Perioperative Coronary Artery Bypass Grafting

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LEARNING OBJECTIVES

1. Develop a patient-specific therapeutic plan for antithrombotic therapy before coronary artery bypass grafting surgery
2. Evaluate critical medications for initiation or discontinuation before coronary artery bypass grafting surgery
3. Justify the importance of glycemic control during and immediately after coronary artery bypass grafting surgery
4. Develop a patient-specific therapeutic plan for rectifying hemodynamic instability after coronary artery bypass grafting surgery
5. Design a pharmacotherapy plan for the secondary prevention of ischemic events after coronary artery bypass grafting surgery

ABBREVIATIONS IN THIS CHAPTER

ACS	Acute coronary syndrome
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CPB	Cardiopulmonary bypass
DAPT	Dual antiplatelet therapy
DOAC	Direct oral anticoagulants
HFrEF	Heart failure with reduced ejection fraction
INR	International normalized ratio
LMCA	Left main coronary artery
MI	Myocardial infarction
OPCAB	Off-pump coronary artery bypass
PCI	Percutaneous coronary intervention
POAF	Postoperative atrial fibrillation
SCAD	Stable coronary artery disease
STS	Society of Thoracic Surgeons
SVG	Saphenous vein graft

Table of other common abbreviations.

INTRODUCTION

Coronary artery disease (CAD) is a major cause of morbidity and mortality across the world. The goals of treatment in of patients with CAD are to alleviate ischemic symptoms, delay or prevent the progression of coronary atherosclerosis, and reduce the risk of death, heart failure, or myocardial infarction (MI). As CAD progresses to the point where medical therapy can no longer achieve the goals of treatment, myocardial revascularization becomes a critical next step to improve patient outcomes. Surgical revascularization by means of coronary artery bypass grafting (CABG) is an important strategy considered to improve morbidity and mortality in patients with complex CAD. Since the introduction of CABG in the 1960s, operative morbidity and mortality continue to improve based on advancements in patient selection, surgical techniques, and perioperative care.

Procedural Characteristics

Standard surgical revascularization through CABG is performed by way of a median sternotomy on an arrested heart while the patient is supported on cardiopulmonary bypass (CPB). Sternotomy provides optimal exposure of the ascending aorta and the epicardial coronary arteries for performance of the surgery. The heart is commonly arrested with a cold, potassium-rich cardioplegia solution to provide myocardial preservation and maintain cardiac standstill for the precision necessary to anastomose the conduits to the coronary artery. While the heart is in arrest, a CPB machine maintains systemic perfusion and oxygenation for the patient until revascularization is complete. Epicardial coronary arteries with clinically significant proximal stenoses and patent distal vessels are considered potentially suitable for grafting. Autologous peripheral arteries or veins are

used as grafts to bypass the obstruction within the coronary arteries. CABG surgery usually takes 3–4 hours and has an average length of hospital stay of 5–7 days.

Coronary artery bypass surgery has evolved to include alternative approaches—most notably, off-pump coronary artery bypass (OPCAB) and minimally invasive direct CABG

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2011;124:e652-735.
- 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2014;64:1929-49.
- Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association. Circulation 2015;131:927-64.
- 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg 2018;53:5-33.
- 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2019;55:4-90.

(MIDCAB). The off-pump approach to CABG executes the procedure on a beating heart without the need for CPB. The surgery is technically more demanding because of the movement of the beating heart. In theory, OPCAB may reduce some of the risks associated with the heart–lung machine, including manipulation of the aorta, leading to stroke, postoperative systemic inflammatory reaction syndrome, and platelet activation. Unfortunately, that has yet to translate into improved patient outcomes and is routinely considered only for high-risk patients with contraindications to CPB at centers with the experience and expertise to minimize graft failure. Minimally invasive direct CABG is a CABG procedure performed without a median sternotomy or cardiopulmonary bypass. The MIDCAB approach harvests the left internal mammary artery by direct vision or with robotic endoscopic techniques through a small, left-anterior thoracotomy to bypass the left-anterior descending (LAD) artery. Avoiding full sternotomy may improve recovery time and the cosmetic result of the surgery but has not been shown to decrease infection rates despite being less invasive (Ng 2000). There is a paucity of high-quality evidence demonstrating the superiority of MIDCAB to a median sternotomy with regard to outcomes of death, stroke, myocardial infarction, or repeat revascularization. The approach cannot provide a multivessel bypass beyond the LAD.

Indications for CABG and Outcomes

The decision to pursue coronary revascularization with CABG over percutaneous coronary intervention (PCI) or medical management is complex and multifactorial. Candidacy for CABG is determined primarily by the anatomical complexity of the CAD, by the presence of concomitant diseases that increase the benefit of surgical revascularization, and by the need for other cardiac surgical interventions. Other considerations include the ability to achieve complete revascularization and the suitability of the coronary vasculature distal to stenosis for conduit anastomoses. Those indications are weighed against the predicted risks of periprocedural complications and surgical mortality in order to assess whether CABG remains superior to alternative management strategies such as PCI or medical management.

Stable Coronary Artery Disease

The primary indications for CABG in patients with stable coronary artery disease (SCAD) are to relieve ischemic symptoms resistant to pharmacotherapy and to improve short- and long-term prognoses. As the level of complexity and the burden of CAD increase, the benefit of CABG over PCI or medical therapy becomes more prominent. A meta-analysis of 100 trials of patients with left main coronary artery (LMCA) or three-vessel disease found revascularization with CABG reduced the risk of acute MI and improved survival compared with medical management (Windecker 2014). Compared with PCI, CABG reduced the risk of death, MI, and stroke in patients with

multivessel CAD with intermediate-to-high anatomical complexity and outcomes similar to patients with low anatomical complexity (Mohr 2013). High-risk anatomical locations of stenosis include the left main coronary artery and the proximal LAD, as well as in three-vessel disease. Patients are further risk stratified by the complexity of the lesions by applying the SYNTAX Score II, an angiographic grading tool that stratifies patients with left main or three-vessel disease into low (0–22), intermediate (23–32), or high (≥33) anatomical complexity by using lesion characteristics and location (Sianos 2005). Patients with comorbidities such as diabetes mellitus or left ventricular ejection fraction of less than 35% derive particular benefit with CABG over PCI (BARI 2D Study Group 2009, Velazquez 2011, BARI 2D Study Group 2009). It is hypothesized that the mortality benefit of CABG over PCI for patients with high-risk CAD is related to surgical collateralization or the bypassing of the CAD-prone proximal segments of multiple vessels (Doenst 2019). Although PCI addresses existing stenotic lesions, CABG circumvents the entire portion of the coronary artery where the vast majority of future acute MIs could occur.

Acute Coronary Syndrome

The evidence in favor of CABG over medical therapy or PCI is almost entirely from patient populations with SCAD. Guidelines recommend applying the definitions for complex SCAD to patients with unstable angina and stable non-ST-segment elevation myocardial infarction (NSTEMI). Fibrinolytic therapy and PCI remain the gold standards for ST-segment elevation myocardial infarction (STEMI) based on their ability to restore coronary perfusion in an emergency. Coronary artery bypass grafting is indicated in a STEMI only for patients who have coronary anatomy not amenable to PCI with ongoing ischemia, for patients in whom PCI has failed, or in patients who have mechanical complications (ventricular septal defect, myocardial free-wall rupture, or papillary muscle rupture) related to their acute coronary syndrome (ACS).

Patient Selection and Complications

The risks associated with CABG are highest in the periprocedural period and must be weighed against the known long-term benefits of the surgical revascularization (Table 1). Numerous risk scores are available to estimate the risk of CABG-related mortality. The most commonly used scores are the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II and the Society of Thoracic Surgeons (STS) Risk Score. Both risk models include demographic variables, cardiovascular and non-cardiovascular comorbidities, CAD complexity, urgency of surgery, and hemodynamic risk factors for adverse clinical outcomes (Nashef 2012, Shahian 2009). The Society of Thoracic Surgeons risk model is unique in that it goes beyond mortality to estimate postprocedural morbidity, including the risks of stroke, renal failure, and sternal wound infection, as well as length of stay. In addition,

Table 1. 2017 STS Complication Rates for Isolated CABG

Complication	Incidence (%)
Atrial fibrillation (new)	25.1
Mortality (in-hospital)	1.8
Mortality (30 day)	2.3
Renal failure	2.2
Reoperation	2.5
Sternal wound infection/mediastinitis	0.3
Stroke	1.4

Information from: D'Agostino RS, Jacobs JP, Badhwar V, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2019 update on outcomes and quality. Ann Thorac Surg 2019;107:24-32.

the model gets recalibrated on a regular basis to account for changes in patient care. There are no thresholds for low versus high predicted risk, and therefore, the need for an individualized risk–benefit assessment remains.

PREOPERATIVE PHARMACOLOGIC CONSIDERATIONS

Preoperative medication management can significantly affect the benefits and complications associated with CABG. Preoperatively, patients can benefit from the introduction or interruption of medications to decrease the odds of procedural complications. Prior to surgery, a patient's complete medication history should be obtained, including prescription, over-the-counter, and herbal medications. The multidisciplinary team caring for the patient undergoing CABG must decide—throughout the perioperative period—whether to introduce, continue, hold, or modify each therapy.

Preoperative Antithrombotic Therapy

Antiplatelet and anticoagulant use is common in patients with CAD. Antithrombotic pharmacotherapy can reduce the risk of perioperative thromboembolic complications at the expense of bleeding. Both CABG-related bleeding and perioperative thrombotic events are associated with worse clinical outcomes. Therefore, patient-specific assessment of the risks of thromboembolism and bleeding is critical to determine the optimal therapeutic plan for each regimen.

Aspirin

Aspirin is a cornerstone treatment for chronic cardiovascular disease and has been shown to reduce the risk of MI, stroke, and vascular death in patients with atherosclerotic cardiovascular disease (ASCVD). Large, nonrandomized cohort studies of preoperative aspirin administration found

Table 2. Studies of Preoperative Aspirin Published After the 2015 AHA Secondary Prevention After CABG Scientific Statement

Trial	Design	Dosing regimen	Efficacy	Safety
Hastings et al. (2015)	Meta-analysis, 13 trials, 2399 patients	Various	MI 2.8% vs. 5.6% (p=0.03) Death (NS)	CT output +168 mL (p=0.01) RBC infusion +141 mL (p=0.001) Reoperation 5.6% vs. 3.0% (p=0.01)
ATACAS (2016)	RCT, multicenter, 2100 patients	100 mg 1–2 hours before surgery	MI 13.8% vs. 15.8% (NS) CVA 1.3% vs. 1.1% (NS) Death 1.3% vs. 0.9% (NS)	CT output +0 mL (NS) RBC infusion 43.9% vs. 42.6% (NS) Reoperation 1.8% vs. 2.1% (NS)
Solo et al. (2018)	Meta-analysis, 13 trials, 4377 patients	Various	MI 8.5% vs. 10.2% (NS) CVA 1.1% vs. 1% (NS) Death 1.2% vs. 0.9% (NS)	CT output +100 mL (p=0.01) RBC Infusion 31.1% vs. 29.5% (NS) Reoperation 4.1% vs. 2.4% (p=0.04)

CT = chest tube; CVA = cerebrovascular accident; MI = myocardial infarction; NS = not significant; RBC = red blood cell; RCT = randomized controlled trial

Information from: Hastings S, Myles P, McIlroy D. Aspirin and coronary artery surgery: a systematic review and meta-analysis. Br J Anaesth 2015;115:376-85; Myles PS, Smith JA, Forbes A, et al. Stopping vs. continuing aspirin before coronary artery surgery. N Engl J Med 2016 25;374:728-37; Solo K, Lavi S, Choudhury T, et al. Pre-operative use of aspirin in patients undergoing coronary artery bypass grafting: a systematic review and updated meta-analysis. J Thorac Dis 2018;10:3444-59.

substantial reductions of in-hospital mortality without increased blood loss or reoperation for bleeding compared with holding aspirin before surgery (Bybee 2005, Dacey 2000). Based on those results, the most-recent American Heart Association (AHA) recommendations for aspirin before CABG surgery endorse aspirin 81–325 mg daily preoperatively in all patients undergoing CABG (Class I, Level of Evidence [LOE] A) (Kulik 2015). Studies published since 2015 have demonstrated inconsistent efficacy—but reasonable safety with preoperative aspirin (Table 2). The largest randomized, controlled trial to date, Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS), was a multicenter trial of 2100 patients randomized to receive 100 mg of enteric-coated aspirin given 1–2 hours before CABG surgery (Myles 2016). Preoperative administration of aspirin did not reduce the composite end point of death or thrombotic event (nonfatal MI, stroke, pulmonary embolism, renal failure, or bowel infarction) 30 days postsurgery. Likewise, overall blood loss, transfusion requirement, and reoperation for bleeding were similar. The delayed and blunted response to enteric-coated aspirin as well as the definition of periprocedural MI used in the study raises questions about the trial results. It is important to note that ATACAS did not address the question of aspirin continuation compared with holding 5–10 days in advance because it required aspirin washout before CABG, with reinitiation within 24 hours of the surgery. Overall, the initiation or continuation of aspirin before CABG may reduce perioperative cardiovascular events and mortality with a modest, if any, increase in CABG-related bleeding. The mortality benefit with contemporary CABG practices is unknown. Aspirin 81–325 mg should be started at the time

of CAD diagnosis and continued in most patients managed with surgical revascularization. Doses of 325 mg are preferential when initiation occurs within 1–2 days before surgery, whereas lower doses are sufficient when surgery is planned further into the future. In light of ATACAS, enteric-coated formulations should be avoided because of the known risk of diminished antiplatelet effects. Few studies have explicitly investigated the benefits of aspirin in patients undergoing CABG for a recent ACS—a population likely to benefit greatly. Aspirin interruption 3–10 days before CABG may be considered in patients at very high risk of bleeding or in patients who refuse blood transfusions (Sousa-Uva 2018).

P2Y12 Receptor Antagonists

P2Y12 receptor antagonists (clopidogrel, prasugrel, ticagrelor) are added to aspirin to reduce the risk of recurrent MI and coronary stent thrombosis in patients with ACS treated with or without PCI or indefinitely for secondary prevention in SCAD, ischemic stroke, and peripheral artery disease. Continuing dual antiplatelet therapy (DAPT) until the day of major cardiac surgery such as CABG increases the risk of reoperation for bleeding, tamponade, and blood transfusions (Firanescu 2009, Mehta 2009). The antiplatelet effect of P2Y12 antagonists cannot be completely reversed with platelet transfusion or desmopressin. The risk of perioperative bleeding with continuation must be weighed against the risk of MI, stent thrombosis, and other adverse ischemic outcomes.

The necessary hold duration to eliminate bleeding risk is dependent on specific pharmacokinetic/pharmacodynamic characteristics of each agent (Figure 1). Thienopyridine P2Y12 antagonists clopidogrel and prasugrel require extended holding durations because of their irreversible antagonism of the P2Y12
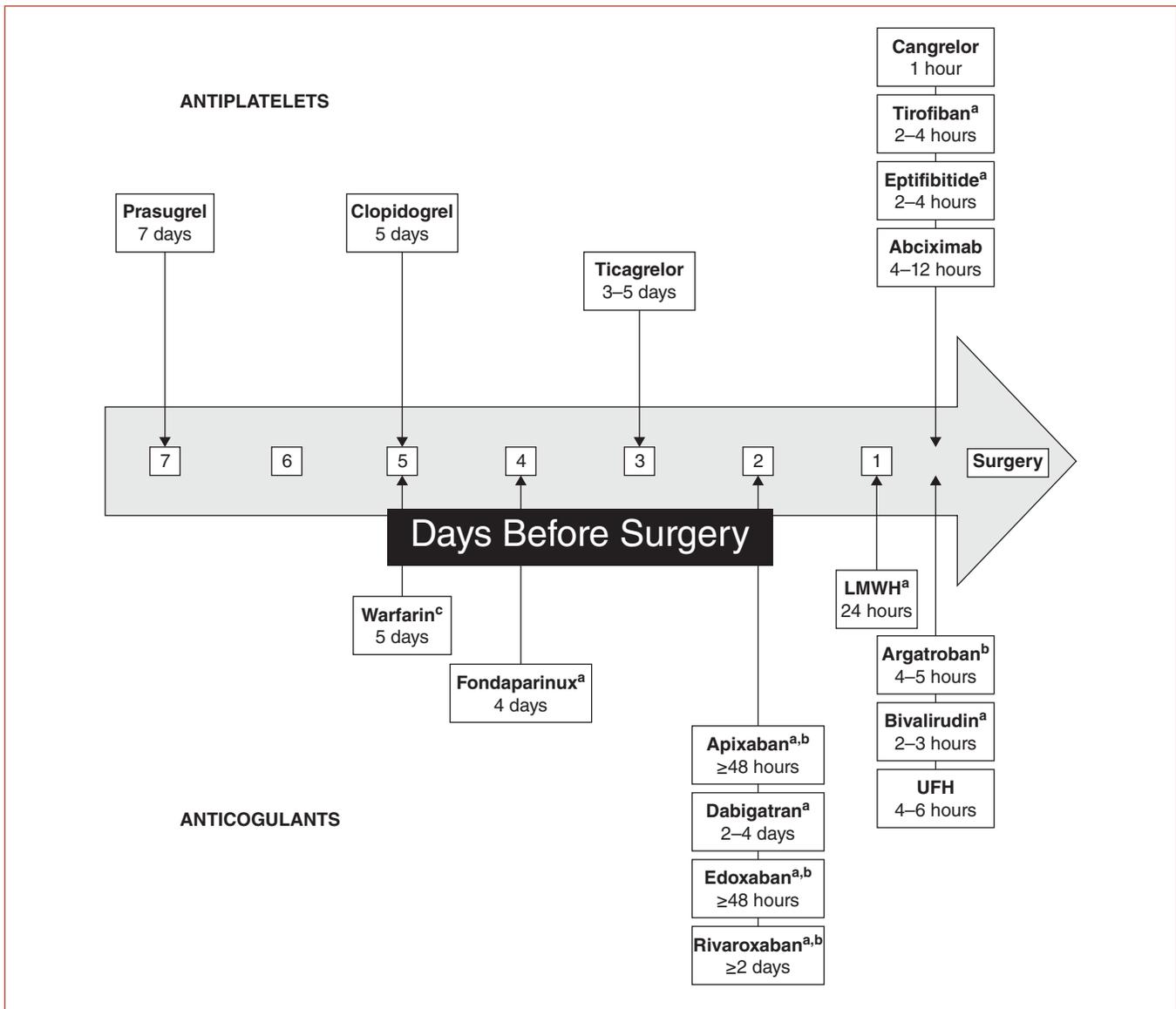
Figure 1. Recommended hold duration for antithrombotics before elective CABG.

[a]Longer duration may be necessary in the setting of renal dysfunction.

[b]Longer duration may be necessary in the setting of hepatic dysfunction.

[c]May be shorter or longer based on INR at the time of holding.

CABG = coronary artery bypass grafting; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin

Information from: Sousa-Uva M, Head SJ, Milojevic M, et al. 2017 EACTS guidelines on perioperative medication in adult cardiac surgery. Eur J Cardiothorac Surg 2018;53:5-33; Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons. J Am Coll Cardiol 2011;58:e123-210.

receptor, which prolongs antiplatelet activity until the production of new platelets. The guideline-recommended interval for holding clopidogrel before CABG is at least 5 days because of a significant increase in the need for any blood transfusion (odds ratio [OR] 1.36) and transfusion requirements greater than four units (OR 1.70; 95% CI, 1.32–2.19), although 24 hours is considered reasonable for urgent or emergent surgery (Hillis 2011, Mehta 2006).

For prasugrel, the recommended interval is at least 7 days. A subgroup analysis of 448 patients who underwent CABG during the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis In Myocardial Infarction 38 (TRITON-TIMI 38) found prasugrel treatment resulted in a significantly higher mean 12-hour blood loss compared with clopidogrel—without significant differences in

transfusions (Smith 2012). This was despite over two-thirds of patients holding prasugrel for at least 7 days.

Ticagrelor, a cyclopentyltriazolopyrimidine, shares the same increased potency in platelet inhibition as prasugrel, but reversibly binds to the P2Y12 receptor. Percent inhibition of platelet aggregation falls from 85% to near 20% within 72 hours of discontinuation (Gurbel 2009). The guideline-recommended interval for holding ticagrelor is a minimum of 5 days, but like clopidogrel, emergency CABG within 24 hours of the most recent dose is reasonable (Hillis 2011). The treatment protocol in the Platelet Inhibition and Patient Outcomes (PLATO) study, which compared ticagrelor with clopidogrel in patients with ACS recommended holding clopidogrel for at least 5 days and ticagrelor for 24–72 hours before CABG. There was no difference in CABG-related bleeding, chest tube output, transfusion requirements, or reoperation for bleeding between the two agents despite ticagrelor's being held for less than 5 days in more than 60% of patients (Held 2011). The safety of holding ticagrelor for less than 5 days is further supported by a Swedish observational study that found that holding ticagrelor for 3 days before CABG, as opposed to 5 days, did not increase the incidence of major bleeding complications (Hansson 2016). There are currently no P2Y12 antagonist reversal strategies, although an intravenous neutralizing monoclonal antibody fragment that binds ticagrelor and its major active metabolite with high affinity is currently in development (Bhatt 2019).

Platelet Function Testing

Standardized, one-size-fits-all holding intervals for P2Y12 receptor antagonists before CABG do not account for significant, interpatient variability in platelet function recovery over time. Preoperative platelet-function monitoring has the potential to tailor the holding interval to individual patient response. Testing can identify patients with high platelet reactivity on treatment who may proceed immediately to cardiac surgery as well as those with an accelerated recovery of platelet function after discontinuation. The Timing Based on Platelet Function Strategy to Reduce Clopidogrel-Associated Bleeding Related to CABG (TARGET-CABG) study tailored patients' clopidogrel-holding times before CABG with adenosine-diphosphate-induced platelet-fibrin clot strength measured by thromboelastography (Mahla 2012). There were no significant differences in hemoglobin change, chest tube output, transfusions, or reoperations compared with clopidogrel-naive patients. Platelet-function testing to guide individualized holding durations resulted in a 50% shorter hold duration than current guidelines recommend. Another study compared platelet-function testing-guided holding with the PFA-100 System, empiric holding of clopidogrel for 5 days, and clopidogrel-naive patients before isolated OPCAB for ACS (Mannacio 2014). The interval between clopidogrel cessation and CABG averaged 3.64 ± 1.7 days in patients who had had platelet-function testing. Testing resulted in significantly less blood loss, fewer transfusions, and shorter length of stay compared with empiric holding for 5 days. Reoperation for bleeding was rare in both management strategies. All outcomes with platelet-function testing were comparable to patients who had not received any clopidogrel. Numerous platelet-function assays are currently available, each one with its own advantages and disadvantages. Large clinical studies are required to determine the superiority of one assay over another as well as to determine the ideal platelet-function cutoffs that would minimize bleeding risk. Point-of-care testing is feasible with some of the tests, and therefore, measurement of platelet reactivity can occur as frequently as daily. Table 3 summarizes suggested high platelet-reactivity thresholds with common platelet-function tests (Mahla 2018).

Antiplatelet Bridging

Stopping P2Y12 receptor antagonist therapy—especially early after PCI with stenting—is associated with increased risk of death or AMI, although event rates are often reported as accumulations of the first 6–12 weeks after discontinuation (Ho 2010). The incremental daily risks associated with subtherapeutic P2Y12 receptor inhibition for the brief time therapy is held before CABG are less understood. Furthermore, the promising data that support platelet-function testing to minimize the time between drug cessation and surgery may further mitigate the risk of adverse ischemic events before surgery. The practice of bridging antiplatelet therapy with a short-acting intravenous agent is based on mitigating the risk of rare but clinically important ischemic events. If antiplatelet bridging is chosen, daily platelet reactivity testing may be useful as a guide for when to start the bridging agent so as to avoid excessive overlap, to minimize bleeding risk, and to reduce cost. Aspirin should be continued to maintain DAPT. Patients with recent ACS not treated with coronary stenting are unlikely to derive a significant benefit that exceeds the risk of bleeding.

Table 3. Available Platelet Function Tests and Proposed Thresholds for Safe CABG

Platelet function assay	Threshold for surgery
VerifyNow	>208 PRUs
Multiplate	>46 U
VASP-PRI	>50%
TEG	>47 mm MA ADP

ADP = adenosine diphosphate; CABC = coronary artery bypass graft; MA = maximum amplitude; PRUs = platelet reactivity units; TEG = thromboelastography; VASP-PRI = vasodilator-stimulated phosphoprotein phosphorylation.

Information from: Mahla E, Tantry US, Prüller F, et al. Is there a role for preoperative platelet function testing in patients undergoing cardiac surgery during antiplatelet therapy? Circulation 2018;138:2145-59.

Therapeutic options for intravenous platelet inhibition include glycoprotein (GP) IIb/IIIa inhibitors abciximab, eptifibatide, and tirofiban as well as intravenous P2Y12 receptor antagonist cangrelor. Abciximab should be avoided as a bridging agent because of (1) its long duration of antiplatelet activity that requires infusion discontinuation 12 hours before surgery, (2) the increased risk of blood product administration found in ACS studies when CABG was needed, and (3) the risk of drug-induced thrombocytopenia. Eptifibatide and tirofiban have similar antiplatelet potency (80% – 90% platelet inhibition) but a shorter time to restoration of platelet activity (4–8 hours). Evidence in support of their use in perioperative bridging is limited to case reports, retrospective analyses, and small prospective studies. Studies dosed eptifibatide 2 mcg/kg/min with or without a 180-mcg/kg loading dose and tirofiban 0.4 mcg/kg/min for 30 minutes and then a 0.1-mcg/kg/min infusion—lower than ACS dosing. Overall, studies have found comparable efficacy and safety with eptifibatide and tirofiban for perioperative bridging (Van Tuyl 2019). The data indicate that both agents prevent stent thrombosis but increase the risk of postoperative bleeding despite holding appropriately before surgery. Both agents are eliminated renally, and avoidance of both agents when CrCl is less than 30 mL/min may help limit bleeding risk.

Cangrelor is a short-acting, reversible, intravenous P2Y12 receptor antagonist that achieves rapid, potent, and predictable platelet inhibition with an offset of effect of 60 minutes. The Maintenance of Platelet Inhibition with Cangrelor (BRIDGE) trial compared platelet reactivity units between a cangrelor 0.75-mcg/kg/min continuous infusion and placebo in patients with CAD who required cessation of oral P2Y12 receptor antagonist before CABG surgery (Angiolillo 2012). Platelet reactivity was maintained at less than 240 platelet reactivity units (PRUs) in 98.8% of patients who received cangrelor. Cangrelor did not significantly increase CABG-related bleeding, and preoperative ischemic events were similar between cohorts (2.8% vs. 4.0%). The study was not powered to detect a difference in ischemic events or bleeding. Cangrelor's advantageous pharmacokinetic/pharmacodynamic profile and matching mechanism of action to oral P2Y12 receptor antagonists make cangrelor an appealing bridging agent for patients requiring CABG. Unfortunately, the BRIDGE trial was not designed to assess clinical outcomes. The primary end point—platelet reactivity—has not been established as a reliable therapeutic target with P2Y12 receptor antagonists. Cangrelor may be preferential in patients with significant renal insufficiency because decreased clearance of eptifibatide and tirofiban can increase the risk of bleeding.

Glycoprotein IIb/IIIa Inhibitors
Early studies with GP IIb/IIIa inhibitors demonstrated reductions in ischemic events in patients undergoing PCI but at the expense of major bleeding. Utilization continues to decline because contemporary studies question the overall net benefit in the setting of routine P2Y12 receptor antagonist treatment. Currently, GP IIb/IIIa inhibitors are reserved for high-risk patients undergoing PCI for ACS with significant intracoronary thrombus burden or coronary dissection or in the absence of P2Y12 receptor antagonist pretreatment. Initiation before identification of coronary anatomy is not recommended, and the duration of infusion post-PCI is often reduced or eliminated. In the rare occurrence that a patient gets exposed to GP IIb/IIIa inhibitors before CABG, appropriate holding before surgery is important in order to minimize the risk of perioperative bleeding (see Figure 1) (Dyke 2000, Lincoff 2000). The recommended time interval for discontinuation before CABG is based mainly on the anticipated pharmacokinetics and dynamics of each agent. Short-acting GP IIb/IIIa inhibitors (eptifibatide and tirofiban) should be discontinued for at least 2–4 hours before surgery (Class I, LOE B) to limit blood loss and transfusions (Hillis 2011). Both agents are eliminated renally, and therefore the hold interval should be extended to 6–8 hours or more in patients with a CrCl of less than 30 mL/min. The recommended holding interval for abciximab is 12 hours (Class I, LOE B) (Hillis 2011), but a pooled analysis of two PCI trials showed no difference in blood loss compared with placebo when the study treatment was held within 6 hours before incision (Lincoff 2000). There is no antidote or transfusion strategy to promptly reverse the antiplatelet activity of GP IIb/IIIa inhibitors.

Oral Anticoagulation
Preoperative management of patients who are receiving chronic oral anticoagulation is based on assessment of patient risk for thromboembolism and risk of perioperative bleeding. All coronary artery bypass graftings are universally considered high-bleeding-risk surgeries because of extensive tissue damage from the operation. Moreover, postoperative bleeding poses serious clinical consequences. Interruption of warfarin or direct oral anticoagulants (DOACs) is required to minimize perioperative bleeding (see Figure 1). The residual anticoagulant effects are associated with the time necessary to regenerate vitamin-K-dependent coagulation factors II, VII, IX, and X. It is assumed that at the time of surgery, an international normalized ratio (INR) greater than or equal to 2 will increase the risk of bleeding and that a near-normal INR of less than 1.5 will diminish any bleeding risk associated with treatment. Patients treated with warfarin should have therapy stopped 5 days before planned CABG. An INR assessment on the day before surgery may allow time to correct elevated INRs so as to minimize postoperative blood product use or the rescheduling of surgery.

Direct oral anticoagulants (apixaban, dabigatran, edoxaban, rivaroxaban) are widely used as standards of care for stroke prevention in atrial fibrillation and the management of venous thromboembolism. They provide direct, reversible inhibition of thrombin or inhibition of factor Xa with

Table 4. Criteria for High Risk of Thromboembolism in Which Anticoagulation Bridging May Be Indicated

Anticoagulation Indication	High-risk Populations
Atrial fibrillation	• CHA_2DS_2-VASc score of 7−9 • CHA_2DS_2-VASc score of 5−6 *and* history of ischemic stroke, transient ischemic attack, or systemic embolism • Recent ischemic stroke, transient ischemic attack, or systemic embolism (past 3 months) • Active left atrial appendage thrombus • Direct-current cardioversion in the past 1 month • Concomitant mitral stenosis
Venous thromboembolism	• Recent venous thromboembolism (past 3 months) • Severe thrombophilia (deficiency of protein C, protein S, or antithrombin; antiphospholipid antibodies; multiple abnormalities)
Prosthetic valve	• Mechanical mitral valve • Caged-ball or tilting-disc aortic valve prosthesis • Recent ischemic stroke or transient ischemic attack (past 6 months)
Other disease considerations	• Cancer • History of thromboembolic events during anticoagulation cessation • Recent heparin-induced thrombocytopenia (past 3 months)

Information from: Douketis JD, Spyropoulos AC, Spencer FA, et al. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2012;141:e326S-50S; Doherty JU, Gluckman TJ, Hucker WJ, et al. 2017 ACC expert consensus decision pathway for periprocedural management of anticoagulation in patients with nonvalvular atrial fibrillation. J Am Coll Cardiol 2017;69:871-98.

predictable dose response and relatively short half-lives. All DOACs should be stopped before CABG for a duration dependent on the specific agent as well as the patient's renal function. In one study, withdrawal period and renal dysfunction significantly influenced postoperative blood loss in cardiac surgery patients (33% CABG) treated with DOACs preoperatively (Hassan 2018). Hepatic metabolism is an important pathway of drug clearance with DOACs—particularly Xa inhibitors—and hepatic impairment can prolong the half-life. There are currently no recommendations for the perioperative management of DOACs in patients with hepatic impairment. An estimated half-life in that setting may be applied to guide the holding interval before surgery. Centers with calibrated drug-specific assays may test for preoperative dabigatran, rivaroxaban, and apixaban levels of less than 30 ng/ml. If assays are not available for Xa inhibitors, a standard heparin-calibrated anti-Xa level of less than 0.1 units/mL suggests minimal anticoagulant effect (Beyer 2016).

Preprocedural Anticoagulation Bridging

The decision to bridge interrupted oral anticoagulation before CABG is based on the patient's short-term, thromboembolic risk of the patient if all anticoagulation were held. Overall, the pooled rate of periprocedural thromboembolism with unbridged oral anticoagulation interruptions is low— estimated at about 0.53%—but it varies greatly based on patient-specific factors (Rechenmacher 2015). Routine low-molecular-weight-heparin (LMWH) bridging of low-risk patients was found to be noninferior compared with no bridging in the prevention of thromboembolism, with a nearly threefold increase in major bleeding (Douketis 2015). Certain clinical scenarios are considered to be sufficiently high risk for thromboembolism for which the benefit of bridging exceeds the bleeding risk (Table 4). The anticoagulant effect of warfarin takes longer to dissipate, and therefore the patient will spend a greater duration of time below the therapeutic threshold before complete normalization of INR. Short-acting, parenteral anticoagulation with unfractionated heparin or LMWH is ideal for preprocedural bridging of warfarin. Therapeutic dosing of either agent is recommended to provide levels of anticoagulation comparable to therapeutic warfarin. In the inpatient setting, unfractionated heparin is preferable to LMWH because of its shorter half-life. Preoperative use of enoxaparin was associated with increased incidence of rehospitalization for hemorrhage requiring reexploration compared with unfractionated heparin (7.9% vs. 3.7%, p=0.03) (Jones 2002). Preoperative bridging is not recommended in DOAC-treated patients unless surgery is planned days beyond the anticipated offset of the anticoagulant. DOACs have predictable and brisk offset of the anticoagulation effect, which allows for short-term cessation before surgery and has been associated with increased bleeding risk (Beyer-Westendorf 2014).

Reversal of Oral Anticoagulation

Most CABG surgeries are elective procedures for SCAD, for which planned cessation of oral anticoagulation is feasible. Patients who require urgent or emergency CABG within the time frame that warfarin or a DOAC is held should be considered for reversal. Rapid reversal of warfarin can be achieved with four-factor prothrombin complex concentrate (4F-PCC) or fresh-frozen plasma (FFP) along with intravenous vitamin K to maintain an INR of less than 1.5 through the early postoperative period. Four-factor PCC was superior to FFP for achieving an INR of ≤1.3 within 30 minutes of infusion (54% vs. 6%, p<0.0001) and effective hemostasis (88% vs. 73%, p=0.02) in patients needing warfarin reversal for urgent surgical procedures (Goldstein 2015). Thromboembolic events did not differ (7% vs. 8%) but only 3.5% of surgical procedures were cardiothoracic. Urgent CABG is most commonly performed in the setting of ACS. The acute thrombotic pathophysiology of ACS may heighten the risk associated with concentrated-factor products like 4F-PCC. The FDA's labeling says 4F-PCC may not be suitable in patients with thromboembolic events in the prior 3 months, and therefore, FFP may be a safer reversal strategy in CABG after ACS despite its slower onset, its less-complete reversal, and its higher propensity for volume overload.

The anticoagulant effects of dabigatran may be reversed with idarucizumab—a humanized monoclonal antibody fragment with high affinity and specificity for dabigatran. Idarucizumab sequestered dabigatran rapidly (in less than 10 minutes) and completely (achieving a free-dabigatran level of less than 20 ng/mL), and reversal was maintained for 24 hours in most patients (Pollack 2017). Periprocedural hemostasis was assessed as normal or mildly abnormal in 98.5% of patients, although the number of enrolled emergency-CABG patients is unknown. The published experience with idarucizumab before CABG is limited to few case reports. Unlike direct-coagulation-factor replacement, idarucizumab has no known procoagulant activity.

Emergen direct-Xa-inhibitor reversal poses a greater challenge because the antidote—andexanet alfa—carries several limitations for periprocedural use. Andexanet alfa has limited trial experience and no dosing recommendations for Xa inhibitors other than apixaban and rivaroxaban. Direct-Xa inhibitors rapidly dissociate from andexanet alfa upon completion of the infusion, and a rebound in anticoagulation ensues 3–4 hours later, which may occur at inopportune times such as during surgery or immediately postop. A prolonged infusion through the CABG procedure has not been studied and may interfere with anticoagulation during CPB given andexanet alfa's activity against unfractionated heparin. Andexanet alfa is currently not FDA approved for periprocedural anticoagulation reversal. Activated PCC and 4F-PCC are alternatives that have been shown to restore coagulation status in Xa-inhibitor-treated patients, but they have limited experience in preprocedural anticoagulation reversal apart from warfarin. The thromboembolic risks of concentrated-factor reversal are likely similar to warfarin reversal, and therefore caution is warranted. There is no role for FFP in DOAC reversal because it has not been shown to substantially restore coagulation status.

Parenteral Anticoagulation

Patients referred for CABG may require therapeutic parenteral anticoagulation before CABG for bridging outpatient oral anticoagulation or as a part of ACS treatment. There is a paucity of clinical evidence to support specific time intervals for stopping therapeutic parenteral anticoagulants (unfractionated heparin, LMWH, fondaparinux, bivalirudin, and argatroban) before surgery. Recommendations for holding are generally based on the expected pharmacokinetics of each specific agent (see Figure 1). Unfractionated heparin has a dose-dependent half-life of 30−90 minutes, which supports the recommendation to hold 4−6 hours before surgery (Douketis 2012). Therapeutic, twice-daily dosing of LMWH should be held about 24 hours before surgery. When held for a median of 14 hours, preoperative anti-Xa levels were detectable (≥0.1 units/mL) in 99% of patients and above the therapeutic threshold (≥0.5 units/mL) in 68% (O'Donnell 2007). The clinical significance of this is unknown given that anti-Xa levels are surrogate markers of anticoagulation without an established association with bleeding. In patients on therapeutic, once-daily dosing, half the total dose should be given the morning before surgery (Douketis 2012). Enoxaparin is cleared renally, and therefore a prolonged holding interval with or without anti-Xa monitoring may be warranted. Fondaparinux has a long half-life (17−21 hours) and should be avoided if possible before CABG. In patients with histories of heparin-induced thrombocytopenia, transitioning to a short-acting direct thrombin inhibitor such as bivalirudin or argatroban will allow for a shorter holding interval and less time below the threshold of therapeutic.

Postoperative Atrial Fibrillation Prophylaxis

Postoperative atrial fibrillation (POAF) is the most common complication after CABG; it occurs in up to 25% of isolated CABG and is as high as 60% with concomitant valve surgery. The incidence continues to rise when older age is a major independent risk factor for POAF among the aging surgical population. After surgery, the risk of POAF is bimodal, with the higher risks from 0 to 18 hours and 24 to 48 hours postoperatively. By postoperative day 6, 94% of patients who will experience POAF will have their first episode. It is generally self-limiting, with conversion to normal sinus rhythm within 24 hours in 80% of patients and with most patients remaining arrhythmia free 6 weeks postop. Despite its relatively short disease course, POAF is strongly associated with an up to 4-fold risk of perioperative stroke and a twofold increase in in-hospital and 6-month mortality. Furthermore, POAF is associated with increased ICU and hospital length of stay,

cost of care, and rates of readmission. Patient factors, cardiac surgical factors, and postoperative factors converge to predispose to POAF those patients undergoing CABG. There is currently no widely accepted risk model for predicting post-CABG AF. Unfortunately, many of the preoperative risk factors are nonmodifiable—and the intraoperative risk factors unavoidable—leaving pharmacologic prophylaxis important for mitigating risk (Echahidi 2008).

Beta-Blockers

Beta-receptor antagonism remains the cornerstone prophylactic strategy for POAF after cardiac surgery. Beta-blockers interfere with the increased sympathetic tone during and after CABG, which increases atrial refractoriness and suppresses the initiation of arrhythmias. A meta-analysis of 33 trials found that preoperative beta-blockade significantly reduced the incidence of POAF compared with placebo (16.3% vs. 31.7%, OR 0.33; 95% CI, 0.26–0.43) (Arsenault 2013). Moreover, an STS database analysis of more than 600,000 patients who underwent isolated CABG found preoperative beta-blocker use was associated with reductions in 30-day all-cause mortality, reductions in ventilator days, reductions in renal failure, and a trend toward reduction in stroke (Ferguson 2002). In patients treated with chronic beta-blockers before surgery, abrupt discontinuation was associated with an up to fivefold increase in the incidence of POAF (Jidéus 2000).

The AHA and European Society of Cardiology guidelines recommend that a beta-blocker be administered for at least

24 hours before CABG to all patients without contraindications and reinstituted as soon as possible afterward in order to reduce the incidence or clinical sequelae of POAF (Kulik 2015, Sousa-Uva 2019). Only a paucity of data suggest superiority of one beta-blocker over another or the target dose to maximize the benefit of perioperative beta-blockade. Ideally, a beta-blocker would be initiated well in advance of surgery and titrated to a maximally tolerated dose. Common total daily doses used in clinical trials include atenolol 50 mg, carvedilol 25 mg, metoprolol 100–150 mg, and propranolol 60–80 mg. The optimal duration of treatment of patients without additional compelling indications for beta-blocker treatment is unknown. If a patient does not develop POAF by postoperative day 7, then the risk of dysrhythmia is negligible, and the benefit of beta-blockade diminishes.

Amiodarone

Amiodarone has (1) antagonistic activity at the beta-adrenergic receptor and (2) the antiarrhythmic effects of potassium channel blockade, which prolongs the repolarization phase of the cardiac cycle. A meta-analysis of 33 trials found a significant reduction in POAF after cardiac surgery in patients who received prophylactic amiodarone compared with that in controls (19.4% vs. 33.3%, OR 0.43; 95% CI, 0.34–0.54), with a borderline significant reduction in postoperative stroke (1.6% vs. 2.8%, OR 0.60; 95% CI, 0.35–1.02) (Arsenault 2013). Separate analyses demonstrate that the reduction in POAF translates into a reduction in length of stay but not in mortality (Burgess 2006). The reduction in POAF was maintained regardless of prophylactic beta-blocker use (Mitchell 2005).

The timing of initiation, the dosage regimens, and the administration routes vary significantly between studies. Preoperative administration has not been shown superior to postoperative administration—or vice versa— potentially in patients undergoing CABG, because the highest risk of POAF is at postoperative day 2, which allows time for postoperative administration to take effect (Buckley 2007, Chatterjee 2013). In addition, there was no difference in POAF with total administered amiodarone dose regimens of less than 3 g, of 3–5 g, or of greater than 5 g (Buckley 2007). The most-common adverse effects associated with amiodarone regimens for POAF include bradycardia, QT prolongation, and hypotension. The greatest risk occurred when with regimens containing intravenous amiodarone, with postoperative initiation, and with average daily doses greater than 1 gram (Patel 2006). Based on the risk of adverse effects and potential drug interactions, guidelines say preoperative administration of amiodarone is reasonable in order to reduce POAF in patients at high risk who have contraindications to beta-blockers (Class IIa, LOE B) (January 2014, Sousa-Uva 2019). Amiodarone is proven effective with background beta-blockade and may be considered in combination with beta-blockers in high-risk patients such as those with elevated POAF or P-wave signal-averaged electrocardiogram score (Sousa-Uva 2019). The optimal duration

of prophylaxis is unknown, but few contemporary protocols exceed postoperative day 7 in the absence of arrhythmias. Minimizing the duration of prophylaxis is especially important with amiodarone given its cumulative dose-related toxicities.

Antibiotic Prophylaxis and Decolonization

Infection is an infrequent but major complication of CABG surgery. The most-common sites of surgical-site infection are superficial sternal wound infection (up to 8%), deep sternal wound infection/mediastinitis (up to 1%), wound infections of the saphenous-vein-graft (SVG) harvest site (10% – 15%), and bacteremia (up to 3%). Surgical-site infections—especially deep sternal wound infections, mediastinitis, and bacteremia—are associated with substantial increases in mortality, hospital length of stay, and cost. In addition to standard preoperative patient preparation, perioperative decolonization of patients with *Staphylococcus aureus* colonization and systemic antibiotic prophylaxis are important medication-related interventions for minimizing the risk of infection after CABG.

Decolonization of S. aureus

Nasal carriage of *S. aureus* is a well-defined risk factor for subsequent infection. Deoxyribonucleic acid (DNA) analyses of *S. aureus* isolates from mediastinal wound infections after cardiac surgery found identical genotypes in patients' nares in the majority of cases (San Juan 2007). Rapid screening by real-time polymerase-chain-reaction assays facilitates assessment of *S. aureus* carrier status within hours after admission. Decolonization of patients with methicillin-resistant and methicillin-sensitive *S. aureus* nasal colonization reduced deep surgical-site infections and lengths of stay in a trial of surgical patients (Bode 2010). Topical intranasal treatment with mupirocin is a commonly recommended method to eradicate staphylococcal colonization (Hillis 2011, Lazar 2016, Sousa-Uva 2018). Treatment with intranasal mupirocin should begin in colonized patients as early as possible before surgery and continued for a total of 5 days. Empiric decolonization may be considered in patients whose culture results are not available or not obtained at the time of surgery, but that approach is more controversial.

Systemic Antibiotic Selection

Perioperative antibiotics reduce the risk of postoperative infection fivefold compared with no prophylaxis (Kreter 1992). Antibiotic selection is dictated by (1) the organisms most likely to cause infection and (2) the risk of toxicity from the agent itself. Coronary-bypass-related surgical infections are most commonly caused by gram-positive organisms—particularly coagulase-negative *Staphylococcus* and *S. aureus*. Less-common organisms include *Corynebacterium* and enteric gram-negative bacilli. Studies have consistently shown that first- and second-generation cephalosporins—specifically cefazolin or cefuroxime—effectively and safely minimize the risk of surgical-site infection from cardiac

Table 5. Perioperative Prophylactic Antibiotic Regimens for CABG

Antibiotic	Recommended dose	Timing of preoperative dose (minutes)	Redosing interval (hours)[a]
Cefazolin	<120 kg: 2 g ≥120 kg: 3 g	<60	4
Cefuroxime	1.5 g	<60	4
Clindamycin	900 mg	<60	6
Vancomycin	15 mg/kg	120	NA

[a]From initiation of preoperative dose.

NA = not applicable

Information from: Bratzler DW, Dellinger EP, Olsen KM, et al. Clinical practice guidelines for antimicrobial prophylaxis in surgery. Am J Health Syst Pharm 2013;70:195-283; Leaper DJ, Edmiston CE. World Health Organization: global guidelines for the prevention of surgical site infection. J Hosp Infect 2017;95:135-6; Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg 2017;152:784-91.

surgery, including CABG (Lador 2012) (Table 5). In a meta-analysis of seven trials, vancomycin was no more effective than beta-lactam antibiotics for prevention of surgical infections after cardiac surgery and was inferior for prevention of chest and deep-chest infections (Bolon 2004). Vancomycin should be reserved for patients with true histories of anaphylactic reactions to cephalosporins or for patients with proven or suspected methicillin-resistant *S. aureus* colonization. Similarly, clindamycin can serve as an alternative to vancomycin when anaphylaxis is of concern with the use of cephalosporins. When vancomycin or clindamycin is used, the addition of an aminoglycoside, or aztreonam, or a fluoroquinolone may be considered if patient-specific gram-negative pathogens are of concern.

Dosing, Timing, and Duration

To prevent surgical infections, perioperative antibiotics must obtain—and maintain—antibiotic serum and tissue concentrations higher than the minimum inhibitory concentrations for organisms at the time of incision and for the duration of a procedure. To achieve that, surgical-prophylaxis guidelines recommend the specific timing of preoperative and intraoperative dosing (see Table 5). Complete administration of short half-life antibiotics is recommended within 60 minutes of incision while vancomycin gets up to 120 minutes to achieve maximal drug concentrations—both of them at standard doses (Berrios-Torres 2017, Bratzler 2013). For patients on antibiotics for infections before surgery, it is important

to assess agent appropriateness for surgical prophylaxis. If the current antibiotic is insufficient for prophylaxis before CABG, then a different antibiotic should be added at the recommended time before surgery. If the active antibiotic is therapeutically appropriate, the administration of an extra dose within 60 minutes before surgical incision is sufficient for wide-therapeutic-index drugs. An alternative strategy is to delay the next scheduled dose of an agent until the right preoperative time. To maintain therapeutic levels of an antibiotic throughout the procedure, guidelines recommend redosing if the duration of the procedure exceeds two half-lives of the antibiotic or if blood loss exceeds 1500 mL. The optimal prophylactic course of antibiotics is 24 hours and should not exceed 48 hours (Berrios-Torres 2017). Single-dose courses of less than 24 hours reported higher rates of superficial- and deep-incisional surgical-site infections compared with 24 hours of antibiotics; courses exceeding 48 hours are ineffective and associated with both increased antibiotic resistance and *Clostridioides difficile* (Gelijns 2014, Harbarth 2000, Tamayo 2008).

Renin-Angiotensin-Aldosterone-System-Inhibitor Cessation

Many patients undergoing CABG are taking long-term renin-angiotensin-aldosterone-system inhibitors for hypertension, CAD, or heart failure with reduced ejection fraction (HFrEF). The optimal use of angiotensin-converting-enzyme inhibitors (ACEIs) around the time of CABG is controversial. The 2011 AHA CABG guidelines acknowledge the potential association between ACEIs and angiotensin receptor blockers (ARBs) with decreased systemic vascular resistance, perioperative hypotension, and vasodilatory shock but assert that the safety of preoperative administration in patients on chronic therapy is uncertain (Class IIb, LOE B) (Hollis 2011). The potential mechanism of risk includes reduced levels of angiotensin II, which modulates catecholamine release, reuptake, and response. In a 2015 meta-analysis of 13 studies comprising 31,390 patients, preoperative ACEI treatment increased the risks of hypotension (RR 2.36, 95% CI 1.11-5.02), postoperative myocardial infarction (risk ratio [RR] 1.14; 95% CI, 1.02–1.27), and renal dysfunction (RR 1.26; 95% CI, 1.00–1.60) but did not reduce the risks of POAF or stroke (Zhang 2015). Early mortality was unaffected (p=0.12). In the absence of a clear benefit and a potential for risk, long-acting ACEIs and ARBs may be held 24 hours before surgery or switched to short-acting captopril and held for 12 hours. Parenteral antihypertensives (nitroprusside, nicardipine, nitroglycerin) may be used as bridges to maintain blood pressure management in patients with hypertension and/or cardiopulmonary pressures in heart failure. Patients treated with sacubitril/valsartan should have the same preoperative assessment performed. There is no data evaluating the benefits and risks of preoperative aldosterone receptor antagonist treatment before CABG or other cardiac surgery.

Preoperative Statin Therapy

Coronary artery bypass surgery—especially when performed in CPB—is known to lead to a profound systemic inflammatory response. Inflammation plus enhanced thrombogenicity from the foreign surfaces of a CPB can mimic the pathophysiology of ACS. The pleiotropic benefits of statin treatment include anti-inflammatory effects; preoperative treatment reduces C-reactive protein and interleukin-6 after cardiac surgery. Increasing evidence shows that perioperative statin therapy improves the morbidity associated with CABG, including POAF, stroke, and acute kidney injury (Barakat 2016). In some studies, that translated into both a 0.5- to 1-day reduction in length of stay and improved mortality.

Atorvastatin and simvastatin are associated with the strongest-outcomes data—at doses of at least 20 mg and 40 mg, respectively—when administered up to the day of surgery (Curtis 2017). That is consistent with the greater pleiotropic effects of lipophilic statins compared with hydrophilic statins such as rosuvastatin. The incidence of traditional statin-related adverse effects during perioperative treatment was similar to incidence with no-statin therapy. The AHA guidelines say to start high-dose statin preoperatively (Class I, LOE A) and to avoid discontinuation of statin before CABG unless there are adverse reactions to therapy (Class III, B) (Kulik 2015).

POSTOPERATIVE PHARMACOLOGIC MANAGEMENT

Postoperative management after CABG surgery can significantly influence both short- and long-term outcomes. The treatment focuses on correcting metabolic and hemodynamic derangements from surgery. Furthermore, patients should be started on therapeutic regimens for secondary prevention of ASCVD.

Glycemic Control

Perioperative hyperglycemia, defined as a blood glucose level exceeding 140 mg/dL, occurs in up to 80% of patients undergoing cardiac surgery. Hyperglycemia can arise from worsening glycemic control in up to 90% of patients with preexisting diabetes or from transiently elevated blood glucose in 60% of nondiabetics because of physiologic stress. Hormonal responses to stress include increased secretion of endogenous catecholamines, glucagon, cortisol, and growth hormone that (1) suppresses insulin production in the pancreas, (2) increases glucose production in the liver, and (3) reduces uptake in peripheral tissues. Other iatrogenic causes of hyperglycemia are vasopressor or inotropic support, corticosteroids, maintenance fluids, and nutritional support. Hyperglycemia after CABG surgery—with or without a preoperative diagnosis of diabetes—is associated with higher complication rates, including increased mortality.

Hyperglycemia and Outcomes

The pathophysiologic link between hyperglycemia and perioperative adverse outcomes is unknown, but several plausible mechanisms exist. Acute renal failure may be the result of osmotic diuresis leading to prerenal azotemia. Mean intraoperative glucose level was identified as a significant predictor of acute or worsening renal failure or a new requirement for dialysis after cardiac surgery (Gandhi 2005). Average blood glucose was roughly 180 mg/dL for patients with renal events compared with 130 mg/dL for patients without renal events. Impaired collagen synthesis and leukocyte function can negatively affect wound healing and increase the risk of infection—most notably, deep sternal wounds and mediastinitis. A hyperglycemic episode exceeding 180 mg/dL in the first 48 hours after cardiac surgery was associated with a 32% increase risk of infection (p=0.04) (Gelijns 2014). In addition, targeting a blood glucose of 125– 200 mg/dL, as opposed to less than 250 mg/dL, resulted in fewer recurrent wound infections (1% vs. 10%, p=0.03) (Lazar 2004). Hyperglycemia's deleterious effects on endothelial function, increased platelet activation, and reduced fibrinolytic activity may pose significant harm to CABG patients with extensive CAD. Stricter blood glucose control has been associated with decreased episodes of recurrent ischemia (5% vs. 19%, p=0.01), reduced postoperative length of stay (6.5 vs. 9.2 days, p=0.003), and a survival advantage over the initial 5 years after surgery (p=0.04) (Lazar 2004). In addition, every 30-mg/dL increase in blood glucose above 200 mg/dL has been associated with a 1-day increase in total length of hospital stay; a peak measurement greater than or equal to 360 mg/dL tripled the mortality rate (6% vs. 2%) compared with patients without such a peak measurement (Doenst 2005, Fish 2003). Hormonal, inflammatory, and hematologic abnormalities associated with stress hyperglycemia return to baseline with treatment and are associated with improved outcomes.

Perioperative Blood Glucose Targets

The exact blood glucose threshold above which stress hyperglycemia becomes harmful during and after CABG remains unknown. Liberal blood glucose targets—especially those that include levels greater than 200 mg/dL—are associated with more morbidity and more mortality compared with moderate targets of 120–180 mg/dL (Figure 2). Further intensification of antihyperglycemic treatment in order to target blood glucoses of less than 120 mg/dL have not been shown to further improve outcomes but do result in higher rates of hypoglycemia. Some studies suggest heterogeneity in the treatment effect of lower blood glucose targets according to preoperative diabetes status. In the Intensive Insulin Therapy in Patients Undergoing Coronary Artery Bypass Surgery (GLUCO-CABG) trial, patients without preoperative diabetes had reductions in composites of hospital complications (mortality, wound infection, pneumonia, bacteremia, respiratory
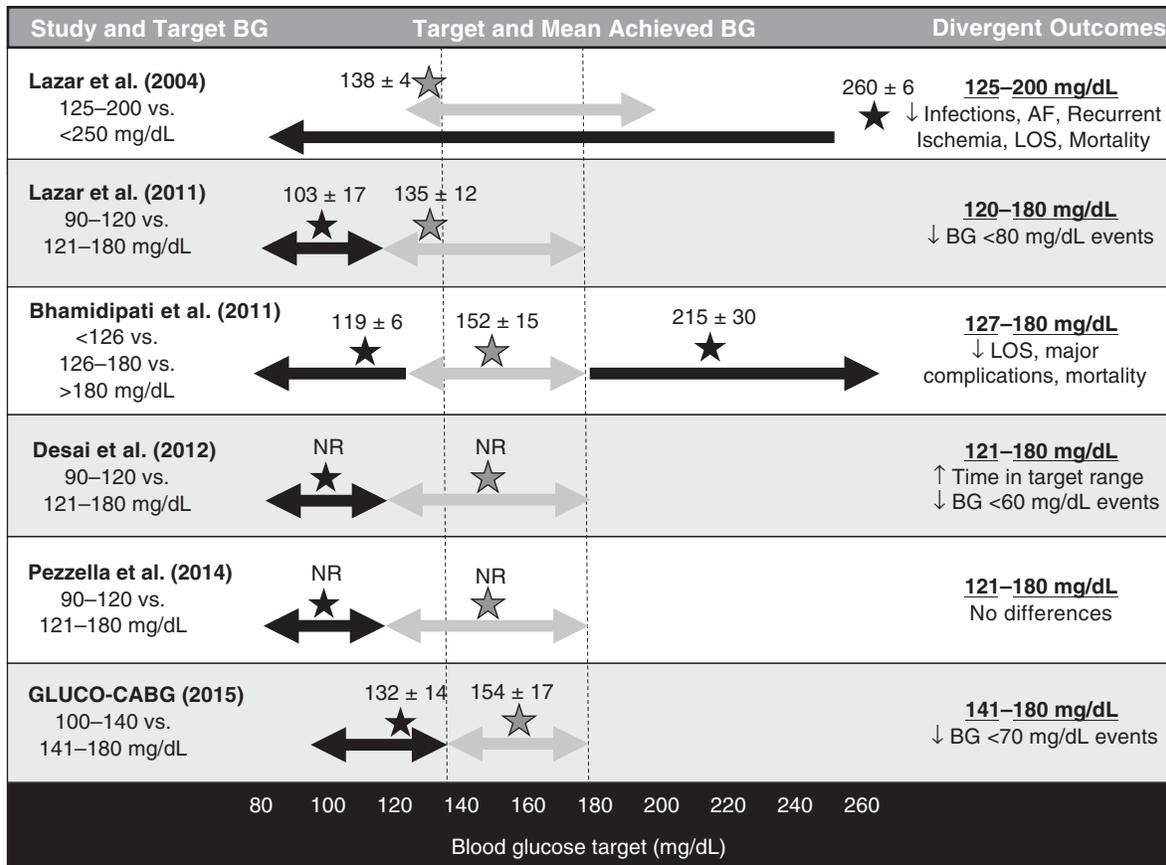
Figure 2. Perioperative blood glucose targets and outcomes in CABG.

AF = atrial fibrillation; BG = blood glucose; LOS = length of stay; NR = not reported; ↔ = no difference; ↓ = less incidence; ↑ = greater incidence

Double arrow = target blood glucose ranges for each treatment arm, Star = the average blood glucose with standard deviation for each treatment arm

Information from: Lazar HL, Chipkin SR, Fitzgerald CA, et al. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. Circulation 2004;109:1497-502; Lazar HL, McDonnell MM, Chipkin S, et al. Effects of aggressive versus moderate glycemic control on clinical outcomes in diabetic coronary artery bypass graft patients. Ann Surg 2011;254:458-63; Bhamidipati CM, LaPar DJ, Stukenborg GJ, et al. Superiority of moderate control of hyperglycemia to tight control in patients undergoing coronary artery bypass grafting. J Thorac Cardiovasc Surg 2011;141:543-51; Desai SP, Henry LL, Holmes SD, et al. Strict versus liberal target range for perioperative glucose in patients undergoing coronary artery bypass grafting: a prospective randomized controlled trial. J Thorac Cardiovasc Surg 2012;143:318-25; Pezzella AT, Holmes SD, Pritchard G, et al. Impact of perioperative glycemic control strategy on patient survival after coronary bypass surgery. Ann Thorac Surg 2014;98:1281-5; Umpierrez G, Cardona S, Pasquel F, et al. Randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: GLUCO-CABG trial. Diabetes Care 2015;38:1665-72.

failure, acute kidney injury, and major adverse cardiovascular events) with a targeting of blood glucose of 100–140 mg/dL compared with 141–180 mg/dL (Umpierrez 2015). Patients with diabetes did not derive the same benefit. Similarly, a study of patients undergoing cardiac surgery who were treated with a target blood glucose of 80–110 mg/dL found patients without diabetes experienced reduced rates of perioperative complications, whereas patients with diabetes did not (Bláha 2015). Whether target glucose thresholds should be tailored to preoperative diabetic status requires further studies. The AHA guidelines for CABG recommend maintaining an early postoperative blood glucose concentration less than or equal to 180 mg/dL while avoiding hypoglycemia (Class I, LOE B), which aligns with the STS practice guideline for blood glucose management in adult cardiac surgery (Hillis 2011, Lazar 2009). Additional guidelines for inpatient blood glucose management set the lower end of the target range at 140 mg/dL (American Diabetes Association 2018).

Strategies for Managing Hyperglycemia

Intravenous insulin infusion is considered the standard of care for intraoperative and postoperative blood glucose management. Compared with subcutaneous insulin administration, continuous intravenous insulin treatment is associated with lower mean postoperative blood glucose levels on the day of surgery (242 ± 61 mg/dL vs. 187 ± 41 mg/dL, p<0.001) through postoperative day 2 (195 ± 39 mg/dL vs. 176 ± 39 mg/dL, p<0.001) despite targeting identical blood glucose ranges (Furnary 2003). Improved blood glucose control with intravenous insulin translated into reduced observed mortality (2.5% vs. 5.3%, p<0.0001) and was independently protective against death (OR 0.43; 95% CI, 0.26−0.70). Most institutions implement standard nursing-driven protocols to titrate dosing and to avoid errors, but there is no definitive evidence for superiority of one published intravenous insulin protocol or algorithm over another. Important components of an intravenous insulin protocol include rate adjustments that consider current and previous glucose values, current rate of insulin infusion, rate of change of blood glucose change, and frequent monitoring. Generally, intravenous insulin is started when blood glucose exceeds 180 mg/dL.

The optimal duration of intravenous insulin postop is unknown. In general, infusions are continued for 24−72 hours after CABG surgery. Transition to subcutaneous insulin should be considered once a patient is hemodynamically stable and reliably tolerating oral intake. Patients without diabetes and with stress hyperglycemia who require less than 2 units/hr of intravenous insulin can usually maintain blood glucose control on correctional subcutaneous insulin alone. Patients without diabetes requiring rates greater than 2 units/hr can be started on basal insulin dosed at 50% of the 24-hour insulin requirements and then followed closely. The first basal dose should be administered 2−4 hours before stopping the insulin infusion—so as to prevent rebound hyperglycemia. Most patients with histories of diabetes before CABG require transition to a basal/prandial subcutaneous-insulin regimen. Patients can be started at 80% of the calculated daily intravenous insulin requirements, with total insulin dose given as 50% basal and 50% prandial. Ultimately, patients with well-controlled diabetes who were not insulin dependent before surgery should be transitioned to their chronic diabetes regimens while the clinician considers transition to agents that improve cardiovascular outcomes, such as sodium glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists.

Hemodynamic Instability

Hemodynamically unstable patients after CABG represent a therapeutic challenge because of the potential for any combination of obstructive, cardiogenic, distributive, or hypovolemic shock. Hypotension is common in the early postoperative period. Often self-limiting and requiring less than 24 hours of support, persistent hemodynamic instability is associated with significant morbidity and mortality. The primary determinants of a perfusing blood pressure (mean arterial pressure [MAP] >65 mm Hg) are (1) sufficient vascular tone (systemic vascular resistance [SVR] >700 dynes · sec · cm^{-5}) and cardiac output (cardiac index >2.2 L/min/m^2). Cardiac output is further influenced by adequate blood volume, heart rate, and ventricular contractility. Each component of blood pressure can be an important therapeutic target (Figure 3).

Management of Cardiac Vasoplegia Syndrome

Cardiac vasoplegia syndrome (CVS) is a subset of vasodilatory shock that occurs in up to 44% of patients after cardiac surgery (Gomes 1998). It is a complex inflammatory response to surgical trauma and CPB that results in loss of systemic vascular resistance. Severe hypotension ensues despite high cardiac output and fluid resuscitation. Vasoplegia after cardiac surgery is associated with prolonged length of stay and a mortality rate as high as 25% (Gomes 1998).

The management of CVS consists of (1) treatment of underlying reversible causes of hypotension, (2) the use of high-dose vasopressors, and (3) nonvasopressor rescue therapies if vasoplegia persists. Common reversible causes of postoperative hypotension are metabolic acidosis, severe hypocalcemia, relative adrenal insufficiency, and iatrogenic causes (sedation). Hypotension often persists despite the absence of or the correction of reversible causes of vasoplegia. Vasopressors with peripheral vasoconstrictive properties—such as norepinephrine, phenylephrine, and vasopressin—are mainstays of treatment. Synthetic angiotensin II is a vasopressor with a novel mechanism of action that aligns with the pathophysiology of CVS (Shaefi 2018). To date there is only limited trial experience with CVS-related hypotension, and the prothrombotic-adverse-effect profile is of concern in the setting of high-risk CAD and new coronary bypass grafts. There is insufficient evidence to suggest any particular vasopressor is clinically superior or safer than another. Commonly, a single vasopressor is titrated to a target MAP. If dosing that limits adverse effects or if failure to achieve MAP goals occurs, additional vasopressors—ideally with different mechanisms of action—are added.

If the goal MAP still is not reached with multimodal vasopressors, then nonvasopressor rescue therapies for refractory shock may be considered (see Figure 3 and Table 6). The rescue therapy with the most published and most clinical experience in cardiac surgery is methylene blue, which is thought to neutralize the vasodilatory effects of nitric oxide and other endogenous vasodilators through competition in binding to soluble guanylate cyclase in endothelium and vascular smooth muscle—a major contributor to CVS pathophysiology. Clinically significant increases in systemic vascular resistance and MAP, as well as decreases in norepinephrine dose requirements were observed in 51 patients—with vasoplegia who were undergoing cardiac surgery—within 1 hour after a 2-mg/kg methylene blue infusion,

Postoperative Hypotension

Bleeding?
Hypovolemic?
Acidotic?
Hypocalcemic?

— Yes → Correct reversible causes

Yes → Persistent hypotension?

Yes → No

Signs of Low Cardiac Output
Cool, clammy extremities
Narrow pulse pressure
Ventricular dysfunction on echocardiogram
CI <2 L/min/m^2

Signs of Vasoplegia
Warm, flush extremities
Wide pulse pressure
Normal/hyperdynamic echocardiogram
CI >3 L/min/m^2
SVR <600 dynes · sec · cm^{-5}

Correct reversible cause ← Yes — Tamponade?

Yes

Persistent hypotension? — Yes → No

First-Line Treatments
IV norepinephrine
IV vasopressin
IV phenylephrine
IV epinephrine

Rescue Therapies
IV methylene blue
IV hydrocortisone
IV ascorbic acid + IV thiamine
IV hydroxocobalamin

Right Ventricular Failure
Dilated RV
Flat septum
RAP >/= PCWP

Left Ventricular Failure
Pulmonary edema
Low LVEF on echocardiogram
PCWP >15 + RAP < 2/3PCWP

Treatment Options
IV milrinone
IV dobutamine
IV epinephrine
Inhaled epoprostenol
Inhaled nitric oxide
Inhaled milrinone

Treatment Options
IV dobutamine
IV milrinone
IV epinephrine

Rescue Therapies
Mechanical circulatory support

Figure 3. Treatment pathway for postoperative hypotension.

CI = cardiac index; IV = intravenous; LVEF = left ventricular ejection fraction; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; SVR = systemic vascular resistance.

Information from: Jentzer JC, Vallabhajosyula S, Khanna AK, et al. Management of refractory vasodilatory shock. Chest 2018;154:416-26; Omar S, Zedan A, Nugent K. Cardiac vasoplegia syndrome: pathophysiology, risk factors and treatment. Am J Med Sci 2015;349:80-8; Konstam MA, Kiernan MS, Bernstein D, et al. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. Circulation 2018;137:e578-e622; Lomivorotov VV, Efremov SM, Kirov MY, et al. Low cardiac output syndrome after cardiac surgery. J Cardiothorac Vasc Anesth 2017;31:291-308.

which persisted for 12 hours (Leyh 2003). A multicenter, randomized, controlled trial of 56 patients with postoperative CVS after cardiac surgery found methylene blue 1.5 mg/kg administered intravenously over 1 hour reduced mortality (0% vs. 21.4%, p=0.01) compared with standard care (Levin 2004). Methylene blue resolved vasoplegia within 2 hours in all patients, whereas 28.6% of patients treated with placebo did not achieve resolution at 48 hours. Other nonvasopressor

Table 6. Rescue Therapies for Persistent Vasoplegia after Cardiac Surgery

Agent	Mechanism of action	Dosing	Considerations
Ascorbic acid + thiamine	• AA: Increased catecholamine/ vasopressin synthesis • T: Improved lactate clearance	AA: 25 mg/kg IV every 6 hr or 1.5 g IV every 6 hr T: 200 mg IV every 12 hr	• Caution in renal dysfunction
Hydrocortisone	• Augment vascular alpha-adrenergic responsiveness • Reduce inflammation-mediated vasodilation	50 mg every 6 hr or 100 mg every 8 hr OR Infusion: 10 mg/hr	• Hyperglycemia • Hypernatremia
Hydroxocobalamin	• NO scavenger that • can reverse NO-mediated vasodilation	5 g IV one time	• Interfere with heme sensors during HD • Chromaturia • Falsely alter numerous lab values up to 48 hours postdose
Methylene blue	• Antagonize endothelial NOS activity • Scavenge NO directly • Inhibit guanylate cyclase activity	IV Bolus: 1–2 mg/kg every 4–6 hr OR Infusion: 0.25–1 mg/kg/hr	• Serotonin syndrome with concomitant serotonergic agents • G6PD deficiency • Hemolytic anemia • False lowering of pulse oximetry readings • Pulmonary vasoconstriction • Green/blue coloration of urine and skin

AA = ascorbic acid; HD = hemodialysis; IV = intravenous; NO = nitric oxide; NOS = nitric oxide synthase; T = thiamine.

Information from: Jentzer JC, Vallabhajosyula S, Khanna AK, et al. Management of refractory vasodilatory shock. Chest 2018;154:416-26; Ortoleva JP, Cobey FC. A systematic approach to the treatment of vasoplegia based on recent advances in pharmacotherapy. J Cardiothorac Vasc Anesth 2019;33:1310-4.

rescue therapies for refractory CVS may be considered in patients who do not respond to vasopressor plus methylene blue and in those with contraindications to use (see Table 6).

Management of Low-Cardiac-Output Syndrome

Low-cardiac-output syndrome (LCOS) is a syndrome of decreased heart pump function leading to reduced oxygen delivery and end-organ dysfunction. A common definition of LCOS is a cardiac index pf less than 2 L/min/m^2, with hypotension and signs of hypoperfusion (cold extremities, confusion, acute kidney or liver injury, elevated lactate). After CABG, LCOS may be related to myocardial ischemia during cross clamping, reperfusion injury, cardioplegia-induced myocardial dysfunction, inflammation, and/or previous cardiac disease. It is associated with postoperative renal, neurologic, and pulmonary complications; increased length of stay; and a mortality rate exceeding 20% (Algarni 2011).

Hypovolemia or bradycardia, which can be common after CABG, should be corrected before initiation of therapies for LCOS. Decreases in preload may be caused by postoperative bleeding, brisk diuresis, warming, or fluid redistribution. Patients with hypotension and with low filling pressures should be transfused to a hemoglobin of at least 8 g/dL or should be volume resuscitated with intravenous fluid in the early postoperative period. Bradycardia is treated with

temporary pacing as well as intravenous chronotropic agents such as epinephrine or dopamine.

Low cardiac output may result from left ventricular systolic dysfunction, right ventricular systolic dysfunction, or both. Reduced contractility of either ventricle can be improved with an intravenous catecholamine (dobutamine, epinephrine, dopamine) inotropes or with phosphodiesterase inhibitor (milrinone) inotropes. Catecholamine inotropes have the advantage of rapid titration and minimal vasodilatory effects compared with milrinone. Epinephrine and dopamine have no advantage over dobutamine but are associated with greater incidences of adverse effects such as tachycardia, hyperglycemia, and lactic acidosis. Milrinone offers the advantages of less tachycardia, improved diastolic relaxation, and increased mammary artery graft flow. Its use may be limited by the risk of systemic vasodilation leading to hypotension as well as accumulation in renal failure. Milrinone is especially beneficial in right ventricular failure based on its positive inotropy and reduction in right ventricular afterload because of pulmonary vasodilation. Isolated or concomitant postoperative right ventricular failure may be identified by echocardiography or cardiopulmonary hemodynamics (central venous pressure >15 mm Hg and/or a pulmonary capillary wedge pressure ratio >0.63–0.86). Inhaled pulmonary vasodilators—specifically, epoprostenol and nitric oxide—represent another therapeutic option for

right ventricular afterload reduction. Both agents are usually administered through a ventilator and have minimal systemic vasodilatory response. Efficacy is similar between inhaled epoprostenol and nitric oxide, but nitric oxide is higher cost (Rao 2018). Regular methemoglobinemia— monitoring is indicated with extended durations of nitric oxide treatment. Overall, the effects of specific medications on major clinical outcomes or survival are unknown, so agent selection is tailored to individual patient circumstances.

Postoperative Atrial Fibrillation Treatment

Postoperative atrial fibrillation remains common after CABG despite taking appropriate preventive measures before and during surgery. Most cases are self-limiting, with restoration of sinus rhythm within 24 hours. Treatment strategies for POAF are determined by the presence or absence of hemodynamic stability and clinical symptoms while the patient is in atrial fibrillation. Treatment is normally continued for 4–6 weeks after the last episode of POAF unless there is a compelling reason to continue as specific therapy.

Rate Control

Studies comparing rate control strategies with rhythm control for hemodynamically stable POAF found no differences in time to conversion to sinus rhythm, in freedom from atrial fibrillation at 30 days, in freedom from stroke, in hospital length of stay, or in rates of mortality. In addition, rate control therapies avoid the higher rates of adverse drug events associated with antiarrhythmic medications. The recommended target ventricular rate varies from 80 to 110 beats/minute, but ultimately, the goal heart rate should be the threshold at which symptoms are eliminated while avoiding bradycardia or other adverse drug reactions. Beta-blockade is considered the first-line rate control strategy (Table 7). Multiple beta-blockers have been studied and found to be effective for rate control, although the most commonly used are esmolol and intravenous metoprolol. Nondihydropyridine calcium channel blockers verapamil and diltiazem are considered in patients who have contraindications to beta-blockers or in conjunction with beta-blockers (see Table 7). Trials comparing beta-blockers with nondihydropyridine calcium channel blockers have found that that beta-blockers are more effective for rate control when used as the sole agents. They are associated with more hypotension, which may be because of their vasodilatory properties and/or calcium depletion after cardiac surgery secondary to cardioplegia or citrate in blood transfusions. This is potentially related to the role of perioperative adrenergic stress in POAF. Either drug class should be used with caution in patients with hypotension and decompensated ventricular systolic dysfunction. Caution with bradycardia is warranted when spontaneous cardioversion has been achieved. Digoxin is less effective in settings with high adrenergic tone and is usually reserved for add-on therapy to other rate control strategies. Digoxin may be considered in patients with borderline

Table 7. Rate Control Strategies for POAF

Agent	Recommended dosing
Beta Blocker	
IV esmolol	500 mcg/kg IV bolus over 1 min, then 50–300 mcg/kg/min
IV metoprolol	2.5–5 mg IV bolus over 2 min; up to 3 doses
Calcium Channel Blocker	
IV diltiazem	0.25 mg/kg IV bolus over 2 min, then 5–15 mg/hr
IV verapamil	0.075–0.15 mg/kg IV bolus over 2 min; may give an additional 10 mg after 30 min if no response, then 0.005 mg/kg/min infusion
Other	
IV amiodarone	150 mg over 10 min, then 1 mg/min for 6 hr, then 0.5 mg/min for 18 hr
IV digoxin	0.25 mg IV, with repeat dosing to a maximum of 1.5 mg over 24 hr

IV = intravenous.

Information from: January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2014;130:e199-267.

hypotension or ventricular systolic dysfunction because it has little effect on blood pressure and does not negatively affect inotropy.

Rhythm Control

The rhythm control strategy is reserved for patients who are hemodynamically unstable or those who remain significantly symptomatic despite adequate ventricular rate control. Direct-current electrical cardioversion is the treatment of choice to rapidly restore sinus rhythm in patients with hemodynamic instability, acute heart failure, or myocardial ischemia. Recommendations for pharmacologic restoration of sinus rhythm are extrapolated from the recommendations for patients with chronic atrial fibrillation. Amiodarone is commonly used because of its superior efficacy over other antiarrhythmics, its rapid onset of rate control and cardioversion when given intravenously, and its ability to rate control patients with hypotension, heart failure, or left ventricular dysfunction (January 2014). Flecainide and propafenone should be avoided after CABG based on their contraindication for patients with coronary artery disease.

Antithrombotic Therapy

Despite the well-established association between POAF after CABG and perioperative risk of stroke, few studies have evaluated the benefits of anticoagulation for primary prevention of ischemic stroke. In addition, therapeutic levels of anticoagulation within 48 hours of major cardiovascular surgery can increase risks of perioperative bleeding and tamponade. The results of a limited number of studies assessing anticoagulation in POAF range from no benefit with ischemic stroke prevention to significant reductions in ischemic stroke and mortality. Guidelines say it is reasonable to administer antithrombotic medication in patients who develop POAF, as advised for nonsurgical patients (Class II, LOE B) (January 2014). Recommendations for pericardioversion anticoagulation remain the same as well. Anticoagulation therapy should be initiated when the risk–benefit ratio is favorable. Warfarin with a goal INR of 2–3 is generally accepted as the oral anticoagulant of choice, because the role of DOACs in this setting has not been established. Therapeutic anticoagulation is typically continued for a minimum of 4–6 weeks after return to sinus rhythm but may be continued for longer depending on the patient's stroke risk. Long-term treatment is not warranted in the absence of recurrent atrial fibrillation.

Secondary Prevention Strategies After CABG Surgery

Patients revascularized with CABG remain at significant risk of ischemic events because of the progression of native CAD and because surgical revascularization does not prevent disease progression. In addition, bypass grafts are prone to failure either acutely or over time. Typical pathophysiologies of graft occlusion are thrombosis within the first month after CABG, intimal hyperplasia from 1 month to 1 year, and development of atherosclerosis beyond 1 year (Motwani 1998). Disease progression and bypass graft failure can be mitigated by secondary-prevention medical therapy, which is critical for maintaining the long-term benefits of CABG over other treatments.

Antiplatelet Therapy

Antiplatelet therapy is a mainstay of secondary prevention in patients with known CAD, including patients surgically revascularized with CABG. Treatment consists of aspirin, a P2Y12 antagonist, or both. Important patient-, surgical-, and disease-specific variables determine the optimal antiplatelet strategy. In general, antiplatelet monotherapy is initiated immediately postop and continued indefinitely; DAPT may be considered for a prespecified time frame in certain patients.

Aspirin

After CABG, aspirin has the additional benefit of improved vein graft patency rates, especially during the first postoperative year. The benefits of aspirin after CABG are apparent early after surgery. Administration of aspirin within 6 hours after surgery was associated with improved graft patency without increased incidence of bleeding (Musleh 2003). The resumption of aspirin within 48 hours of CABG reduces the risk of death (1.3% vs. 4%, p< 0.001), myocardial infarction (2.8% vs. 5.4%, p<0.001), and stroke (1.3% vs. 2.6%, p=0.01) compared with patients who resumed aspirin beyond 48 hours (Mangano 2002). Lack of aspirin prescription at hospital discharge was the strongest predictor of death at 4 years in the SYNTAX trial (hazard ratio [HR] 3.56; 95% CI, 2.04– 6.21, p<0.001) (Farooq 2012). Aspirin doses from 81 mg daily to 325 mg three times a day appear to be efficacious, but doses exceeding 325 mg daily have been shown to have a higher risk and to offer limited additional benefit (Fremes 1993). The AHA recommends that aspirin 81–325 mg be administered within 6 hours after CABG and continued indefinitely (Kulik 2015). Moreover, the AHA says it is reasonable to consider an aspirin dose of 325 mg daily rather than the lower, 81 mg daily, but the benefits have not been well established (Class IIa, LOE A).

Alternatives to Aspirin Monotherapy

Clopidogrel 75 mg daily indefinitely is recommended as a reasonable alternative to aspirin after CABG for patients who are intolerant of or allergic to aspirin (Class IIa, LOE C) (Hillis 2011). The literature supporting that recommendation is extrapolated from ticlopidine, which effectively inhibited platelet aggregation in patients who underwent CABG but which provided no clear advantage over aspirin. Clopidogrel, unlike aspirin, did not inhibit platelet aggregation in the first 5 days after CABG—likely related to clopidogrel's known genetic and pharmacokinetic limitations. This is of concern considering the benefits of aspirin in the first 48 hours after CABG. A loading dose can overcome that shortcoming, as seen in PCI trials, but the safety of the approach after CABG has yet to be studied. No outcomes study has compared aspirin and clopidogrel after CABG. Ticagrelor results in greater platelet inhibition and faster onset of action in the absence of a loading dose. In the Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery (DACAB) study, ticagrelor produced similar rates of venous graft patency at 1 year compared with aspirin (82.8% vs. 76.5%, p=0.10), although the relative risks of most outcomes trended toward a benefit with ticagrelor (Zhao 2018). Major bleeding was rare in both groups, making ticagrelor 90 mg twice daily a viable alternative to aspirin for patients revascularized with CABG.

Dual Antiplatelet Therapy After CABG

Patients revascularized with CABG often meet criteria for very-high-risk ASCVD and are at risk of future events. In addition, early graft failure—particularly after SVG—continues to be a significant limitation of CABG despite the routine use of aspirin. Several randomized and nonrandomized trials evaluated the use of DAPT after CABG to improve graft patency and postoperative ischemic outcomes. To date, the benefits

of DAPT after CABG have been evident only in patients who receive OPCAB and those whose CABG was preceded by ACS.

DAPT in OPCAB

The benefits of DAPT after OPCAB may be associated with higher postoperative platelet activity and decreases in platelet sensitivity to aspirin after off-pump surgery compared with those who receive CPB. A meta-analysis of 12 studies found a reduction in early SVG occlusion (RR = 0.59; 95% CI, 0.43–0.82, p=0.02) and 30-day mortality with aspirin plus clopidogrel compared with aspirin alone, with a trend toward increased major bleeding (RR = 1.17; 95% CI, 1.00−1.37, p=0.05) (Deo 2013). The benefit was driven primarily by patients who received OPCAB who also experienced significant reductions in perioperative myocardial infarctions by 68%. Studies assessing DAPT after CABG with more-potent P2Y12 inhibitors are emerging. The first randomized, controlled trial of DAPT with ticagrelor 90 mg twice daily resulted in improved SVG patency rates 1 year post-CABG with DAPT compared with aspirin alone (88.7% vs. 76.5%, p<0.001) (Zhao 2018). It is notable that more than 75% of patients were managed with OPCAB. Several additional randomized, controlled trials are under way to evaluate the most-appropriate antiplatelet strategy after CABG. The AHA recommends DAPT for 1 year after OPCAB to reduce graft occlusion (Class I, LOE A), and combination therapy may be considered in on-pump CABG, but the benefits are not well established (Class IIb, LOE A) (Kulik 2015).

DAPT in CABG for ACS

Continuation of DAPT in patients with ACS who undergo CABG with DAPT may, theoretically, improve outcomes because of (1) stabilization of the culprit unstable plaque, (2) prevention of subsequent myocardial infarction resulting in nonculprit plaques, (3) improvement of saphenous vein graft patency, and/or (4) prevention of stent thrombosis in patients treated with coronary stenting before CABG (Levine 2017). Only data from post hoc analyses of large ACS trials are available on the utility of DAPT after CABG. Clopidogrel's role post-CABG was evaluated in a subgroup analysis of the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, which found that the benefits of DAPT were consistent across CABG, PCI, or medical therapy treatment strategies. In patients revascularized with CABG, the benefit of DAPT was relegated to the preoperative phase of care that averaged 25 days between treatment initiation and surgery. A retrospective analysis of patients who underwent CABG in the TRITON-TIMI 38 trial found a significant reduction in 30-day mortality with prasugrel-based DAPT over clopidogrel-based DAPT (Smith 2012). A post hoc analysis of the PLATO trial found a significant reduction in cardiovascular mortality with ticagrelor plus aspirin after CABG compared with clopidogrel and aspirin (Held 2011). Current guidelines recommend DAPT for all patients with ACS regardless of the choice of revascularization treatment (Levine 2016). The optimal timing for restarting DAPT should be as soon as it is considered safe but ideally within 48 hours after surgery in patients with a recent ACS.

Lipid Management

Elevated low-density-lipoprotein cholesterol (LDL-C) levels are strongly associated with progression of CAD in native coronary arteries as well as of intimal hyperplasia and atherosclerotic plaques in coronary bypass grafts. Statins are cornerstone treatments of ASCVD because of their effectiveness in reducing LDL-C and improving critical vascular outcomes, including mortality. Specifically in CABG, the POST-CABG trial determined that moderate-dose lovastatin (achieved LDL-C 93–97 mg/dL) lowered the incidence of new vein graft occlusions and the progression of atherosclerosis compared with low dose (Post Coronary Artery Bypass Graft Trial Investigators 1997). Long-term follow-up found reductions in the need for repeat revascularization and in adverse cardiovascular events (30% and 24%, respectively, p=0.001). Subsequent post hoc analyses and observational studies in postoperative CABG treatment established significant associations between statins and lower all-cause mortality and cardiac events after CABG. The AHA/ACC Guideline on the Management of Blood Cholesterol recommends high-intensity statin therapy (atorvastatin 40−80 mg or rosuvastatin 20−40 mg) in all patients younger than 75 years of age who undergo CABG (Class I, LOE A) and moderate-intensity statin therapy in patients who are intolerant of high-intensity statin therapy or those at greater risk of drug-drug interactions (Class I, LOE A) (Grundy 2019). There is no evidence to support the use of one statin over another as long as the intensity threshold is achieved. In patients older than 75 years, it is reasonable to initiate moderate- or high-intensity statin therapy, although the evidence is less robust. Careful consideration of the potential for ASCVD risk reduction, of the risk of adverse effects, and of patient preferences is warranted. Postoperatively, statin use should be resumed when the patient is able to take oral medications and should be continued indefinitely.

The surrogate marker of optimal statin therapy is a 50% reduction in LDL-C and is the goal for statin therapy in all patients with ASVCD, including those after CABG. In very-high-risk ASCVD, the use an LDL-C threshold of 70 mg/dL is useful in consideration of the addition of nonstatin therapy to statins. Very high risk includes a history of more than one major ASCVD event or one major ASCVD event and more than one high-risk condition. Surgery for CABG, along with the common comorbidities in patients who require CABG, makes most CABG patients candidates for the LDL-C target. In patients who are receiving maximum-tolerated statin therapy and whose LDL-C remains 70 mg/dL or higher, it is reasonable to add ezetimibe. The addition of ezetimibe to a statin has

been shown to lower the risk of cardiovascular death, myocardial infarction, or stroke (HR 0.77; 95% CI, 0.66–0.91) in patients with histories of CABG, driven primarily by a reduction in myocardial infarction (HR 0.72; 95% CI, 0.59–0.88) (Eisen 2016). If further antilipidemic therapy is warranted, it is reasonable to add a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (Class IIa, LOE A) (Grundy 2019). There is no direct evidence for the use of PCSK9 inhibitors after CABG, although their benefits are well established in ASCVD, in which group patients with CABG are included. A prespecified analysis of 2028 patients who had histories of CABG and ACS in the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) found alirocumab provided consistent relative risk reduction of a composite of major adverse cardiovascular events in patients with histories of CABG compared with the overall study (Goodman 2019). Absolute risk reduction was most pronounced among patients with CABG before ACS compared with patients who were surgically revascularized for ACS. Additional trials investigating the benefits of PCSK9 inhibitors on SVG function and outcomes after CABG are under way.

Hypertension Management

Hypertension is a common chronic condition in patients before and after CABG and an important independent risk factor for ischemic cardiovascular events. Few clinical trials have specifically assessed blood pressure and antihypertensive selection of patients who have undergone CABG. The 2017 AHA guidelines for the management of high blood pressure in adults recommend antihypertensive medications for secondary prevention of recurrent ischemic events in patients with clinical ASCVD and an average systolic blood pressure greater than or equal to 130 mm Hg or an average diastolic blood pressure greater than or equal to 80 mm Hg (Whelton 2018).

Antihypertensive medications should be chosen similarly as they are chosen for patients who have not had CABGs, with an emphasis on compelling indications (Figure 4). There are high incidences of diabetes mellitus, chronic kidney disease, systolic heart failure, and recent myocardial infarctions in patients who receive CABGs, and medications for such patients should be selected based on established benefits when those comorbidities are present. Beta-blockers should be administered as soon as possible after CABG to reduce the risk of POAF (Class I, LOE A); they may also help facilitate blood pressure control (Kulik 2015). The benefits of routine beta-blocker therapy beyond the duration needed for POAF suppression or treatment are questionable because no clinical benefit was found after 2 years of treatment with metoprolol post CABG (Sjöland 1995). If blood pressure is not controlled in the perioperative period after CABG—despite indicated medications—it is reasonable to add a calcium channel blocker or a diuretic agent as an additional therapeutic choice (Class IIa, LOE B) (Whelton 2018). Despite their known benefits in SCAD, ACEI treatment

was associated with significantly higher incidences of the composite outcomes of cardiovascular death, cardiac arrest, nonfatal myocardial infarction, unstable angina or heart failure requiring hospitalization, and stroke in the first 3 months after CABG (Rouleau 2008). Furthermore, the primary composite end point and drug-related adverse events were significantly higher in the first 3 months after CABG with ACEI treatment. It is notable that this study excluded patients with compelling indications for ACEI therapy. Guidelines discourage routine ACEI therapy early after CABG among patients without histories of recent myocardial infarction, left

Practice Points

- CABG is an important revascularization strategy associated with improved mortality for patients with complex CAD, diabetes, and HFrEF compared with PCI or medical therapy alone
- Mitigation of the short- and long-term complications of CABG further enhances the reduction of morbidity and mortality with regard to CABG
- Initiation or cessation of certain medications in the preoperative and postoperative periods can significantly diminish the risks of several CABG complications
- Aspirin should be started at the time of CAD diagnosis and continued up to the day of surgery so as to reduce the risk of periprocedural ischemic events and death
- P2Y12 antagonists should be either empirically held for their respective durations or guided by platelet function testing
- Oral and parenteral anticoagulation should be held for their respective durations or reversed in the setting of emergency CABG
- Beta-blockers should be initiated in all patients who can tolerate treatment before CABG so as to reduce the risk of POAF
- Statins should be started at the time of CAD diagnosis and continued up to the day of surgery
- The risks associated with RAAS inhibitors before surgery are controversial, but given the possible increase in vasoplegia and death in the setting of no known benefit, holding therapy for 24 hours before surgery is reasonable
- Perioperative antibiotic prophylaxis, ideally with cefazolin, should be properly timed before surgery, redosed as needed intraoperatively, and continued for 24 hours after CABG
- Perioperative hyperglycemia is associated with a multitude of CABG-related complications and should be controlled with intravenous insulin to a target blood glucose of less than 180 mg/dL
- Patients can experience hemodynamic compromise that is cardiogenic or vasoplegic in origin. Vasoactive pharmacotherapy should be tailored to a patient's specific hemodynamic profile and patient-specific circumstances
- Aspirin should be resumed as soon as safe after CABG, ideally within 6 hours of surgery
- DAPT is indicated for 1 year in patients with OPCAB and recent ACS leading to CABG
- Hypertension and hyperlipidemia adversely affect long-term outcomes after CABG. Manage secondary risk factors with the guidance of established hypertension and hyperlipidemia guidelines
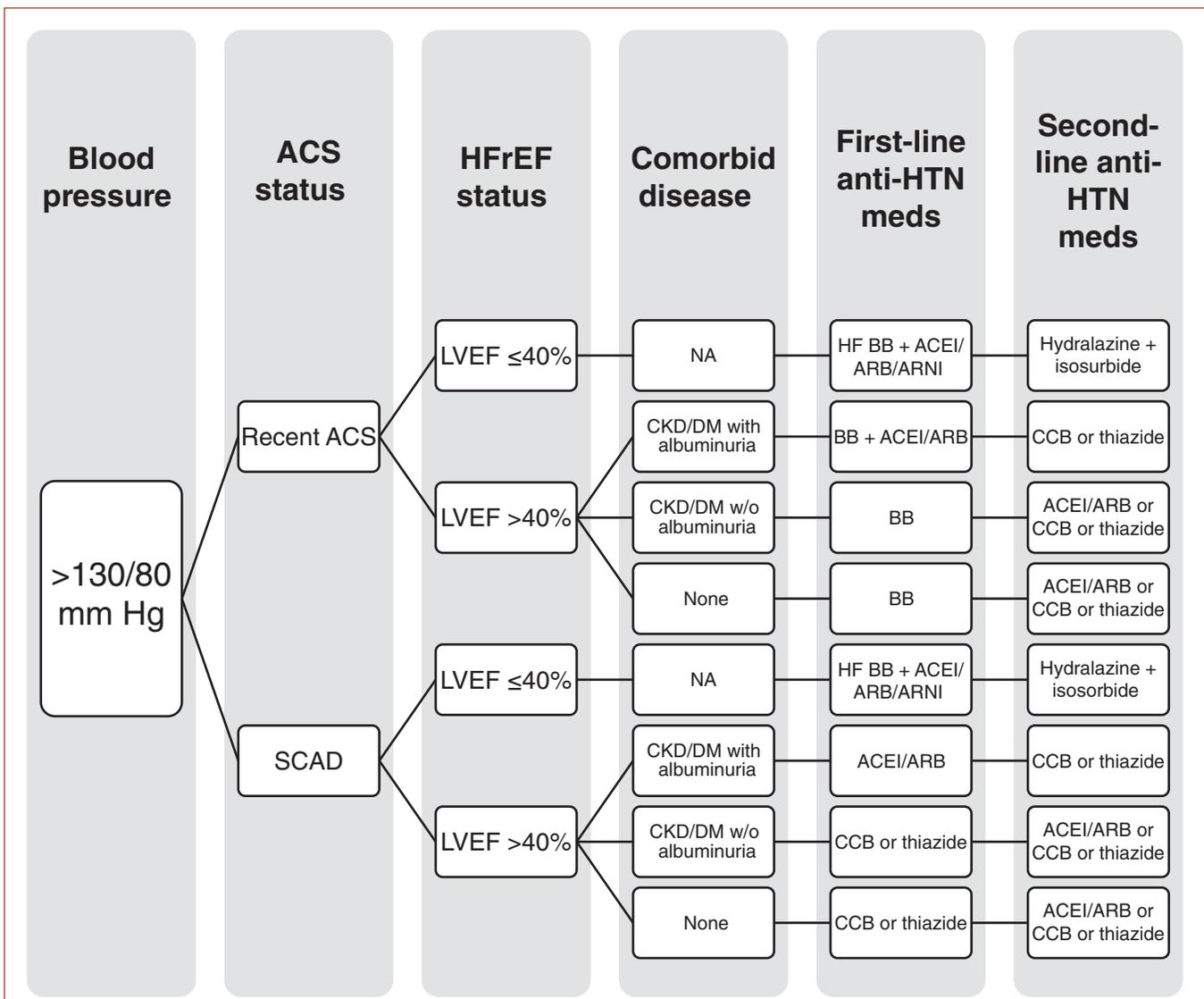
Figure 4. Antihypertensive selection after CABG.

Blood pressure	ACS status	HFrEF status	Comorbid disease	First-line anti-HTN meds	Second-line anti-HTN meds
>130/80 mm Hg	Recent ACS	LVEF ≤40%	NA	HF BB + ACEI/ARB/ARNI	Hydralazine + isosurbide
		LVEF >40%	CKD/DM with albuminuria	BB + ACEI/ARB	CCB or thiazide
			CKD/DM w/o albuminuria	BB	ACEI/ARB or CCB or thiazide
			None	BB	ACEI/ARB or CCB or thiazide
	SCAD	LVEF ≤40%	NA	HF BB + ACEI/ARB/ARNI	Hydralazine + isosorbide
		LVEF >40%	CKD/DM with albuminuria	ACEI/ARB	CCB or thiazide
			CKD/DM w/o albuminuria	CCB or thiazide	ACEI/ARB or CCB or thiazide
			None	CCB or thiazide	ACEI/ARB or CCB or thiazide

ACEI = ACE inhibitor; ACS = acute coronary syndrome; ARB = angiotensin receptor blocker; ARNI = *angiotensin receptor neprilysin inhibitor*; BB = beta-blocker; CABG = coronary artery bypass graft; CCB = calcium channel blocker; CKD = chronic kidney disease; DM = diabetes mellitus; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; LVEF = left ventricular ejection fraction; NA = not applicable; SCAD = stable coronary artery disease.

Information from: Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2018;138:e484-e594; Kulik A, Ruel M, Jneid H, et al. Secondary prevention after coronary artery bypass graft surgery: a scientific statement from the American Heart Association. Circulation 2015;131:927-64.

ventricular dysfunction, diabetes mellitus, or chronic kidney disease (Class III, LOE B) (Kulik 2015).

CONCLUSION

Surgical revascularization with CABG remains an important strategy to improve morbidity and mortality in patients with complex CAD—particularly in patients with diabetes mellitus or HF. CABG outcomes continue to improve based on advancements in patient selection, surgical techniques, and perioperative care. Preoperative and postoperative medication management can significantly influence the benefits—and the complications—associated with CABG. As the medication experts, clinical pharmacists on multidisciplinary teams are positioned to optimize care by recommending the introduction, continuation, holding, or modification of

individual elements of a therapy plan throughout the perioperative period. In addition, long-term outcomes are greatly influenced by effective secondary-prevention strategies for ASCVD.

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Self-Assessment Questions

Questions 1 and 2 pertain to the following case

L.L., a 53-year-old man with a new diagnosis of HFrEF, undergoes a routine ischemic evaluation with an elective angiogram. His medical history includes hypertension, paroxysmal atrial fibrillation (on warfarin with an INR goal of 2–3), gout, and anxiety. Angiography shows severe three-vessel disease that includes the left main coronary artery (LMCA). L.L. has good conduit targets, and elective coronary artery bypass graft (CABG) is scheduled in 2 weeks.

1. Which one of the following is best to recommend for aspirin initiation before L.L.'s surgery?

    A. Do not start until after surgery.
    B. Initiate immediately, then hold at least 5 days before surgery.
    C. Initiate the day before CABG and continue through surgery.
    D. Initiate immediately and continue through surgery.

2. Which one of the following is the most appropriate aspirin dose to recommend for L.L.?

    A. 81 mg daily
    B. 81 mg daily and check aspirin sensitivity; if resistant, increase to 325 mg daily
    C. 81 mg enteric coated tablet daily
    D. 325 mg daily

3. A 60-year-old man has a medical history of type 2 diabetes mellitus, hypertension, hyperlipidemia, and gout. He presents to an outside hospital without percutaneous coronary intervention (PCI) capabilities with chest pain and is diagnosed with NSTEMI. He is treated with aspirin 325 mg, prasugrel 60 mg, and heparin 4000 units, then transferred to a PCI-capable center. Angiography reveals a 70% stenosis in the LMCA and an 80% stenosis in the proximal left anterior descending artery. His calculated SYNTAX score is 33. The patient is hemodynamically stable and is now chest pain free. His PCI is not performed with a plan for surgical revascularization with CABG. Because the patient presented with NSTEMI, the surgeon is concerned about delaying CABG for longer than necessary. Which one of the following is best to recommend to safely reduce the duration of prasugrel holding before this patient's surgery?

    A. Transfuse one 6-pack of platelets and perform the surgery in 2 hours.
    B. Perform daily platelet function testing to determine optimal surgery timing.
    C. Give 0.4 mg/kg of desmopressin and perform the surgery in 2 hours.
    D. Continue with surgery without regard to last prasugrel dose administration.

4. Which one of the following patients is most likely to benefit from parenteral anticoagulation bridging when oral anticoagulation is held before CABG?

    A. 48-year-old man with a medical history of a single unprovoked, lower extremity deep vein thrombosis 2 years ago treated with rivaroxaban indefinitely
    B. 67-year-old man with a medical history of hypertension, type 2 diabetes mellitus and non-valvular atrial fibrillation treated with warfarin for stroke prevention
    C. 63-year-old woman with a medical history of type 2 diabetes mellitus and bicuspid aortic value status post bi-leaflet mechanical aortic valve replacement 10 years ago treated with warfarin
    D. 56-year-old man with a medical history of type 2 diabetes mellitus, paroxysmal atrial fibrillation, and severe mitral stenosis treated with warfarin for stroke prevention.

5. A 69-year-old woman has a medical history of type 2 diabetes mellitus, non-valvular atrial fibrillation, transient ischemic attack (6 years ago), and hypertension. She is scheduled for elective CABG in 5 days. Her liver panel is normal and her CrCl is 70 mL/min. The patient is anticoagulated with rivaroxaban 20 mg daily with her largest meal (lunch). She is not taking any medications that may reduce the metabolism or excretion of rivaroxaban. Which one of the following is best to recommend for reversing this patient's anticoagulation before surgery?

    A. Hold rivaroxaban for 48 hours before incision. Do not bridge with parenteral anticoagulation.
    B. Hold rivaroxaban for 48 hours before incision. Start a therapeutic heparin infusion 24 hours after the last rivaroxaban dose and stop the infusion 4 hours before incision.
    C. Hold rivaroxaban 24 hours before incision. Do not bridge with parenteral anticoagulation.
    D. Continue rivaroxaban until the day the day of surgery. Infuse andexanet alpha starting 3 hours before incision to reverse the anticoagulation before surgery.

Questions 6 and 7 pertain to the following case

L.M. is a 48-year-old man (weight 125 kg) with a medical history of hypertension, stage 3 chronic kidney disease, general anxiety disorder, gout, and stable coronary artery disease (SCAD) (diagnosed 3 weeks ago). He is admitted at 0800 with a plan for elective on-pump CABG at 1300 the next day. He has no known medication allergies. Current home drugs are allopurinol 150 mg daily, aspirin 81 mg daily, amlodipine 5 mg

daily, lisinopril 20 mg daily, metoprolol tartrate 25 mg twice daily, and sertraline 100 mg daily. L.M.'s blood pressure is stable with MAPs in the 70s-80s. The PCR from his nares swab is positive for methicillin-susceptible *Staphylococcus aureus*.

6. Which one of the following is best to recommend for L.M. before CABG?

   A. Hold amlodipine 48 hours before surgery to avoid postoperative vasoplegia syndrome.
   B. Hold lisinopril 24 hours before surgery to avoid postoperative vasoplegia syndrome.
   C. Hold metoprolol the night before surgery to avoid postoperative low cardiac output syndrome.
   D. Initiate amiodarone 200 mg twice daily immediately for postoperative atrial fibrillation (POAF) prophylaxis.

7. Which one of the following is best to recommend as a perioperative antibiotic regimen for L.M.?

   A. Cefazolin 2 g fully administered less than 60 minutes before incision and continued for 24 hours post-op
   B. Cefazolin 3 g fully administered less than 120 minutes before incision and continued for 48 hours post-op
   C. Cefazolin 3 g fully administered less than 60 minutes before incision and continued for 24 hours post-op
   D. Vancomycin 15 mg/kg fully administered less than 60 minutes before incision and continued for 24 hours post-op

Questions 8 and 9 pertain to the following case.

B.B. is a 59-year-old woman with a history of insulin dependent type 2 diabetes mellitus, chronic kidney disease Stage 1, CAD, atrial fibrillation, and hyperlipidemia; she is admitted for elective CABG. Current medications include aspirin 162 mg daily, atorvastatin 80 mg daily, insulin glargine 20 units daily in morning with insulin aspart sliding scale for QID blood glucose corrections, lisinopril 10 mg daily, and metformin 1000 mg twice daily. B.B. undergoes an uncomplicated, three-vessel coronary bypass with 162 minutes of cardiopulmonary bypass (CPB) time. She is transferred to the ICU intubated and on phenylephrine 40 mcg/min. With extubation anticipated shortly, a feeding tube is not placed. Upon arriving to the ICU, B.B.'s first two blood glucoses are 187 mg/dL and 231 mg/dL, respectively.

8. Which one of the following is the most appropriate perioperative blood glucose target for B.B.?

   A. 80-120 mg/dL
   B. 100-140 mg/dL
   C. 140-180 mg/dL
   D. 160-220 mg/dL

9. Which one of the following is best to recommend to manage B.B.'s postoperative hyperglycemia?

   A. Hold insulin glargine because the patient is NPO with no feeding tube and correct elevated blood glucose levels with sliding scale insulin aspart alone.
   B. Give half dose insulin glargine (10 units) now because the patient is NPO and continue insulin aspart sliding scale.
   C. Resume PTA insulin glargine 20 units now because the patient is hyperglycemic and continue insulin aspart sliding scale.
   D. Hold all PTA insulin and start a nursing managed IV insulin protocol titrated to the desired blood glucose range.

10. A 75-year-old man is undergoing urgent redo CABG complicated by intraoperative bleeding and a prolonged CPB time. He is admitted to the ICU hypotensive (MAPs 45–55 mm Hg) on norepinephrine 20 mcg/min, vasopressin 0.04 units/min, phenylephrine 300 mcg/min, and epinephrine 15 mcg/min. The patient's peripheral extremities are warm to the touch; his lactate is 6 mmol/L and urine output is 20 mL/hr. He was volume resuscitated and is afebrile. His pH is 7.3, ionized Ca of 1.2 mmol/L, and Hgb is 8.7 g/dL. Which one of the following is best to recommend to achieve a target MAP greater than 65 mm Hg in this patient?

    A. Dobutamine 5 mcg/kg/min
    B. Methylene blue 1–2 mg/kg every 4-6 hours
    C. 2 units of packed red blood cells
    D. Angiotensin II at 10 mcg/min and titrate to a target MAP of 65 mm Hg

11. A 66-year-old woman (weight 82 kg) has a medical history of hypertension, HFrEF (EF = 30%), SCAD, tobacco use, and moderate COPD. She undergoes two-vessel CABG complicated by hemorrhage requiring 20 units of packed red blood cells. Despite adequate resuscitation, the patient remains hypotensive. Intraoperative TEE shows a severely dilated right ventricle and an LVEF of 30%. The patient is cold and anuric. Notable labs are a pH of 7.33, ionized Ca 1.17 mmol/L, and SCr of 2.3 mg/dL (baseline 0.8 mg/dL). Continuous renal replacement therapy is initiated. Empiric dobutamine 5 mcg/kg/min was started and Swan-Ganz catheter is placed 1 hour after the start of the infusion for presumed cardiogenic shock. Initial cardiopulmonary hemodynamics suggest right ventricular dysfunction (RA 22 mm Hg [normal 1–8 mm Hg] and PCWP 12 mm Hg [normal 8-12 mm Hg]) with pulmonary hypertension (mean pulmonary artery 40 mm Hg [normal 10–20 mm Hg]). The patient's cardiac index is 1.8 L/min/m^2 (normal 2.5–4 L/min/m^2) and SVR is 1650 dynes · sec/cm^{-5} (normal 900–1300 dynes · sec/cm^{-5}). Her MAPs are 58-62 mm Hg and HR is 120s in normal

sinus rhythm. The patient shows no signs of any active bleeding. Which one of the following is best to recommend adding to improve this patient's hemodynamics?

A. Inhaled epoprostenol 50 ng/kg/min
B. Inhaled nitric oxide at 40 ppm
C. Milrinone 0.5 mcg/kg/min
D. Phenylephrine titrated to a MAP of 65 mm Hg

Questions 12–15 pertain to the following case

A.K. is a 61-year-old man with a medical history of hypertension, hyperlipidemia, type 2 diabetes mellitus, ischemic stroke, and HFrEF (EF = 30%). He undergoes elective three-vessel on-pump CABG for SCAD. Upon returning to the ICU, A.K. is hemodynamically stable on no vasoactive drugs, extubated, and his hyperglycemia is managed by an insulin infusion. Estimated blood loss from the surgery was 450 mL and his current chest tube output is 20 mL/hr and decreasing. Other pertinent medications are metoprolol tartrate 25 mg three times a day, atorvastatin 20 mg daily, and heparin 5000 units subcutaneously every 8 hours.

12. Which one of the following is the best time to resume aspirin after CABG for A.K.?

A. Within 6 hours of surgery
B. Within 24 hours of surgery
C. Within 48 hours of surgery
D. Upon hospital discharge

13. There is no longer any chest tube output and A.K. is able to tolerate oral medications. Which one of the following is best antiplatelet regimen to recommend for in A.K. after CABG?

A. Aspirin 81 mg and clopidogrel 75 mg daily for 1 year then aspirin 81 mg indefinitely
B. Aspirin 325 mg and ticagrelor 90 mg twice daily for 1 year then aspirin 325 mg indefinitely
C. Aspirin 325 mg daily indefinitely
D. Ticagrelor 90 mg twice daily indefinitely

14. On postoperative day 4, A.K. is hypertensive with MAPs consistently in the 90s. His chest tubes were removed and his pain control is 2/10. He passed his swallow evaluation. Pertinent labs include SCr 0.89 mg/dL and potassium 4.0 mEq/L. Urine output is 150 mL/hr. Heart rate is 84 beats per minute and A.K. has not had any POAF. His post-op TTE showed an EF of 35%. Which one of the following is best to recommend to optimize A.K.'s blood pressure control?

A. Discontinue metoprolol tartrate because it is not an effective antihypertensive and he is beyond the high risk per period for POAF (first 48 hours). Start lisinopril 5 mg daily.

B. Change metoprolol tartrate to carvedilol 6.25 mg twice daily for better blood pressure control and HFrEF. Avoid ACE inhibitors or ARBs for at least 3 months after surgery because of their association with worse outcomes after CABG.
C. Continue metoprolol 25 mg three times a day for HFrEF management and POAF prevention. Add amlodipine 5 mg daily to achieve blood pressure goal of less than 130/80 mm Hg.
D. Change metoprolol tartrate to metoprolol succinate 75 mg daily and start lisinopril 5 mg daily for blood pressure control and HFrEF management.

15. A.K.'s preoperative lipid panel included a TC of 245 mg/dL, LDL-C 105 mg/dL, HDL-C 30 mg/dL, and serum triglycerides of 180 mg/dL after taking atorvastatin 20 mg for 3 months and watching his diet. He previously took pravastatin 20 mg daily and was switched to atorvastatin 20 mg daily at the time of his CAD diagnosis. The multidisciplinary team is looking to optimize his management of hyperlipidemia. Which one of the following is best to recommend to improve A.K.'s hypercholesterolemia and reduce ASCVD risk?

A. Continue atorvastatin 20 mg daily because high-intensity statin dosing is associated with adverse drug events in the perioperative CABG period. Repeat lipid panel at the first follow-up visit after discharge with plans to increase to 40 mg daily if LDL remains greater than 100 mg/dL.
B. Increase atorvastatin to 80 mg daily to maximize LDL reduction with statin therapy. Recheck lipid panel in 1–3 months to determine if addition anti-lipidemic therapies are indicated.
C. Add ezetimibe 10 mg daily because the patient meets criteria for very-high risk ASCVD and the IMPROVE-IT trial found benefit in CABG patients treated with moderate dose statin.
D. Increase atorvastatin to 80 mg daily and add alirocumab 75 mg subcutaneously every 2 weeks because he meets criteria for very high-risk ASCVD and it has shown to improve MACE in patients with a history of CABG.