirmed that HDL levels can be increased through pharmacological intervention, including the use of niacin,[143,144,154,155] gemfibrozil,[156] bezafibrate,[157] fenofibrate,[158–160] and torcetrapib.[145] Although some studies have demonstrated modest biological effects such as the reduction of either carotid artery intimal thickness[144,154] or angiographic CAD progression,[156–158] the majority of the studies in the field have produced negative clinical results.[143,145,155,159,160]

Focusing on non-CABG populations, 2 large, placebo-controlled, clinical trials have evaluated the use of fenofibrate therapy for the prevention of cardiac events in patients with diabetes mellitus. Fenofibrate, with or without concurrent statin therapy, led to significant increases in HDL levels in both studies but failed to significantly reduce the primary clinical end points of fatal or nonfatal MI in either trial.[159,160] Most recently, 2 large clinical trials received much attention by evaluating the impact of niacin treatment to reduce vascular events among statin-treated patients with well-controlled LDL levels. In Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes (AIM-HIGH), 3414 patients with a history of cardiovascular disease were randomized to receive high-dose extended-release niacin or placebo. Niacin increased HDL levels by 20% but failed to reduce the rate of cardiovascular events over the 5-year trial duration (5.8% versus 5.6%, niacin versus placebo; *P*=NS). The trial was halted prematurely because of the absence of clinical benefit, and a small increase in ischemic stroke was noted in the niacin group.[143] Presented in 2013, the Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) trial yielded similarly disappointing results for niacin. In this trial, 25 673 patients with

well-controlled LDL levels were randomized to extended-release niacin plus an antiflushing agent (laropiprant) or placebo. Niacin increased HDL by 14% but failed to reduce the primary clinical end point (fatal or nonfatal MI, stroke, or coronary revascularization; 14.5% versus 15.0%, niacin versus placebo; *P*=NS). Moreover, niacin increased the risk of myopathy in this trial.[155] Although it increases HDL levels, adding niacin to statin therapy does not improve cholesterol efflux or the antioxidant functions of HDL, which may explain the lack of clinical effect in clinical trials.[161]

Casting doubt on the HDL theory, no therapy to date has been shown to increase HDL levels and to improve outcomes in a clinical trial enrolling CAD patients already treated with statins.[143,145,155,159,160] Therapies to increase HDL appear to be ineffective in terms of reducing adverse cardiovascular events, and no evidence exists to support the premise that raising HDL cholesterol leads to clinical benefit in CAD (and specifically non-CABG) patient populations.

Less is known about the relevance of HDL after CABG,[162–165] although data from the prestatin era suggested that a relationship exists between lower HDL levels and higher risk of atherosclerosis progression and adverse events after surgery.[156,163–165] Through reverse cholesterol transport, HDL prevents the development of foam cells in a vessel wall.[142,144] Moreover, independently of its involvement in cholesterol metabolism, HDL has properties that reduce vascular inflammation and thrombosis, improve endothelial function, and promote endothelial repair.[142] Ultimately, higher levels of HDL particles may help slow the process of saphenous vein graft disease and decrease the risk of adverse outcome after surgery.[166] Previous observational studies have demonstrated associations between lower HDL and both worse long-term survival and higher risk of cardiovascular events after CABG.[163,164]

In the only HDL clinical trial involving CABG patients, the Lopid Coronary Angiography Trial (LOCAT) enrolled 395 men with HDL levels <42.5 mg/dL who had undergone CABG on average 2 years earlier. From an era before the routine use of statins after CABG, patients were randomized to receive either slow-release gemfibrozil 1200 mg/d or matching placebo. Coronary angiography was performed at baseline and after a mean of 32 months of therapy. Gemfibrozil therapy led to significant increases in HDL levels ($P<0.001$) and slowed the progression of native CAD ($P=0.009$). Moreover, gemfibrozil significantly reduced the risk of developing new lesions in bypass grafts on follow-up angiography (2% versus 14%, gemfibrozil versus placebo; $P<0.001$).[156] Despite the notable results of LOCAT, gemfibrozil never became incorporated into the routine care of CABG patients. This was likely a reflection of the impressive data published that same year promoting the use of statins after CABG,[68] as well as the high risk of side effects associated with gemfibrozil, particularly when combined with statin therapy.[167,168]

Lower HDL levels are associated with worse long-term survival and higher risk of cardiovascular events after CABG.[163,164] Although there is strong evidence supporting the use of statins after CABG, adding gemfibrozil to a patient's medication regimen can increase the risk of side effects such as myopathy and rhabdomyolysis. Theoretically, HDL modulation may help slow the process of saphenous vein graft disease, but this concept must be tempered by the absence of data on the administration of fenofibrate or niacin therapy after CABG. Moreover, in the non-CABG population, the administration of these agents on top of statins has proven to be futile in recent clinical trials.[143,145,155,159,160] Future research may help further explore this possible strategy of administering second-line agents such as fenofibrate to elevate low levels of HDL after surgery, with a view toward improving post-CABG vein graft patency.

Triglyceride Management

Although LDL remains the primary therapeutic target for hyperlipidemia, high triglyceride levels are also associated with an elevated risk of developing CAD.[169,170] Elevated triglyceride levels are a marker of atherogenic remnant lipoproteins, which are more easily oxidized, leading to increased cardiovascular risk.[171] Triglyceride levels >150 mg/dL tend to be associated with a greater burden of small and dense LDL, making the calculation of the LDL level with the Friedewald formula inaccurate. Therefore, using the non-HDL cholesterol level, defined as the difference between total cholesterol and HDL levels, has been suggested as a more accurate tool for risk and treatment assessment in the presence of high triglyceride levels. Non-HDL cholesterol includes all cholesterol present in lipoprotein particles considered to be atherogenic, including LDL, lipoprotein(a), intermediate-density lipoprotein, and very-low-density lipoprotein remnants.[172]

In patients with hypertriglyceridemia, first-line therapies usually include diet modification, exercise, and weight loss, with a focus on restriction of refined carbohydrates and reduced alcohol intake, in association with increased intake of omega-3 fatty acids. Statins may be of benefit in lowering non-HDL cholesterol levels in patients with high triglyceride levels >200 mg/dL.[173] In an era before the routine use of statins, 2 placebo-controlled trials reported that gemfibrozil treatment caused marked reductions in triglyceride levels and increased HDL levels, leading to significant reduction in cardiovascular events.[156,174]

Because of the dangers associated with gemfibrozil,[167,168] fenofibrate therapy has been the focus of more recent studies as a treatment option for dyslipidemia and elevated triglyceride levels. Fenofibrate is a fibric acid derivative that activates the peroxisome proliferator–activated receptor-α, leading to lower triglyceride levels and increased HDL levels. Compared with statin monotherapy, fenofibrate monotherapy tends to improve triglyceride and HDL cholesterol levels to a greater extent, whereas statins improve LDL and total cholesterol levels to a larger degree.[175] In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9797 patients with diabetes mellitus who were not taking statins were randomized to micronized fenofibrate 200 mg daily or matching placebo for 5 years. Treatment with fenofibrate did not significantly reduce the risk of the primary outcome of cardiovascular death or nonfatal MI (HR, 0.89; 95% CI, 0.75–1.05; $P=0.16$), but it was associated with a reduction in the secondary end point of total cardiovascular events (including nonfatal MI and coronary revascularization).[160]

Published more recently, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was a double-factor, randomized, clinical trial that studied intensive glucose and blood pressure (BP) control and the addition of fenofibrate therapy to statin treatment. In the lipid arm of ACCORD, 5518 participants who were treated with open-label simvastatin to achieve LDL levels <80 mg/dL were randomized to receive either fenofibrate or placebo. Treatment with fenofibrate therapy led to significant decreases in triglyceride levels and increases in HDL levels, but no difference was seen between groups in the primary composite outcome of a major fatal or nonfatal cardiovascular event (HR, 0.92; 95% CI, 0.79–1.08; *P*=0.32).[159] Subsequent subgroup analyses of the FIELD and ACCORD Lipid trials confirmed the safety of fenofibrate when used alone or in combination with a statin. Moreover, potential benefits with fenofibrate therapy were suggested in terms of decreasing cardiovascular risk among patients with the most pronounced dyslipidemia, including those with the highest levels of triglycerides and lowest levels of HDL.[159,160,175,176]

After CABG, elevated triglyceride levels may increase the risk of postoperative adverse outcomes. In an observational study of >25 000 patients who underwent primary isolated CABG between 1971 and 1998, investigators noted that a higher baseline triglyceride level at the time of surgery was significantly associated with a higher risk of repeat coronary revascularization (stent or reoperation) during long-term follow-up (*P*=0.002).[164] Similarly, Sprecher et al[177] reported that higher triglyceride levels at the time of surgery were associated with significantly greater risk of mortality and worse event-free survival in a prospective study of 6602 CABG patients. Of interest, after CABG, women with high triglyceride levels have far worse long-term survival (HR, 1.5; 95% CI, 1.1–2.1) compared with men with high triglyceride levels (HR, 1.1; 95% CI, 0.9–1.3). Other studies also have demonstrated that elevated triglyceride values after surgery predict vein graft occlusion,[178] recurrent angina and MI,[179–181] and the need for redo CABG.[182,183] In a secondary analysis of the Post-CABG Trial, the study investigators demonstrated that a high triglyceride level was a significant prognostic factor for vein graft atherosclerosis progression.[165] Although the mechanism by which elevated triglyceride levels increase cardiovascular risk is not entirely clear, triglyceride-rich lipoproteins in the vessel wall may lead to fatty streaks, which are noted in saphenous vein grafts as early as 18 months after CABG.[184,185]

High triglyceride levels have been shown to be a marker of worse outcomes after CABG. However, very few data are available to support the use of medical therapy to lower triglyceride levels after CABG. Before the advent of routine statin therapy, Barbir et al[186] performed a small pilot trial of combination therapy with colestipol 10 mg and bezafibrate 400 mg/d for 2 months after CABG, noting a reduction in total cholesterol of 17%, in LDL cholesterol of 23%, and in triglyceride levels of 19%. In the previously described LOCAT study in which gemfibrozil reduced the development of new bypass graft lesions, gemfibrozil increased HDL levels and led to a 36% reduction in triglyceride levels (*P*<0.001).[156]

To date, no trial has investigated the use of fenofibrate therapy to reduce triglyceride levels and to potentially improve outcomes after CABG, highlighting the need for more research on the subject. For CABG patients with severely elevated triglyceride levels >500 mg/dL, fenofibrate therapy should be administered in addition to statin therapy to help prevent acute pancreatitis.[2] The use of combination fenofibrate-statin therapy may also be considered in diabetic patients recovering from CABG who have high triglyceride levels and low HDL cholesterol levels that persist despite statin therapy,[141] as indicated by post hoc subgroup analyses from the FIELD and ACCORD trials.[159,160,175,176]

Lipid Management Recommendations

1. **Unless contraindicated, all CABG patients should receive statin therapy, starting in the preoperative period and restarting early after surgery (*Class I; Level of Evidence A*).**
2. **High-intensity statin therapy (atorvastatin 40–80 mg, rosuvastatin 20–40 mg) should be administered after surgery to all CABG patients <75 years of age (*Class I; Level of Evidence A*).**
3. **Moderate-intensity statin therapy should be administered after CABG for those patients who are intolerant of high-intensity statin therapy and for those at greater risk for drug-drug interactions (ie, patients >75 years of age) (*Class I; Level of Evidence A*).**
4. **Discontinuation of statin therapy is not recommended before or after CABG unless patients have adverse reactions to therapy (*Class III; Level of Evidence B*).**

β-Blocker Therapy

Activation of the adrenergic nervous system to excessive levels contributes to the pathophysiology and symptoms of many cardiovascular diseases. β-Blockers are competitive antagonists at the β-adrenergic receptors, thus modulating activities in this pathway. Although most of the pharmacological effects are attributed to this receptor blockade, some β-blockers are relatively selective for the β_1-adrenergic receptor, others are nonselective, and still others have intrinsic sympathomimetic activity, α-adrenergic receptor blockade, and direct vasodilating effects.[187]

Data to support the use of β-blocker therapy in ischemic heart disease date back to the early 1980s, when randomized trial data were first generated evaluating the use of β-blocker therapy in patients with acute MI.[188] At that time, it was not uncommon for CABG operations to be postponed if patients were treated with β-blocker therapy (ie, propranolol) because of the presumption of increased risk of surgical mortality. This sentiment undoubtedly contributed to the lower use of β-blocker therapy at discharge among MI patients undergoing CABG compared with those treated with medical therapy.[189] Subsequently, Chen et al[189] noted in a cohort study that β-blocker therapy was just as effective in reducing 1-year mortality for patients undergoing revascularization as it was for patients not undergoing revascularization.

In the Chen et al[189] study, 33.1% of patients undergoing CABG in 1994 to 1995 were not prescribed β-blocker therapy at discharge. Thereafter, in 2002, Ferguson and colleagues[190] raised awareness of the importance of β-blocker

therapy among CABG patients by documenting an association between preoperative β-blocker therapy and improved 30-day mortality. Evaluating the outcomes of >600 000 CABG patients in the Society of Thoracic Surgeons Database from 1996 to 1999, these authors noted that patients who received β-blockers before surgery had significantly lower 30-day mortality rates compared with those who did not (adjusted OR, 0.94; 95% CI, 0.91–0.97).

However, it remained for a number of quality-improvement projects that emerged in the early-to-mid-2000s to link secondary prevention and β-blockade therapy in CABG. These studies created the environment for attention to and adoption of β-blocker therapy after CABG. Foody et al[191] documented in a national database that only 61.5% of CABG patients received β-blocker therapy after presenting with MI between 1998 and 1999, which was lower than the non-CABG patient population. This study laid the foundation for establishing baseline secondary prevention benchmarks for aspirin, angiotensin-converting enzyme (ACE) inhibitors, and lipid-lowering medications.

With this study as a call to action, a number of regional and national quality-improvement efforts using a variety of techniques established increases in postdischarge β-blocker therapy. The Alabama CABG project demonstrated an increase in β-blocker therapy at discharge from 65% to 78% over a 2-year period.[192] Similarly, Williams et al[193] reported a significant increase in adherence for all secondary prevention medications, including β-blocker therapy, in a national quality-improvement program. Single centers during the same time frame were able to achieve even more impressive results, with the University of Kentucky improving its β-blocker use after CABG from 95% to 100% by implementing an intensive quality-improvement initiative.[194] Finally, in a study exploring the Get With The Guidelines database, investigators noted that 90.8% of patients were discharged on β-blocker therapy after CABG.[195] Interestingly, this was less than comparable patients discharged after percutaneous coronary intervention.

All of these studies were limited by their observational nature, and only 1 randomized trial of β-blocker therapy after CABG has been performed. In 1995, Sjoland et al[196] conducted a double-blind, placebo-controlled, randomized, controlled trial of 967 patients undergoing CABG. In this study, patients were randomized 4 to 21 days after CABG to 50 mg metoprolol twice a day for 2 weeks and 100 mg metoprolol twice a day thereafter versus placebo for 2 years. The authors found no difference between the 2 arms of the trial with respect to the risk of death or the development of cardiac events, and there was no improvement in exercise capacity among the 618 patients who received an exercise test at follow-up. However, patients treated with placebo were found to have a higher (worse) chest pain score compared with patients treated with metoprolol.[197]

Contraindications to β-blocker therapy can be particularly relevant in the post-CABG population because of the prevalence of reactive airway and pulmonary disease in these patients. However, the management of this comorbid condition in the perioperative setting has improved substantially, and the specificity of β_1- and β_2-blockers has minimized the cross-reactivity between the cardiac and pulmonary effects of β-blockade. Even more recently, the pharmacogenetics of β-adrenergic receptor antagonists have become clear, with certain genes being identified that influence the pharmacodynamic and pharmacokinetic effects of β-blocker compounds.[187]

To clearly establish the benefit of β-blocker therapy and secondary prevention after CABG, a link to improved mortality is needed. An important study by Goyal et al[198] from 2007 assessed both the use and clinical impact of secondary prevention medications after CABG. The use of aspirin, β-blockers, ACE inhibitors or angiotensin receptor blockers (ARBs), and lipid therapy was measured in patients enrolled in the Project of Ex-Vivo Vein Graft Engineering via Transfection (PREVENT IV) trial of 3014 patients. In ideal candidates for these therapies, β-blocker rates at discharge (88.8%) and 1 year (76.9%) were suboptimal, but in this trial context, the rates of use were substantially higher than in contemporaneous observational studies. The authors noted a stepwise association between medication use at discharge and a lower risk of adverse patient outcomes (death or MI).[198]

Most recently, a study by Bangalore et al[199] evaluated the use of β-blocker therapy in stable patients with risk factors for CAD or a history of CAD or MI. This longitudinal, observational registry study demonstrated that the use of β-blocker therapy was not associated with a lower risk of cardiovascular events, including cardiovascular death, nonfatal MI, or nonfatal stroke, whether patients had risk factors only, a known prior MI, or known CAD without MI.[199] Many patients undergoing CABG would likely fall into one of these categories. However, it is not yet clear how this information should be directly applied to the postoperative patient because many CABG patients have additional clinical conditions that warrant β-blocker therapy after surgery, including hypertension and AF. Because AF continues to occur at a high rate after heart surgery,[200] β-blocker therapy remains the mainstay of both AF prevention and rate control through its β_1-adrenergic blockade effect.[201] A meta-analysis of contemporary clinical trials illustrated a 50% reduction in the risk of postoperative AF with prophylactic β-blocker therapy.[202] Moreover, many patients on preoperative β-blocker therapy have rebound tachycardia if β-blocker therapy is not resumed early in the postoperative period.

The role of β-blocker therapy in the perioperative period remains controversial. A substantial percentage of patients undergoing CABG receive preoperative β-blocker therapy because it has been demonstrated to convey a mortality benefit.[190] Consequently, preoperative β-blocker therapy was determined to be a quality metric for cardiac surgery by the National Quality Forum and was included in the Society of Thoracic Surgeons Composite Score for CABG Quality programs.[203] However, other more recent studies have questioned whether preoperative β-blocker therapy actually affects mortality.[204] It is possible that the outcomes from surgical revascularization have improved to the point where a benefit from preoperative β-blocker therapy can no longer meet the threshold of statistical significance.[204] Nevertheless, continuation of preoperative β-blockade therapy into the postoperative period remains an important consideration.

The use of β-blocker therapy for the treatment of hypertension remains a controversial subject. In a critical review of the

literature, Bangalore et al[205] documented that β-blockade was not as effective long-term compared to other antihypertensive therapies (eg, diuretic therapy). In addition, β-blockers are often associated with side effects such as weight gain, fatigue, and sexual dysfunction, reducing rates of adherence. Thus, for long-term secondary prevention therapy, the use of β-blockers for hypertension is influenced by the presence or absence of other cardiovascular conditions (such as previous MI and heart failure).

The most compelling data on β-blocker therapy exist after an acute MI, and this circumstance pertains to most post-CABG patients. Several studies from the 1980s and 1990s demonstrated the benefits associated with β-blockade during and after MI.[188,206] In a meta-analysis of >54 000 patients, Freemantle et al[207] reported a 23% reduction in the odds of death with β-blocker therapy for long-term secondary prevention after MI. These studies and others laid the foundation for routine β-blocker therapy after MI.

The use of β-blockade in chronic heart failure has also evolved over the years, from a relative contraindication in the past to a mainstay of therapy now, leading to a consistent 30% reduction in mortality, improved well-being, and an improvement in symptoms.[205] β-Blockers likely protect the heart from the chronic upregulation of adrenergic receptors on the myocardium from epinephrine and norepinephrine, thus reducing remodeling and fibrosis in congestive heart failure. Three β-blockers have been shown to be effective in reducing the risk of death in patients with chronic heart failure: bisoprolol[208] and sustained-released metoprolol (succinate),[209] both of which selectively block β_1-receptors, and carvedilol,[210,211] which blocks α_1-, β_1-, and β_2-receptors. Many CABG patients with left ventricular (LV) dysfunction have significant heart failure both before and after surgical revascularization, and β-blocker therapy can be administered safely and effectively to the majority. As a rule, LV dysfunction alone is not a contraindication to β-blocker therapy after CABG.

In summary, β-blocker therapy is a mainstay of secondary prevention strategies after surgical revascularization for ischemic heart disease.

β-Blocker Therapy Recommendations

1. **All CABG patients should be prescribed perioperative β-blocker therapy to prevent postoperative AF, ideally starting before surgery, unless contraindicated (ie, bradycardia, severe reactive airway disease) (*Class I; Level of Evidence A*).**
2. **CABG patients with a history of MI should be prescribed β-blocker therapy unless contraindicated (*Class I; Level of Evidence A*).**
3. **CABG patients with LV dysfunction should be prescribed β-blocker therapy (bisoprolol, sustained-release metoprolol succinate, or carvedilol), unless contraindicated (*Class I; Level of Evidence B*).**
4. **Chronic β-blocker therapy for hypertension treatment after CABG (in the absence of prior MI or LV dysfunction) may be considered, but other antihypertensive therapies may be more effective and more easily tolerated (*Class IIb; Level of Evidence B*).**

Hypertension Management

Hypertension is a common antecedent condition before CABG, occurring in as many as 80% of patients.[212] The preoperative antihypertensive regimens used in patients undergoing CABG can be quite varied but generally include a β-blocker or an ACE inhibitor, in part because of their cardioprotective features.[213,214] Despite the routine use of these drug classes, however, pre-CABG and post-CABG BP control remains suboptimal.[215] Previous AHA guidelines recommended a BP goal of <130/80 mm Hg for patients with CAD.[216] More recent guideline statements have proposed less aggressive BP target ranges (<140/85[217] or <140/90[218,219] mm Hg) for patients with CAD risk factors such as diabetes mellitus and chronic kidney disease. This is a controversial subject. Inconsistent benefits have been noted in clinical trials comparing intensive BP reduction (systolic <130 mm Hg) and standard BP treatment goals (systolic <140 mm Hg) for patients with previous coronary events and a history of hypertension and diabetes mellitus, therefore justifying the currently recommended systolic target value of <140 mm Hg.[220–225] With regard to diastolic BP goals, targeting a value of <85 mm Hg appears to be safe and has been shown in 3 randomized trials to improve the clinical outcomes of patients with a history of hypertension, diabetes mellitus, or multiple cardiovascular risk factors compared with higher diastolic values.[226–228] Admittedly, no clinical trials to date have specifically assessed BP targets after CABG with respect to clinical outcomes. However, given the high incidence of diabetes mellitus and other cardiovascular risk factors in the CABG population, a BP goal of <140/85 mm Hg[217] appears reasonable and broadly applicable to all patients who have undergone CABG.

Achieving the BP goal for secondary prevention in the patient having undergone CABG requires an understanding of the effectiveness of pre-CABG antihypertensive therapies and the temporary reduction in BP that occurs during recovery from postoperative surgical circumstances such as anemia and reduced myocardial function. With an emphasis on BP control in the broad context of secondary prevention measures, antihypertensive medication regimens and BP goals should be adapted to the individualized circumstances of each patient.[198]

BP patterns and the response to treatment can be best assessed with the use of home BP monitoring.[229] Lifestyle measures such as exercise, reducing weight, and limiting sodium intake are useful adjunct measures in the post-CABG patient with hypertension. In addition, identifying comorbid risk factors for hypertension such as the BP change seen with post-CABG cognitive disorders, anxiety, depression, and sleep abnormalities and providing the indicated therapies can improve the overall effectiveness of the chosen antihypertensive therapies. No studies have prospectively evaluated the rapidity with which BP should be reduced in the post-CABG patient with hypertension. In addition, it is not known whether the J-curve relationship for morbidity and mortality occurs at a higher BP level in the post-CABG patient than in the patient without CAD.

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, as much as they are used for BP reduction.[213,214] β-Blockers should be administered as soon as possible after CABG in those patients without contraindications to reduce the risk of AF[201,202] and to improve outcomes in those patients with congestive heart failure and LV dysfunction.[205] However, their effect on BP has not been systematically explored. In the only randomized trial to date, Sjoland et al[196] found no clinical benefit associated with a 2-year treatment with metoprolol after CABG. Compared with placebo, metoprolol did not reduce the incidence of repeat revascularization, unstable angina, nonfatal MI, or death.[197]

ACE inhibitors should also be considered for CABG patients after surgery, particularly for those with recent MI, LV dysfunction, diabetes mellitus, and chronic kidney disease. The BP-lowering effect of ACE inhibitors is dependent on a patient's volume state, thus the basis for their frequent administration together with a diuretic.[230] ACE inhibitor use can be associated with a syndrome of functional renal insufficiency or hyperkalemia. This form of acute kidney injury develops shortly after the initiation of ACE inhibitor therapy but can be observed after months or years of therapy, even in the absence of prior ill effects. It may relate to the drug dose or level of hydration, as well as to the degree of small and large renal artery obstructive disease.[231] An ARB may be considered as an alternative in an ACE inhibitor–intolerant patient.

Two randomized, controlled trials have studied the use of ACE inhibitors after CABG. In a 149-patient trial evaluating the use of quinapril after surgery, investigators noted a reduction in the composite outcome of angina, death, MI, repeat revascularization, stroke, or transient ischemic attacks in patients who received quinapril for 1 year compared with placebo (3.5% versus 15%, quinapril versus placebo; P=0.02).[232] However, these findings were not confirmed in the larger, multicenter Ischemia Management With Accupril Post-Bypass Graft via Inhibition of the Converting Enzyme (IMAGINE) trial of 2253 stable CABG patients. In this study, patients were excluded from randomization if they already had indications for ACE inhibitor therapy such as LV dysfunction, insulin-dependent diabetes mellitus, or renal dysfunction. Quinapril (40 mg daily) had no benefit compared with placebo when initiated within 7 days after surgery, with a 13.7% incidence of the primary composite end point (cardiovascular death, cardiac arrest, nonfatal MI, unstable angina or heart failure requiring hospitalization, and stroke) among quinapril patients and 12.2% in the placebo group (HR, 1.15; 95% CI, 0.92–1.42; P=0.21) over a median follow-up of 2.95 years. The incidence of the primary composite end point increased significantly in the first 3 months after CABG in the quinapril group (P=0.04), and adverse events (such as hypotension) were also increased in the quinapril group, particularly during the first 3 postoperative months.[233] Thus, in this select trial population, routine ACE inhibitor therapy led to more harm than benefit when initiated early after CABG.

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 be used to reduce BP and prevent graft spasm (radial artery conduit) and may offer an antianginal effect. Nondihydropyridine calcium channel blockers such as verapamil and diltiazem are effective antihypertensive agents, but they are generally reserved for rate control in patients with coexisting chronic obstructive pulmonary disease and normal LV function. Diuretic therapy can be used in the CABG patient with hypertension either for volume removal if the patient is edematous or for further BP reduction when given together with an ACE inhibitor or a β-blocker.[230] 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 >30 mL/min and loop diuretics used for patients with lower glomerular filtration rates and the need for a diuretic of greater potency.[234]

Resistant hypertension is no more common in the post-CABG patient than in the general hypertensive population, and the approach to treatment is fairly similar. In patients already treated with an ACE inhibitor, β-blocker, diuretic, and calcium channel blocker who remain above goal BP, other treatment options include compounds that reduce adrenergic activity such as clonidine or doxazosin. In addition, a mineralocorticoid receptor antagonist such as spironolactone or eplerenone can be effective in lowering BP in the patient with resistant hypertension, particularly in the setting of LV dysfunction, while affording cardiovascular benefits, including reduced myocardial fibrosis, prevention or reversal of cardiac remodeling, or a reduction in arrhythmogenesis.[235]

Hypertension Management Recommendations

1. **β-Blockers should be administered as soon as possible after CABG, in the absence of contraindications, to reduce the risk of postoperative AF and to facilitate BP control early after surgery (*Class I; Level of Evidence A*).**
2. **ACE inhibitor therapy should be administered after CABG for patients with recent MI, LV dysfunction, diabetes mellitus, and chronic kidney disease, with careful consideration of renal function in determining the timing of initiation and dose selection after surgery (*Class I; Level of Evidence B*).**
3. **With the use of antihypertensive medications, it is reasonable to target a BP goal of <140/85 mm Hg after CABG; however the ideal BP target has not been formally evaluated in the CABG population (*Class IIa; Level of Evidence B*).**
4. **It is reasonable to add a calcium channel blocker or a diuretic agent as an additional therapeutic choice if the BP goal has not yet been achieved in the perioperative period after CABG despite β-blocker therapy and ACE inhibitor therapy as appropriate (*Class IIa; Level of Evidence B*).**
5. **In the absence of prior MI or LV dysfunction, antihypertensive therapies other than β-blockers should be considered for chronic hypertension management long term after CABG (*Class IIb; Level of Evidence B*).**
6. **Routine ACE inhibitor therapy is not recommended early after CABG among patients who do not have**

mellitus, or chronic kidney disease because it may lead to more harm than benefit and an unpredictable BP response (*Class III; Level of Evidence B*).

Previous MI and LV Dysfunction

Surgical revascularization is commonly performed for patients with reduced ejection fraction (EF) <40%.[236] The most common cause of reduced EF is previous MI, although other abnormalities such as valvular heart disease and hypertension are also recognized causes. Some patients have post-MI stunning or myocardial hibernation attributable to chronic ischemia from severe CAD. Although many have improvement or recovery in their cardiac function after surgical revascularization, others have persistent heart failure and LV dysfunction after CABG.[236] The current discussion focuses on the application of secondary prevention therapies, including medical and device therapy after CABG, for patients with persistently reduced EF despite revascularization.

β-Blocker Therapy

Elevated plasma catecholamine levels and direct sympathetic activity have deleterious effects on the heart by causing tachycardia, vasoconstriction, increased contractility, and ventricular hypertrophy.[237] β-Blockers blunt these effects and impede the maladaptive ventricular remodeling from chronic sympathetic activation. As described above, in addition to preventing heart failure, β-blockers prevent recurrent ischemia and AF, a common postoperative condition.

Most patients with persistently reduced EF after CABG are likely to have had a prior MI, and in this patient population, evidence supports the use of β-blockers on top of background therapy with ACE inhibitors, even in the absence of heart failure. Three specific β-blockers (carvedilol, bisoprolol, and sustained-release metoprolol succinate) have documented benefits for morbidity and mortality and are highly recommended for patients with active or past symptoms of heart failure.[208–211] In addition, these medications reduce heart failure symptoms, enhance patients' overall sense of well-being, and reduce hospitalization, even among patients already taking ACE inhibitors.[197,208,238,239] Contraindications to β-blocker use include bradycardia, hypotension, severe bronchospastic airway disease, low-output state, or severe, actively decompensated heart failure.

ACE Inhibitor and ARB Therapy

ACE inhibitors exert their effects by suppressing the effects of angiotensin II, a potent vasoconstrictor that reduces renal perfusion, stimulates LV hypertrophy and cardiac remodeling, and enhances the release of arginine, vasopressin, proinflammatory cytokines, and aldosterone.[237] Inhibition of ACE results in decreased levels of angiotensin II and inhibits the breakdown of bradykinin, a peptide with favorable properties, including antihypertensive, antiremodeling, and natriuretic effects. ARBs directly inhibit the action of angiotensin II by blocking the type 1 receptor, but their effects on bradykinin remain controversial.[240]

Oral ACE inhibitors have been shown to reduce symptomatic heart failure and mortality among patients with previous MI and reduced EF.[241–243] Among patients with reduced EF and active or prior heart failure symptoms, ACE inhibitors reduce mortality and heart failure hospitalization, improve New York Heart Association (NYHA) classification, reduce heart size, and prevent the need for escalating medical therapy.[244–246] The routine initiation of an ACE inhibitor early after CABG is not recommended for patients with an EF >40%.[233] However, it is unlikely that surgical revascularization mitigates the benefits of an ACE inhibitor in the post-CABG patient with a persistently reduced EF.

Among patients with reduced EF who are intolerant of ACE inhibitors, an ARB can be used as an alternative therapy for those with a prior MI or symptoms of heart failure unless contraindicated.[247–251] Angiotensin II can be generated by alternative pathways, and its production is only partially inhibited by ACE inhibitors.[237] Therefore, concomitant treatment with both an ARB and ACE inhibitor (on a background of β-blocker therapy) among patients with reduced EF may be selectively considered in patients with persistent heart failure symptoms and has been shown in clinical trials to reduce cardiovascular death and heart failure hospitalization.[252] Nevertheless, the combination of an ACE inhibitor and an ARB should not be used routinely, and this regimen is contraindicated if an aldosterone antagonist is also being used because of increased side effects. These side effects include excessive hypotension, hyperkalemia, and worsening renal function necessitating discontinuation of therapy.[248,249,252]

Aldosterone Antagonists

Spironolactone is a nonselective aldosterone antagonist that has demonstrated benefits for patients with severe heart failure. In the Randomized Aldactone Evaluation Study (RALES), spironolactone was associated with a 30% RR reduction in overall mortality and a reduction in heart failure hospitalization and symptoms among patients with NYHA class III to IV symptoms and an EF <35%.[253] Subsequently, the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) extended the benefits of aldosterone antagonists to patients with mild heart failure (including NYHA class II symptoms) and an EF <35% with the use of eplerenone.[254] It is important to note that an aldosterone receptor antagonist is indicated as an add-on therapy for patients who have persistent heart failure symptoms despite treatment with both classes of neurohormonal inhibitors (β-blockers and ACE inhibitor/ARBs). In accordance with both aforementioned studies[253,254] and previous guidelines,[236] aldosterone antagonists appear most applicable to post-CABG patients with persistent LV dysfunction (EF <35%) and mild or more severe heart failure symptoms. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and serially thereafter in these patients. Aldosterone antagonists should be avoided in patients with estimated glomerular filtration rate <30 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ or potassium levels >5.0 mEq/L.

Devices

A substantial body of evidence supports the use of implantable cardioverter-defibrillators (ICDs) to prevent sudden cardiac

death among patients with reduced EF.[255–257] However, ICD therapy at the time of surgical revascularization has failed to improve patient outcomes. In the CABG Patch Trial,[258] routine ICD insertion did not improve survival among patients with an EF <35% if an ICD was implanted prophylactically at the time of elective CABG. Notably, 71% of deaths in this trial were not arrhythmogenic, hence the lack of mortality benefit,[258] and empirical ICD therapy was even associated with diminished quality of life 6 months after CABG.[259] As per previous AHA/ACCF guidelines, patients with reduced EF should be treated with optimal neurohormonal therapies after surgical revascularization.[260] If the EF remains severely reduced (<35%) in a noninvasive assessment of LV function 3 months after surgery, then consideration should be given to implantation of an ICD for primary prevention at that time.[260]

In patients with reduced LV function who undergo CABG after resuscitation from cardiac arrest, the decision for ICD therapy early after CABG should be individualized.[260] Among these patients, CABG can suppress malignant arrhythmias and reduce subsequent episodes of cardiac arrest,[261,262] especially if the arrhythmias are related to ischemia.[263] On the other hand, CABG may not mitigate all the conditions predisposing to ventricular arrhythmias, as in the case of patients with sustained monomorphic ventricular tachycardia and prior MI, and concomitant ICD insertion after CABG may be warranted in such patients.

Progression of LV dysfunction to clinical heart failure is frequently accompanied by impaired electromechanical coupling, which may further diminish effective ventricular contractility. Modification of ventricular electromechanical delay with cardiac resynchronization therapy (biventricular pacing) can improve ventricular systolic function, ameliorate functional mitral regurgitation, and in some patients, reduce cardiac chamber dimensions.[260] Cardiac resynchronization therapy is generally indicated among patients with an EF <35% in the presence of left bundle-branch block, QRS interval >150 milliseconds, and NYHA class II to IIII heart failure symptoms, and it may be a reasonable therapeutic strategy if the QRS interval is in the 120- to 149-millisecond range.[260,264–267] After 3 months of goal-directed postoperative medical therapy, patients recovering from CABG with these indications should receive an ICD in addition to cardiac resynchronization therapy, as detailed elsewhere.[260]

Previous MI and LV Dysfunction Recommendations

1. **In the absence of contraindications, β-blockers (bisoprolol, carvedilol, and sustained-release metoprolol succinate) are recommended after CABG to all patients with reduced EF (<40%), especially among patients with heart failure or those with prior MI (*Class I; Level of Evidence A*).**
2. **In the absence of contraindications, ACE inhibitor or ARB therapy (if the patient is ACE inhibitor intolerant) is recommended after CABG to all patients with LV dysfunction (EF <40%) or previous MI (*Class I; Level of Evidence B*).**
3. **In the absence of contraindications, it is reasonable and ACE inhibitor therapy) after CABG for patients with LV dysfunction (EF <35%) who have class NYHA class II to IV heart failure symptoms (*Class IIa; Level of Evidence B*).**
4. **Among patients with LV dysfunction (EF <35%), ICD therapy is not recommended for the prevention of sudden cardiac death after CABG until 3 months of postoperative goal-directed medical therapy has been provided and persistent LV dysfunction has been confirmed (*Class III; Level of Evidence A*).**

Diabetes Mellitus

The effects of diabetes mellitus and the metabolic syndrome on the development and progression of cardiovascular disease are well established. Indeed, diabetes mellitus is associated with increased mortality and morbidity after cardiac surgery in general and CABG specifically.[268] Diabetes mellitus is classified as type 1 if it results from β-cell destruction or as type 2 if it results from a progressive insulin secretory defect and insulin resistance, but other causes of diabetes mellitus exist, including genetic defects in insulin secretion, drug-induced diabetes mellitus, and gestational diabetes mellitus.[269] Traditionally, the diagnosis of diabetes mellitus has been based on a fasting plasma glucose >126 mg/dL, a 2-hour plasma glucose >200 mg/dL after oral administration of 75 g glucose, or a random plasma glucose of >200 mg/dL in a patient with the classic symptoms of diabetes mellitus.[270] In 2009, however, an International Expert Committee recommended the use of the hemoglobin A_{1c} (HbA_{1c}) test be added, with a threshold >6.5% as a diagnostic criterion for diabetes mellitus.[271]

Because it is not always known whether a patient has diabetes mellitus or glucose intolerance before surgery, it is reasonable for all patients undergoing CABG to have preoperative fasting plasma glucose and HbA_{1c} measurements. This may facilitate optimal diabetes mellitus management in the perioperative and postoperative periods. As detailed elsewhere,[272] the perioperative control of serum glucose (glucose goal, 125–200 mg/dL) has been shown to improve both short-term[273] and long-term[274] outcomes after CABG in most studies. However, an overly aggressive lowering of serum glucose during and after CABG surgery (glucose goal, 90–120 mg/dL) may fail to improve clinical outcomes, mainly because of the adverse effects of hypoglycemic episodes, compared with more moderate glycemic control (glucose goal, 120–180 mg/dL).[275,276] In a large observational study involving >4500 CABG patients, Bhamidipati et al[277] noted that mortality and complication rates were lowest among diabetic patients who received moderate glycemic control with glucose levels of 127 to 179 mg/dL compared with those who were treated with tight (≤126 mg/dL) or liberal (≥ 180 mg/dL) insulin protocols.

Patients with diabetes mellitus have less favorable long-term outcomes after CABG compared with nondiabetic patients.[278] However, it is not well understood whether the diminished long-term survival and freedom from adverse cardiovascular events are attributable to a general progression of cardiovascular disease seen in diabetic patients or if CABG patients with poorly controlled diabetes mellitus have specific characteris-

These factors may include decreased early graft patency, a more rapid progression of native vessel atherosclerosis, and a reduction in myocardial function. Vein graft patency has been reported in some studies to be diminished in patients with diabetes mellitus and the metabolic syndrome.[279] This may relate to the association between type 2 diabetes mellitus and impaired endothelial function and intimal degeneration of saphenous vein grafts, changes that inversely correlate with the metabolic control of the diabetes mellitus.[280] Interestingly, diabetes mellitus has much less effect on the properties of the internal mammary artery.

In a long-term patency evaluation of 501 CABG patients, Lytle et al[281] noted that insulin-dependent diabetes mellitus was associated with late vein graft failure ($P<0.004$). Nevertheless, the adverse effects of diabetes mellitus on graft patency have not been seen in all studies. For example, in a 10-year follow-up of the VA Cooperative Study involving 1074 CABG patients, Goldman et al[282] did not find diabetes mellitus to be an independent predictor of vein graft failure. Most recently, in a long-term observational study evaluating risk factors for adverse outcomes after CABG, Sabik et al[164] reported that diabetes mellitus was a strong risk factor for coronary reintervention (either percutaneous coronary intervention or redo CABG) in the years after CABG. Patients treated with insulin or oral medications had a similarly elevated risk of undergoing reintervention ($P<0.0001$), whereas patients with diet-controlled diabetes mellitus also had an increased risk of reintervention, but lower than the risk in those treated pharmacologically ($P=0.005$). Whether the degree of glucose control independently predicts vein graft patency remains unclear.[283] This uncertainty likely relates to the difficulty in separating the effects of glucose control from the progression of cardiovascular disease in general but may also be complicated by the challenges and inaccuracy of graft patency assessment, small study sample sizes, and separation of the effects of associated conditions such as hyperlipidemia and hypertension.

Patients having undergone surgical revascularization are at increased risk for further progression of CAD. Because there is no reason to surmise that CABG patients have any inherent protection from the effects of poorly controlled diabetes mellitus and because well-controlled blood sugar markedly improves survival in patients with cardiovascular disease,[269] long-term glucose control should ideally be optimized for all CABG patients. Tight control of blood glucose is in a patient's best interest because cardiovascular disease is the most prevalent cause of morbidity and mortality in the diabetic population.

In terms of glucose management, CABG patients with diabetes mellitus should receive coordinated medical care from a diabetes mellitus monitoring team. Such teams may include internists and endocrinologists, dieticians, pharmacists, and in certain cases, mental health professionals. Plasma glucose and HbA_{1c} levels should be followed up regularly, with appropriate adjustments made in insulin and oral hypoglycemic therapies. Lowering the HbA_{1c} to 7% is a reasonable goal for most patients because this has been shown to reduce microvascular diabetic complications and, if initiated early, may also be associated with a reduction in macrovascular disease.[269] A stringent HbA_{1c} goal such as ≤6.5% may be beneficial if treatment is not associated with hypoglycemic episodes, but it may be more reasonable to consider a less stringent goal of 8% for elderly patients and others who are prone to hypoglycemia.[269]

Unlike microvascular disease such as retinopathy, the progression of macrovascular disease such as CAD does not always correlate with the intensity of glucose control. However, in the Diabetes Control and Complications Trial, intensive glucose control (target HbA_{1c}, 6%) in type 1 diabetic patients was associated with a lower risk of cardiovascular disease. Patients who were randomized to intensive glucose control after 9 years of follow-up had a 57% reduction in the risk of nonfatal MI, stroke, or cardiovascular death compared with patients in the standard arm.[284] For patients with type 2 diabetes mellitus, evidence also exists that a more intensive control of plasma glucose may reduce macrovascular cardiovascular disease. In the UK Prospective Diabetes Study, a 16% reduction in fatal and nonfatal MI and sudden death was noted with intensive glucose control (target fasting plasma glucose <6 mmol/L), although this failed to reach statistical significance ($P=0.052$).[285,286] Nevertheless, consistent benefits have not always been observed for patients with type 2 diabetes mellitus, with several other trials finding no added benefit of intensive glucose control over standard control on the risk of adverse cardiovascular events, even among patients with baseline cardiovascular disease at the time of trial recruitment.[287]

It must be recognized that none of the aforementioned studies specifically enrolled diabetic patients who had undergone CABG. Regardless, although these study findings are extrapolated from non-CABG patients to the CABG population, a moderate control of plasma glucose with a goal HbA_{1c} of 7% would seem appropriate for most diabetic patients after CABG. In addition to optimal plasma glucose management, it cannot be overstated that all patients recovering from CABG, and especially those with diabetes mellitus, should be counseled to optimize their weight and diet, to quit smoking, and to institute behaviors associated with improved cardiovascular health.

Diabetes Mellitus Recommendations

1. **Striving to achieve an HbA_{1c} of 7% is a reasonable goal for most patients after CABG to reduce microvascular diabetic complications and macrovascular cardiovascular disease (*Class IIa; Level of Evidence B*).**

Smoking Cessation

According to the World Health Organization, ≈100 million deaths resulted from tobacco use in the 20th century, and it has been estimated that 1 billion more deaths may occur in the 21st century.[288] Compared with those who have never smoked tobacco, smokers lose on average ≈1 decade of life expectancy.[289] This mortality risk can be lowered through smoking cessation, and if smoking cessation occurs before the age of 40, the reduction in risk associated with smoking is ≈90%.[289] The risk of cardiovascular disease associated with cigarette smoke exposure increases in a dose-response fashion, with the greatest increase in risk occurring in individuals who have no cigarette exposure compared with those who have low levels of exposure, including secondhand smoke.[1] At the time of the

first report of the Surgeon General's Advisory Committee in 1964, smoking rates in the United States approached 45%. Although significant progress has been made since then, tobacco use remains a leading modifiable cause of death in the United States, with 21.3% of adult men and 16.7% of adult women still engaging in cigarette smoking.[1]

In patients who have had CABG, smoking can adversely affect both short- and long-term clinical outcomes. Early after surgery, smokers have an increased rate of atelectasis and pneumonia and an increased requirement for mechanical ventilation and intensive care support.[290,291] In addition to an increased risk of pulmonary complications, smoking is associated with an increased risk of deep sternal wound infections in adults who undergo cardiac surgery.[292] Smokers have a higher prevalence of myocardial ischemia[293] and require repeat coronary revascularization procedures more frequently.[294,295] Specifically, smoking is associated with a higher rate of saphenous vein graft disease.[165,296]

Interestingly, despite the higher rates of morbidity in smokers, early mortality rates are not significantly different in smokers compared with nonsmokers. On the other hand, significant differences have been observed in long-term mortality rates.[293–295,297] On the basis of 30-year follow-up data, self-reported smoking cessation after CABG was associated with a life expectancy gain of 3 years, and smoking cessation had a greater effect on reducing the risk of mortality than any other intervention or treatment.[295]

Although smoking cessation should be addressed in all clinical encounters,[298] the postoperative period after CABG may be a particularly effective time to use smoking cessation strategies. Smokers undergoing CABG are hospitalized and therefore subject to the smoke-free policies of medical institutions, and they are also free of the usual cues to smoke. The conditions precipitating the need for CABG and the surgery itself may also reinforce the smoker's perceived vulnerability to the harms of tobacco use, motivating the patient to engage in an attempt at smoking cessation.[299] In a Scandinavian cohort of patients undergoing cardiac surgery, approximately one half of current smokers gave up smoking after surgery. These changes in smoking behavior were most likely to occur during the first 6 postoperative months.[300] As a result, CABG can serve as a teachable moment during which smoking cessation strategies may be highly effective.

Smoking cessation strategies should begin with a full assessment of tobacco use and exposure. For instance, a clinician should determine the duration of smoking, the number of cigarettes smoked daily, and the amount of time that passes between the patient waking up and having his or her first morning cigarette. Every smoker should be asked if he or she is interested in quitting smoking. If motivated to quit, smokers should have access to appropriate resources to assist in smoking cessation. For smokers who are not ready to quit, the clinician should assess the patient's perspective of the impact of smoking on his or her health. Education should then be provided to ensure that the patient has a full understanding of the adverse effects of continued smoking (including the effects of secondhand smoke on others) and the expected benefits associated with quitting. In addition, the clinician can use interviewing techniques to facilitate and engage intrinsic motivation within the patient to facilitate smoking cessation.

Patients who are interested in quitting smoking should be offered behavioral approaches to tobacco cessation.[301] Behavioral approaches to smoking cessation can be provided in a variety of formats, including direct patient-clinician encounters, telephone calls, computer programs, text messaging, or group-based sessions. A meta-analysis of 25 randomized trials found that intensive counseling, which consisted of at least 1 contact during the hospital stay with continued support for at least 1 month after discharge, increased the likelihood of smoking cessation.[302]

A point of emphasis in behavioral approaches to smoking cessation is having the patient set a "quit day." A follow-up encounter, either in person or on the telephone scheduled soon after the patient's quit day, can strengthen the significance of the quit day and provide greater motivation for the patient to quit. In a systematic review of 10 randomized trials, no difference was observed in abstinence rates between those who reduced smoking before the quit date and those who quit abruptly.[303] Thus, patients should be given the choice to reduce smoking before a quit date or to stop smoking abruptly on the quit date.

In combination with counseling, nicotine replacement therapy can be an important adjunctive strategy to help achieve smoking cessation. In a randomized trial of 5887 smokers, long-term rates of smoking and mortality were reduced with the application of a 10-week smoking cessation program that included a strong physician message, nicotine gum, and 12 group sessions using behavior modification.[304] On the basis of a systematic review of the literature in 2008, the US Public Health Service advocated the use of 5 nicotine replacement medications (gum, patch, nasal spray, inhaler, and lozenge) and reported that the combination of a long-term nicotine patch and ad lib nicotine spray or gum produced significantly higher long-term abstinence rates than did the nicotine patch by itself.[305] Compared with nicotine replacement medications, electronic cigarettes (e-cigarettes) have not been demonstrated to improve smoking cessation rates, and important concern has been raised about their potential for adverse health effects.[306]

Nicotine replacement therapy has been shown to be safe for patients with stable CAD. In a randomized, double-blind, placebo-controlled trial, a 10-week outpatient course of transdermal nicotine did not increase the rate of cardiovascular events among patients with at least 1 diagnosis of cardiovascular disease.[307] In hospitalized patients, nicotine replacement therapy is commonly used as an effective strategy to manage nicotine withdrawal symptoms,[299] but less is known about the routine use of nicotine replacement therapy during an acute cardiovascular event. In a retrospective analysis of smokers admitted with acute coronary syndromes, transdermal nicotine therapy was not associated with an increased risk of mortality.[308] On the other hand, in a retrospective analysis of smokers hospitalized during CABG, nicotine replacement therapy was associated with an increased mortality rate after adjustment for baseline characteristics.[309] Both of these studies were limited by their observational design and specifically by the biases associated with the use of nicotine replacement therapy such as the degree of prior smoking. As a result, prospective studies

are needed to determine the safety of using nicotine replacement therapy in patients with acute cardiovascular disease. At this time, judicious use and dosing of nicotine replacement therapy are recommended for patients admitted to hospital with an acute cardiovascular event.

In addition to nicotine replacement medications, bupropion and varenicline can be effective adjuncts to smoking cessation strategies, and their use has been supported by the US Public Health Service.[305] Bupropion is generally well tolerated and has been shown to be safe to use in the immediate period after MI.[310,311] Among 629 patients with cardiovascular disease, a 7-week treatment with bupropion resulted in twice as many smokers quitting at 1 year compared with placebo.[312] Varenicline has also been shown to be effective in reducing rates of smoking.[313,314] In a randomized, placebo-controlled trial of 714 smokers with stable cardiovascular disease, varenicline was effective at reducing rates of smoking.[315] Based on data from this trial, however, the US Food and Drug Administration issued an advisory that varenicline may increase the risk of adverse cardiovascular events on the basis of statistically nonsignificant increases in the rates of nonfatal MI, coronary revascularization, and new peripheral vascular disease in this trial population.[315] Although the cardiovascular risk profile of varenicline remains unsettled, the long-term benefits of smoking cessation far outweigh any potential adverse effects with varenicline. Therefore, it should still be carefully considered as a possible medication to assist in smoking cessation for patients with cardiovascular disease.

During the process of smoking cessation, patients may face many potential obstacles to achieving their goal. They may struggle with high dependence on nicotine, severe withdrawal problems, low self-confidence, poor social support, weight gain, comorbid psychiatric illnesses, and suboptimal use of medications.[316] Addressing each of these issues as they arise is critical to achieving smoking cessation. In addition, critical evaluation of the helpful and unhelpful aspects of prior attempts at smoking cessation can guide the development of revised and more effective treatment plans. Even among those smokers who have initial success, it is important to remain focused on these issues because most smokers try quitting several times before they finally achieve durable success.[316] Ultimately, successful smoking cessation strategies require a long-term disease management approach to achieve permanent abstinence.

Smoking Cessation Recommendations

1. **Smoking cessation is critical, and counseling should be offered to all patients who smoke, during and after hospitalization for CABG, to help improve both short- and long-term clinical outcomes after surgery (*Class I; Level of Evidence A*).**
2. **It is reasonable to offer nicotine replacement therapy, bupropion, and varenicline as adjuncts to smoking cessation counseling for stable CABG patients after hospital discharge (*Class IIa; Level of Evidence B*).**
3. **Nicotine replacement therapy, bupropion, and varenicline may be considered as adjuncts to smoking cessation counseling during CABG hospitalization, but their use should be carefully considered on an individualized basis (*Class IIb; Level of Evidence B*).**

Cardiac Rehabilitation

Outpatient CR is a medically supervised, exercise-based program that is designed for patients with recent cardiovascular events to optimize overall health status and to minimize the risks for future adverse outcomes.[317–325] In a meta-analysis of 48 trials involving CAD patients, CR was associated with a 26% risk reduction in the rate of cardiovascular mortality and a 20% risk reduction in overall mortality.[321] Moreover, a strong, inverse dose-response relationship has been observed between the number of CR sessions attended and long-terms rates of MI and death.[326] On the basis of this compelling evidence, CR has been strongly recommended for patients with several different cardiovascular diseases,[327] including those recovering from recent CABG.[3,317] The benefits of CR such as improved survival have been reported for all types of CAD patients, including younger and older patients, as well as men and women, independently of the nature of CAD diagnosis, the form of CR, and the dose of exercise intervention.[317–325]

The very first CR programs were launched in the 1960s, at a time when patients with cardiovascular disease were warned against exercising.[328] These initial CR programs, implemented for post-MI patients recovering in hospital, consisted of graded exercise programs. After a demonstration of their safety and success, these programs were later expanded into the outpatient setting.[328] Over the years, CR programs have continued to adapt and to address the broad range of factors affecting cardiovascular outcomes, which has allowed them to evolve from purely supervised exercise programs to comprehensive secondary prevention programs.

The core components of contemporary CR 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.[329] As a result of the broad effects of exercise training and the multiple components of these programs, CR has been shown to improve a wide range of health factors. Significant improvements have been demonstrated in CAD risk factors, functional capacity, vascular conditioning, and psychosocial well-being, all of which likely contribute to the robust effects of CR on overall clinical outcomes.[329]

Among Medicare beneficiaries who have undergone CABG, patients are covered for up to 36 sessions of CR over the course of 1 year after the incident surgical hospitalization; other medical payers offer similar coverage plans. Despite the wealth of evidence and the presence of insurance coverage, CR use patterns remain poor nationwide.[329–333] In an analysis of Medicare claims data, only 31% of CABG patients received at least 1 session of CR, and there was considerable geographic heterogeneity in CR use patterns.[333]

One of the key barriers to CR use is the process of referral to CR.[327] Even among hospitals using the AHA Get With The Guidelines program, only 56% of eligible patients were referred to CR.[332] Clearly, improving referral patterns to CR programs is a key area in need of greater focus.[331] Recognizing

the importance of CR and the poor referral patterns to CR, the AHA and ACC, in collaboration with the American Association of Cardiac and Pulmonary Rehabilitation, have released performance measures for CR referral.[327]

Although CR referral rates are currently low, newly developed referral strategies hold great promise to overcome this barrier.[334–336] In a randomized trial of 2635 patients with CAD admitted to 11 different hospitals, a referral process that consisted of a combination of CR liaisons and an automated referral system resulted in 85.8% of patients being referred to CR and 73.5% being enrolled in CR compared with 32.2% and 29.0%, respectively, in the control group.[337] In addition, strategies such as educational interventions[335] and early appointments and start dates[338–340] have been shown to improve CR referral and use patterns. However, as new referral strategies become adopted into clinical practice, it will be important for clinicians to remain active in the referral process because physician advocacy remains a strong factor in determining whether patients will enroll in CR programs.[341]

Beyond the challenges in the referral process, many patient and health system factors negatively affect CR use patterns. Referral to CR is particularly low among specific populations such as patients of low socioeconomic status, women, older adults, and ethnic minorities.[323] In addition, CR program locations and hours of operation prohibit the use of this service by some patients, and CR programs may not even be available in some rural or medically underserved areas. Finally, the financial costs, related to copays, transportation, and time off from work, over the course of an entire CR program dissuade some patients from using this service.

To address all these barriers to CR use, multiple strategies will need to be undertaken. First, greater attention will need to be paid in the referral process to identify and address an individual's unique barriers to CR use. This will require greater communication with patients and better coordination between the referring center (hospitals or office-based practices) and CR programs. Second, healthcare reform efforts will need to provide further incentives to patients and healthcare systems to use CR programs. Third, new paradigms for delivering comprehensive CR programs such as home-based CR programs will need to be further developed. Although these challenges are daunting, they are of central importance to improving clinical outcomes after CABG.

CR Recommendations

1. **CR is recommended for all patients after CABG, with the referral ideally performed early postoperatively during the surgical hospital stay (*Class I; Level of Evidence A*).**

Self-Management of Cardiovascular Disease

After CABG, CR programs help patients develop self-management skills to facilitate lifestyle and behavior modification. Self-management is the process by which patients assume control of their health-related behaviors.[342] Ultimately, patients decide what they will eat, if they will exercise, and what medication they will take. As healthcare experiences a paradigm shift from physician-centered to patient-centered care, CR programs play an integral role in education and transitioning patients to adopt health-related behaviors.[342] CR personnel can act as health coaches, providing self-management support, collaborating with patients to establish goals, and developing problem-solving skills to foster risk factor modification. Successful CR programs stimulate patients to acquire the knowledge, skills, and confidence necessary to alter health-related behavior.[342–346]

The Reduction of Atherothrombosis for Continued Health (REACH) international registry reported that among patients who have undergone CABG, when secondary prevention goals are not met at 1 year, the incidence of adverse cardiovascular events increases, regardless of the number of risk factors present at baseline. This highlights the importance of CR programs to help patients achieve their goals and to improve long-term outcomes.[212] Multiple barriers exist to the adoption of preventive therapies, including knowledge deficit, ambivalence, comorbidities, preconceived beliefs, lack of support, employment, and readiness for change.[347–349] For example, older patients with comorbidities who live alone are more likely after 1 year to remain sedentary and to have poor medication and diet compliance.[350]

Interventions for self-management of risk factors should be individualized to meet specific sex concerns. Women in particular have difficulty with self-management of heart disease because of fatigue, anxiety, and depression, as well as feelings of guilt that home and family responsibilities are being neglected.[347,351,352] Adherence to physical activity remains a challenging issue; 35% of women are no longer exercising 3 months after discharge from CR.[353] In contrast, men experience different barriers to secondary prevention compared with women. Some of the obstacles to compliance among men include comprehension of disease, dietary barriers (dependence on others for meals), and activity barriers (such as employment superseding CR).[354]

Participation in a hospital-based outpatient CR program compared with a home-based program helps improve exercise adherence for both men and women, increases knowledge about the condition for men, and improves stress control for women.[354] Continuation of the secondary prevention education after discharge from CR can improve adherence to long-term self-management. Secondary prevention programs should be individualized, considering the patient's knowledge deficit. Self-efficacy and self-management skills can be developed by incorporating education and counseling techniques in either individualized or group sessions and focusing on motivational strategies.[355–357] Applying technology through the use of the Internet and mobile phones can help provide education and trained peer support for CABG patients after surgery, even for those who are unable to access CR programs because of geographic barriers.[358,359] Finally, individual diaries have been shown to increase patient accountability for self-management of exercise activity after CR.[360] Self-efficacy, along with an individualized plan for behavior change, is imperative to help optimize adherence to secondary prevention after CABG.

Mental Health and Cognitive Impairment

The negative impact of mental illness and cognitive impairment after CABG is well recognized, leading to greater risk of

morbidity and mortality in the perioperative period and poor adherence to secondary preventative therapies in the long term. Screening for and preventing these neuropsychological conditions from developing may therefore improve outcomes after CABG. Depression is the most carefully studied mood disorder, having been reported in up to 33% of patients 1 year after CABG.[361] Depression is an important risk factor for the progression of CAD, and it is a more important predictor of CR success than many other variables.[362] Both the presence of depressive symptoms before CABG and the worsening of these symptoms after surgery correlate with poorer physical and psychosocial functioning and poorer quality of life after surgery.[363] Moreover, depression before or after surgery increases the risk of postoperative mortality and other adverse events such as heart failure hospitalization, MI, cardiac arrest, and the need for repeat revascularization.[364,365] Finally, depression after CABG is an important predictor for the recurrence of angina in the postoperative period.[365]

Interventions to help treat depression after CABG have been shown to be beneficial by improving depressive symptoms through cognitive behavioral therapy, telephone-delivered collaborative care, and supportive stress management.[366,367] Participating in a CR program is another method that can help reduce postoperative depressive symptoms.[368] In a randomized, controlled trial, phone calls by nurses to patients after CABG improved depressive mood symptoms in the months after surgery.[367] Although interventions are frequently initiated postoperatively, cognitive behavioral therapy for preoperative depression and anxiety has also been shown to improve depressive symptoms and to reduce the length of stay in hospital, justifying screening for depression even before the operation.[369] Recently, a trial examining the efficacy of treating depression before surgery randomized 361 patients to escitalopram 10 mg daily or placebo starting 2 to 3 weeks before elective CABG. Although the therapy had no effect on morbidity and mortality after CABG, depressed patients treated with escitalopram had a better quality of life and less pain after surgery.[370] Therefore, treating depression before CABG can lead to improved psychological outcomes after surgery.

Alteration of cognitive function has been reported in up to 30% of patients after CABG.[371–374] The exact frequency depends on the timing of the postoperative assessment and the criteria used to measure cognitive decline.[375,376] Studies with appropriate comparison groups (including nonsurgical and healthy control subjects) have demonstrated that most patients do not suffer cognitive decline as a result of CABG.[377,378] For those who do, the postoperative cognitive changes are usually mild and generally resolve within 3 months of surgery.[379] Long-term cognitive decline after CABG has been reported,[380,381] but studies have shown that similar late cognitive decline occurs even among patients with CAD who do not undergo surgery, supporting that the decline is not related to the operation or the use of cardiopulmonary bypass.[382] Cognitive changes have also been reported after general anesthesia for noncardiac surgery.[383–385]

Several risk factors for short-term postoperative cognitive decline have been identified, including preoperative factors for cerebrovascular disease, central nervous system disease, and preexisting cognitive impairment.[371,386,387] It had previously been suggested that cognitive decline might be less frequent after off-pump CABG compared with on-pump surgery.[388] As summarized in a meta-analysis, however, taken collectively, most studies failed to show a benefit of off-pump CABG surgery.[389] In particular, large, robust, randomized, clinical trials comparing late cognitive outcomes after on-pump and off-pump CABG surgery reported no difference.[390,391] Current findings therefore do not support a recommendation for off-pump surgery as an approach to prevent cognitive decline.

Mental Health and Cognitive Decline Recommendations

1. **For patients after CABG, it is reasonable to screen for depression in collaboration with a primary care physician and a mental health specialist (*Class IIa; Level of Evidence B*).**
2. **Cognitive behavior therapy or collaborative care for patients with clinical depression after CABG can be beneficial to reduce depression (*Class IIa; Level of Evidence B*).**

Obesity and Metabolic Syndrome

Obesity is a major risk factor for cardiovascular disease. Many epidemiological studies have shown a clear association between obesity and CAD.[392] The association is mediated mostly through the effect of obesity-related cardiovascular risk factors such as hypertension, dyslipidemia, or diabetes mellitus but also through a direct atherogenic effect by increased circulation of free fatty acids, by adrenergic stimulation, and through the effect of adipose tissue–related hormones. Biologically, obesity is defined as increased body fat, but for simplicity purposes, the World Health Organization defines obesity on the basis of body weight in relation to height. The most widely accepted method to diagnose obesity is the body mass index (BMI), calculated by dividing the weight in kilograms by the height in meters squared. Recent studies have challenged the accuracy of BMI in detecting body adiposity, particularly in patients with established CAD.[393,394] This new evidence suggests that the assessment of adiposity needs to go beyond total body adiposity and the measurement of BMI.[395,396] With a focus on the distribution of adipose tissue, central obesity and greater amounts of visceral fat convey the highest mortality risk in patients with CAD.[395] The assessment of body fat distribution can be performed in a simple manner by measuring the waist and hip circumference to calculate the waist-to-hip ratio.

The metabolic syndrome is defined as the coexistence of several interrelated conditions, including central obesity, hyperglycemia, elevated systemic BP, hypertriglyceridemia, and decreased HDL. The presence of ≥3 of these abnormalities establishes the diagnosis of metabolic syndrome based on the Adult Treatment Panel III consensus.[397] The metabolic syndrome has been associated with numerous pathophysiological mechanisms that can lead to cardiovascular disease, including insulin resistance, increased oxidative stress, endothelial dysfunction, and atherogenic lipid patterns. The presence of metabolic syndrome increases the risk for cardiovascular events

from 2- to 4-fold independently of the presence of diabetes mellitus. As a well-established cardiovascular risk factor, the metabolic syndrome is common among patients undergoing CABG, with some studies reporting the prevalence as high as 50%.[398]

The metabolic syndrome has been associated with increased in-hospital mortality in subjects undergoing CABG. In a study of 5304 consecutive CABG patients, those with metabolic syndrome had a 2.7-times higher in-hospital mortality than those without metabolic syndrome, a risk that was independent of the presence of diabetes mellitus.[399] Moreover, patients with metabolic syndrome also have an increased risk for long-term mortality. Angeloni et al[398] noted that all-cause mortality was 50% higher in those patients with metabolic syndrome compared with those without in a long-term follow-up study of 1726 CABG patients. The metabolic syndrome also increased the long-term risk for cardiac arrhythmias, renal failure, and the composite outcome of major adverse cardiovascular events (52.4% versus 39.5%) in this cohort.[398] Patients with the metabolic syndrome are 2.3-times more likely to develop AF after CABG.[400] This increased risk may be mediated by an elevated C-reactive protein level.[401] Patients with metabolic syndrome are also at risk for decreased patency of saphenous vein grafts after CABG.[402]

Given the multiple pathophysiological mechanisms linking obesity and cardiovascular disease, it is logical to expect favorable clinical outcomes after weight loss in patients with CAD. Unfortunately, there is minimal evidence proving any benefit associated with weight loss after CABG. Retrospective, observational studies assessing the association between weight loss and clinical outcomes after CABG have shown paradoxical results, with worse outcomes among patients losing weight after CABG.[403] However, these studies could not differentiate between purposeful and unintentional weight loss. Unintentional weight loss could reflect comorbidities such as heart failure, cancer, and lung diseases or may reflect the severity of other conditions associated with decreased survival. One of the few studies that showed improved outcomes after weight loss in patients with CAD was based in a CR setting, suggesting that purposeful weight loss in CAD patients may be beneficial.[404] Weight loss has an indisputable benefit for BP, diabetes mellitus, and lipid control and improves quality of life and functional capacity. Therefore, despite the limited scientific evidence, it is generally accepted that weight loss should be recommended for overweight or obese patients after CABG.

Long-term, successful weight loss continues to represent a major clinical challenge. Most studies have noted that much of the weight lost in the first 6 months is regained at 1 year. The therapeutic options to achieve successful weight loss are limited because some of the medications that can promote weight loss are contraindicated in patients with CAD. To date, the only weight-loss strategy with effective long-term results is bariatric surgery. Observational studies have shown significant improvements in cardiometabolic parameters, quality of life, and cardiac mechanics following major weight loss after bariatric surgery.[405] Many patients after CABG with a BMI of $\geq$35 kg/m^2 would qualify for bariatric surgery, and this therapeutic modality may be considered for long-lasting weight loss.[406] Bariatric surgery has been shown to be safe in stable patients with CAD who have not had a recent MI.[407]

The cornerstone of the management of metabolic syndrome is lifestyle modification with increased exercise, improved diet, and weight loss. Lifestyle changes can improve all of the metabolic syndrome components. Diets low in carbohydrates can effectively improve hypertriglyceridemia. High protein intake, along with a high consumption of fruits, vegetables, and nonfat dairy products, can improve BP.[408] Commonly, pharmacological treatment is needed for hypertension, diabetes mellitus, and dyslipidemia despite lifestyle changes. For patients with advanced degrees of obesity, bariatric surgery has been shown to significantly reduce the prevalence of metabolic syndrome.[409]

Obesity and Metabolic Syndrome Recommendations

1. **The assessment of central distribution of fat is reasonable in CABG patients by measuring waist and hip circumference and calculating waist-to-hip ratio, even if the BMI is within normal limits (*Class IIa; Level of Evidence C*).**
2. **Bariatric surgery may be considered for CABG patients with a BMI >35 kg/m^2 if lifestyle interventions have already been attempted without meaningful weight loss (*Class IIb; Level of Evidence C*).**

Nutrition

The nutritional status of patients plays an important role in the results after CABG. Approximately 20% of patients have been identified as having poor preoperative nutritional status before undergoing cardiac surgery.[410] Several nutritional screening tools exist, including the Malnutrition Universal Screening Tool. When the Malnutrition Universal Screening Tool score is added to the EuroSCORE in a multivariable model evaluating perioperative risk, the prediction of the model for both postoperative complications and mortality is significantly improved compared with the use of the EuroSCORE alone.[410] Preoperative malnutrition, whether defined on the basis of a nutritional screening tool or serum albumin level, has been shown to predict adverse postoperative events such as reoperation for bleeding, postoperative renal failure, prolonged ventilatory support, vasopressor treatment for >11 days, antibiotic treatment for >21 days, intensive care unit stay, total length of stay, increased inflammatory response, infection, positive blood cultures, and death.[410–412]

It is well established that BMI decreases after major surgery such as CABG. DiMaria-Ghalili[413] assessed 91 patients undergoing CABG and observed a 5% change between the preoperative BMI level and the level measured 4 to 6 weeks after surgery. This finding corresponded to a 13.8% decrease in self-reported physical health during the same time period. At a mean follow-up of 19 months, this same investigator observed that older patients undergoing elective CABG usually did not regain the weight they lost between the preoperative period and after hospital discharge. Furthermore, patients who lost more weight in the postoperative period were more likely to require subsequent hospital readmission.[414]

In an observational study of 100 consecutive patients undergoing cardiac surgery, van Venrooij et al[415] noted that low preoperative protein intake ($\leq$0.98 g·kg^{-1}·d^{-1}) did not result in more complications or a longer hospital stay compared with a high preoperative protein intake (>0.98 g·kg^{-1}·d^{-1}). On the other hand, a high-energy preoperative diet (>22 kcal·kg^{-1}·d^{-1}) resulted in more postoperative complications. Racca and associates[416] evaluated nutrition biomarkers in 50 nondiabetic patients on admission to a rehabilitation facility after cardiac surgery and 16 days later. Patients received a "standard" cardiac diet with controlled caloric support (30 kcal·kg^{-1}·d^{-1}) providing 15% to 20% dietary protein, 30% fat, and 50% to 55% carbohydrates rich in fruits and vegetables. After 16 days on this standard dietary regimen, low plasma albumin levels increased, anemia improved, and markers of inflammation declined.

From the above data, it would appear that controlled, comprehensive dietary intake is effective in restoring the nutritional insults brought about by major surgery such as CABG but that oversupplementation may be detrimental. Although it seems justified to modulate nutritional intake to promote a quicker recovery from CABG, to date, there are no prospective, randomized trials documenting a benefit associated with perioperative nutritional modification.

Vitamins and Supplements

The use of vitamin supplementation is a widespread practice in the general population that amounts to tremendous expenditure. Many benefits have been attributed to the use of vitamin supplements, particularly those touted to have protective effects against cardiovascular disease and stroke. Observational studies have suggested that some vitamin supplements can reduce adverse cardiovascular events. For example, in the prospective Nurses' Health Study of >80 000 participants, women who voluntarily reported taking vitamin C and vitamin E supplements were noted to have a lower risk of developing CAD over more than a decade of follow-up.[417,418]

However, large, randomized, controlled studies of vitamins have not demonstrated such benefits in a variety of general and high-risk populations. The Physicians' Health Study II was a randomized, double-blind, placebo-controlled trial of vitamin C and vitamin E supplementation that enrolled 14 641 US male physicians ≥50 years of age. In this study, neither vitamin C nor vitamin E supplements reduced the risk of major cardiovascular events, even after more than a decade of treatment and follow-up.[419,420] Among 12 064 MI survivors, a placebo-controlled trial demonstrated that supplementation with folic acid and vitamin B_{12} also did not have beneficial effects on cardiovascular outcomes.[421] This was confirmed in a meta-analysis of >37 000 participants that demonstrated that high-dose B vitamins and folic acid are not effective as a secondary prevention measure for cardiovascular disease.[422] Finally, a meta-analysis of 50 randomized, controlled trials with nearly 300 000 participants showed no benefit of vitamin and antioxidant supplementation in reducing the risk of major cardiovascular events, including subgroup meta-analyses examining the effects of individual vitamins.[423]

Undergoing cardiac surgery leads to considerable stress on the body, which plays a key factor in determining outcome. Along with weight loss and protein catabolism, cardiac surgery is often associated with numerous derangements in stored vitamin and other metabolite levels. CABG is accompanied by a significant acute phase and inflammatory response, leading to oxidative stress, free radical production, and antioxidant depletion.[424–426] Louw and coworkers[427] observed that this early acute-phase reaction was associated with decreases in the levels of both vitamin A and vitamin C, which are important antioxidants that aid in wound healing. Interestingly, both vitamin levels returned to normal after surgery without specific therapeutic intervention. Schindler and colleagues[428] studied serial plasma samples before, during, and up to 48 hours after surgery, demonstrating significant decreases in levels of both vitamin A and vitamin E, with persistently low vitamin E levels 48 hours postoperatively. Similarly, in the early perioperative period after CABG, reductions have been noted in levels of homocysteine and folic acid, which are part of the body's antioxidant first line of defense.[429]

Other studies of CABG patients have documented decreases in B complex vitamins such as B_6, B_{12}, and thiamine, which are essential for mitochondrial function.[416,427,430] Vitamin D levels have been shown to be important predictors of outcome after cardiac surgery. In a study of 4418 patients recovering from cardiac surgery, Zittermann et al[431] noted that 38.0% had deficient 25(OH)D values (<30 nmol/L). In multivariable-adjusted models, a low 25(OH)D value was independently associated with a greater risk of major adverse cardiac events, longer duration of mechanical ventilatory support and intensive care unit stay, and higher 6- and 12-month mortality.

Intuitively, from these data, vitamin supplementation should promote a faster recovery from CABG. However, very little is currently known about the value of vitamin supplementation after cardiac surgery, and studies examining the use of vitamin supplementation in CABG patients either with or without specific deficiencies are lacking. Only in the perioperative period as a means of preventing postoperative AF has the role of vitamin supplementation received some attention. Given the suggestion that oxidative stress may potentiate AF, several investigators have evaluated the prophylactic administration of omega-3 fatty acids and antioxidant vitamins to reduce its incidence after CABG. Meta-analyses on this subject have presented conflicting data, suggesting a potential for vitamins and omega-3 fatty acids to reduce the risk of perioperative AF, but the results are inconsistent, with a lack of high-quality data in the literature.[432–434] Therefore, the available evidence to date remains insufficient, and additional large-scale, adequately powered clinical studies are warranted before routine administration of antioxidant vitamins can be recommended for the reduction of AF after CABG.

Vitamins and Supplements Recommendations

1. **Vitamin supplementation in patients with specific vitamin deficiencies may be considered for patients undergoing CABG, but the effectiveness is not well established (*Class IIb; Level of Evidence C*).**
2. **Supplementation with omega-3 fatty acids and antioxidant vitamins may be considered to prevent postoperative AF after CABG, but additional clinical**

studies are warranted before routine use of antioxidant vitamins can be recommended (*Class IIb; Level of Evidence A*).

Vaccination

Influenza is one of the most common, contagious, and morbid respiratory infections, with a seasonal pattern of affliction during winter climate.[435] Among nontraditional risk factors, a growing interest has developed in the evaluation of influenza infection as a potential cause for subsequent cardiovascular events.[436–439] Previous studies have suggested that seasonal influenza-like illnesses may explain the timing of acute thrombotic events in patients with CAD,[438] and several epidemiological studies have identified an inverse relationship between influenza vaccination and the risk of fatal and nonfatal cardiovascular events.[437,440–442] Although the mechanism underlying that risk of influenza is not clear, it may relate to triggering the rupture of a vulnerable atherosclerotic plaque, fluid overload, and heart failure or to the susceptibility of a frail and vulnerable patient.[435]

Randomized, controlled trials have since been performed to explicitly test whether influenza vaccination can reduce the risk of cardiovascular events. In one of the first trials on the subject, Gurfinkel et al[443,444] randomized 200 patients with MI and 101 patients undergoing elective percutaneous coronary intervention to either multivalent influenza vaccine or placebo. At 1 year of follow-up, the risk of MI and cardiovascular death was significantly lower among patients who received the vaccine. These results were subsequently confirmed in other inpatient and outpatient CAD populations.[445,446] In a randomized trial of 439 patients admitted with acute coronary syndrome, influenza vaccine significantly lowered the composite end point of death or hospitalization for CAD, heart failure, or stroke (vaccine versus placebo, 9.5% versus 19.3%; P=0.004).[446] Most recently, a meta-analysis of 6 randomized trials involving 6735 patients at high risk for cardiovascular disease demonstrated that influenza vaccine significantly lowered the risk of cardiovascular events (RR, 0.64; 95% CI, 0.48–0.86; P=0.003), with the greatest treatment benefit seen among the highest-risk patients with more active CAD.[435] These findings provide support for the current recommendations for influenza vaccination of all patients admitted with acute coronary syndrome.[2,447] Within the general population, the Centers for Disease Control and Prevention currently recommends routine annual influenza vaccination for all people >6 months of age unless specific contraindications are present.[448]

For patients undergoing CABG, there is justification based on the evidence in the cardiology literature to provide influenza vaccination for those in whom no contraindication exists. Hospitalization for cardiac surgery provides an opportunity to vaccinate those people who are not immunized and to potentially lower the risk of subsequent adverse cardiovascular events. However, no studies exist regarding the safety or effectiveness of influenza vaccination in reducing perioperative morbidity or mortality after CABG. Furthermore, perioperative immunological alterations may reduce a patient's ability to respond to and to develop immunity after a vaccination.[449,450] Thus, the optimal timing of perioperative influenza vaccination in patients undergoing cardiac surgery remains unclear. Whether patients should receive the influenza vaccine preoperatively or in the days or weeks after CABG should be the subject of future research.

Vaccination Recommendations

1. **Annual influenza vaccination should be offered to all CABG patients, unless contraindications exist (*Class I; Level of Evidence B*).**

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*Modest.

†Significant.

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*Modest.

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KEY WORDS: AHA Scientific Statements □ coronary artery bypass grafting □ prevention and control □ risk-reduction behavior