Perioperative Management to Reduce Cardiovascular Events

Nathaniel R. Smilowitz, MD; Jeffrey S. Berger, MD, MS

Case Presentation: A 75-year-old man with hypertension and a history of stable coronary artery disease (CAD) presents to your office 1 month before an elective total knee replacement. He states that he underwent percutaneous coronary intervention (PCI) with a drug-eluting stent (DES) to his left anterior descending coronary artery 2 years ago. His medication regimen includes daily aspirin 81, clopidogrel 75 mg, amlodipine 10 mg, lisinopril 5 mg, and atorvastatin 40 mg. He does not smoke cigarettes. Recent laboratory data reveal normal renal function. He asks what he can do to reduce the cardiovascular risks of noncardiac surgery.

The Clinical Problem

Perioperative cardiovascular complications are a source of morbidity and mortality for >200 million patients worldwide who undergo noncardiac surgery each year. In large cohorts and randomized trials, perioperative myocardial infarction (MI) occurs in up to 6.2% of surgeries.[1–4]

Pathogenesis of Perioperative Cardiovascular Events

The pathogenesis of cardiovascular events in the postoperative period is complex (Figure). Induction of anesthesia, surgical trauma, bleeding, anemia, hypoxia, and postoperative pain lead to surges in catecholamines, cortisol production, and a hypercoaguable state. Inflammatory cytokines, including tumor necrosis factor-α, interleukin-1, interleukin-6, and C-reactive protein, rise in the postoperative period. Increased platelet activation contributes to the thrombotic milieu.[5] Tachycardia and elevations in blood pressure increase coronary artery sheer stress and can precipitate coronary plaque destabilization, plaque rupture, coronary thrombosis, and type 1 MI. Postoperative myocardial necrosis and infarction may also be caused by imbalances in myocardial oxygen supply and demand from tachycardia, hypotension, hypoxia, or anemia in the setting of stable CAD (type 2 MI). Microvascular coronary disease, endothelial dysfunction, and excess activation of inflammatory pathways may be contributing mechanisms but require further study.

Methods of Risk Stratification

Systematic evaluation of perioperative cardiovascular risk is recommended before noncardiac surgery. Risk prediction models provide quantitative estimates of risk (Table 1). Current American Heart Association/American College of Cardiology guidelines recommend preoperative noninvasive risk stratification to evaluate for myocardial ischemia in patients with poor functional capacity and an elevated risk for noncardiac surgery, because abnormal myocardial perfusion imaging and stress echocardiography are powerful predictors of postoperative cardiovascular events.[6] Noninvasive anatomic testing with coronary computed tomographic angiography before noncardiac surgery is a promising approach that requires further study.

Perioperative Medical Therapy

Aspirin

Aspirin is a potent, irreversible inhibitor of cyclooxygenase-1 that blocks thromboxane A2 production, prevents platelet aggregation, and mitigates thrombotic risks at a cost of increased bleeding. Although aspirin has a clear role in the secondary prevention of vascular disease, uncertainty regarding

From Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, NY (N.R.S., J.S.B.); Division of Hematology, Department of Medicine, New York University School of Medicine, New York, NY (J.S.B.); and Division of Vascular Surgery, Department of Surgery, New York University School of Medicine, New York, NY (J.S.B.).

Correspondence to Jeffrey S. Berger, MD, MS, FAHA, FACC, Associate Professor of Medicine and Surgery Director of Cardiovascular Thrombosis, Director of Research, Venous Thromboembolic Center, Marc and Ruti Bell Program in Vascular Biology, New York University School of Medicine, 530 First Ave, Skirball 9R, New York, NY 10016. E-mail jeffrey.berger@nyumc.org

(*Circulation.* 2016;133:1125-1130. DOI: 10.1161/CIRCULATIONAHA.115.017787.)

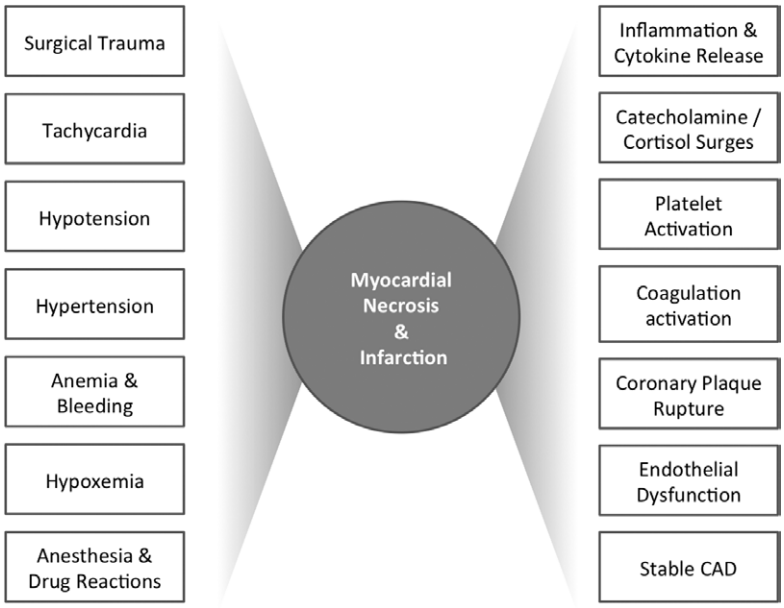

Figure. Pathogenesis of perioperative cardiovascular events. Multiple perioperative events and cardiovascular factors may contribute to the development of myocardial necrosis and infarction. CAD indicates coronary artery disease.

the efficacy and safety of perioperative aspirin use prompted the second Perioperative Ischemic Evaluation (POISE-2) trial, which randomly assigned 10 010 patients at risk for vascular complications to either perioperative aspirin or placebo before noncardiac surgery.[3] At 30 days, there was no difference in death or nonfatal MI (7.0% versus 7.1%, *P*=0.92), but aspirin use was associated with excess of major bleeding (4.6% versus 3.8%, *P*=0.04). No benefit of aspirin was observed in any prespecified subgroup analyses, regardless of Revised Cardiac Risk Index (RCRI) score or aspirin use before randomization.[3] However, fewer than a quarter of the patients in POISE-2 had a history of CAD, only 4.7% had a history of PCI, and only 1.2% had DES, raising questions about whether patients had sufficient perioperative risk to demonstrate a benefit of perioperative aspirin. Although POISE-2 trial results do not support routine perioperative aspirin initiation, there is insufficient evidence to conclude whether perioperative aspirin cessation is safe in patients with previous coronary stent implantation. Thus, individualized risks of thrombotic complications and perioperative bleeding must be considered when formulating a treatment strategy in certain high-risk groups.

Statins and Lipid-Lowering Therapy

Lipid lowering with statin therapy is a promising approach to reduce perioperative cardiovascular events. A retrospective, propensity-matched analysis of 204 885 patients undergoing noncardiac surgery demonstrated that patients prescribed lipid-lowering agents in the first 2 days of hospitalization had a significantly reduced in-hospital mortality (adjusted odds ratio, 0.62; 95% confidence interval, 0.58–0.67).[7] A meta-analysis of randomized, controlled trials and observational studies in vascular surgery, including the controversial Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo III (DECREASE III) study by Poldermans and colleagues[8] in which perioperative fluvastatin was associated with a 53% reduction in death or MI, reported that perioperative statin use was associated with a significant reduction in the composite of MI, stroke, and death (odds ratio, 0.45; 95% confidence interval, 0.29–0.70).[9] In contrast, a 2013 Cochrane review of randomized, controlled trials of statins in unselected noncardiac surgery that excluded studies by Poldermans reported insufficient evidence to conclude that perioperative statins reduce adverse cardiovascular events.[10] Based on available clinical trial data, clinically indicated statins should be continued in the perioperative period of noncardiac surgery. Initiation of statin therapy before surgery should be considered for patients undergoing vascular surgery (class IIa, level of evidence [LOE] B), and may be considered for other patients with indications for lipid-lowering therapy and elevated surgical risks (class IIb, LOE C).[6]

β-Blockers

β-Blockers prolong coronary diastolic filling time, decrease myocardial wall stress, mitigate myocardial oxygen supply-demand mismatch, and can prevent MI. The POISE trial, the largest trial of perioperative β-blockade to date, randomly assigned 8351 patients to extended-release metoprolol succinate 100 mg or placebo within 2 to 4 hours before noncardiac surgery, with continuation of therapy (with a metoprolol dose of 100–200 mg/d or placebo) for 30 days.[2] Although fewer patients in the group randomly assigned to metoprolol had nonfatal MI, nonfatal cardiac arrest, or cardiovascular death (5.8% versus 6.9%, *P*=0.039), β-blocker therapy was associated with a higher incidence of all-cause mortality (3.1% versus 2.3%, *P*=0.0317) and stroke (1.0% versus 0.5%, *P*=0.0053), raising safety concerns.[2] Only 43% of patients enrolled in POISE had a history of CAD, and <20% had ≥3 preoperative RCRI risk factors. Indeed, in retrospective cohort studies of patients undergoing major noncardiac surgery, perioperative β-blocker therapy was associated with reduced in-hospital mortality among high-risk (RCRI ≥2), but not low-risk patients.[11] In addition, all subjects in POISE began the

Table 1. Comparison of Perioperative Risk Calculators

	Goldman Index of Cardiac Risk (1977)	Revised Cardiac Risk Index (1999)	NSQIP Perioperative MI and Cardiac Arrest (MICA) Risk Calculator (2011)	NSQIP Universal Surgical Risk Calculator (2013)
Criteria	• Jugular venous distention or a third heart sound on auscultation • Recent MI within 6 mo • ≥5 PVCs per min • Nonsinus cardiac rhythm or PACs on preoperative ECG • Age >70 • Aortic stenosis • Intraperitoneal, intrathoracic, or aortic surgery • Any emergency surgery	• Cerebrovascular disease • Ischemic heart disease • History of congestive heart failure • Insulin therapy for diabetes mellitus • Serum creatinine ≥2.0 mg/dL • Planned high-risk procedure (intraperitoneal, intrathoracic, or vascular surgery)	• Age • ASA class • Creatinine • Preoperative function • Procedure type (anorectal surgery, aortic, bariatric, brain, breast, cardiac, ENT, foregut/hepato-pancreatobiliary, gallbladder/appendix/adrenal/spleen, intestinal, neck, obstetric/gynecologic, orthopedic, other abdomen, peripheral vascular, skin, spine, thoracic, urology, vein)	• Age group, y • Sex • Functional status • Emergency case • ASA class • Steroid use for chronic condition • Ascites within 30 d preoperatively • System sepsis within 48 h preoperatively • Ventilator dependent • Disseminated cancer • Diabetes mellitus • Hypertension requiring medication • Previous cardiac event • Congestive heart failure in 30 d preoperatively • Dyspnea • Current smoker within 1 y • History of COPD • Dialysis • Acute renal failure • BMI class • CPT-specific linear risk
Outcome	Intraoperative/postoperative MI, pulmonary edema, VT, cardiac death	MI, pulmonary edema, ventricular fibrillation, complete heart block, cardiac death	Intraoperative/postoperative MI or cardiac arrest within 30 d	Cardiac arrest, MI, all-cause mortality within 30 d
Derivation set ROC	0.61	0.76	0.88	0.90 (cardiac arrest or MI) 0.94 (mortality)
Validation set ROC	0.701	0.806	0.874	Not reported

ASA indicates American Society of Anesthesiologists; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CPT, Current Procedural Terminology; ENT, ear nose and throat; MI, myocardial infarction; NSQIP, National Surgical Quality Improvement Program; ROC, area under the receiver operating characteristic curve (C statistic); PAC, premature atrial contractions; PVC, premature ventricular contraction; and VT, ventricular tachycardia.

study drug within 1 day of surgery, but studies suggest that longer durations of β-blocker administration before surgery are associated with improved outcomes.[12]

In summary, the utility of perioperative β-blocker therapy remains questionable. Patients prescribed outpatient β-blockers should continue therapy in the perioperative period (class I, LOE B) in the absence of bradycardia or hypotension.[6] Patients with known ischemic heart disease at a high risk for perioperative MI, or those with ≥3 RCRI risk factors, may warrant initiation of β-blockers before surgery (class IIb, LOE B). However, β-blocker therapy should not be started on the day of surgery, a recommendation endorsed by current guidelines.[6] The optimal timing of initiation and dose of perioperative β-blockade is uncertain, and prospective trials are necessary. However, it is reasonable to begin therapy >1 week before surgery to determine safety and tolerability, and even longer preoperative durations may be preferable.

Venous Thromboembolism Prophylaxis

Venous thromboembolism (VTE) is a significant adverse event following major orthopedic surgery. In addition to early mobilization and mechanical VTE prophylaxis in the postoperative period, a number of pharmacological agents have been studied, including aspirin, warfarin, unfractionated heparin, low-molecular weight heparins, fondaparinux, and new oral direct thrombin and factor Xa inhibitors, dabigatran, rivaroxaban, apixaban, and edoxaban. Guidelines from 2012 endorse the use of any of these agents for VTE prophylaxis after orthopedic surgery (grade 1B), but recommend low-molecular weight heparins in preference to other alternatives (grade 2B/C).[13] In the Pulmonary Embolism Prevention (PEP) trial, which randomly assigned 17 444 patients undergoing hip surgery to 35 days of aspirin or placebo, perioperative aspirin reduced the risk of postoperative VTE by 34% (17%–47%, P=0.0003).[14] Although aspirin was beneficial in comparison with placebo, there are few data comparing aspirin with anticoagulation. A meta-analysis (16 trials, n=38 747) comparing the new oral anticoagulants

versus enoxaparin for VTE prophylaxis after total hip or knee replacement demonstrated a 35% significant reduction in symptomatic VTE with no significant difference in clinically relevant bleeding or net clinical benefit.[15]

Patients With Coronary Artery Disease

Coronary artery disease complicates the care of patients who require noncardiac surgery. Routine perioperative coronary angiography and prophylactic revascularization are not recommended before noncardiac surgery in contemporary guidelines because of an absence of benefit.[6] The Coronary Artery Revascularization Prophylaxis (CARP) trial compared coronary revascularization with a strategy of medical management in 510 patients with significant CAD who were scheduled to undergo nonurgent vascular surgery.[16] In CARP, 59% of patients randomly assigned to revascularization underwent PCI with early generations of bare metal stents, and 41% underwent coronary bypass surgery. The median delay to noncardiac surgery was 36 days. There were no differences in 30-day (3.1% versus 3.4%, P=0.87) and long-term (22% versus 23%, P=0.92) mortality after 2.7 years of follow-up. The CARP trial excluded patients with left main disease or severely reduced ejection fraction, and the effect of preoperative revascularization before noncardiac surgery in these populations is uncertain.

For patients with recent PCI, the timing of noncardiac surgery also remains controversial. Surgery following placement of a coronary stent is associated with increased adverse cardiac events because of the prothrombotic and inflammatory effects of surgery combined with premature cessation of antiplatelet therapy. Risks are highest when surgery is performed within 4 to 6 weeks of a coronary intervention, and recent guidelines recommend delaying elective surgery by ≥30 days after placement of a bare metal stents or ≥1 year for DES (class I, LOE B) based on early studies.[17] A large retrospective cohort study of Veterans Affairs patients undergoing noncardiac surgery within 2 years of a coronary stent demonstrated stable rates of cardiovascular events if surgery was performed at least 6 months after PCI.[18] In this analysis, perioperative cardiovascular risk was similar across stent type (DES versus bare metal stents) but was higher in patients with PCI for recent MI versus those with revascularization for stable CAD.[18] Based on these and other data,[18,19] elective noncardiac surgery may be considered ≥180 days after uncomplicated elective PCI with DES, if the risk of further surgical delay is greater than the risks of ischemic complications (class IIb, LOE B).[6] However, additional prospective studies are necessary to determine optimal antiplatelet management strategies for patients with recent DES who need elective noncardiac surgery but cannot wait the recommended minimum 1-year delay.

Perioperative management of antiplatelet therapy after PCI is another common challenge. Clinical practice guidelines recommend continuation of aspirin monotherapy after PCI in the perioperative period, although this is largely based on expert opinion. In contrast, perioperative continuation of dual-antiplatelet therapy with aspirin and a $P2Y_{12}$ inhibitor is associated with a substantial increase in moderate and severe bleeding.[20] The timing of withdrawal of $P2Y_{12}$ inhibitor therapy must be tailored to the pharmacokinetic and pharmacodynamic properties of each drug. Clopidogrel and ticagrelor should be discontinued ≥5 days before surgery, and prasugrel should be held for ≥7 days. Continuation of dual-antiplatelet therapy can be considered for patients with the highest risks of perioperative thrombotic events or those with minimal surgery-specific risks of bleeding. Clinical trials investigating the use of perioperative platelet activity testing and short-acting intravenous antiplatelet agents are needed in certain high-risk patients.

Novel Approaches to Risk Reduction

Efforts are currently underway to identify novel approaches to reduce perioperative cardiovascular events in high-risk patients and to manage patients who develop postoperative myocardial injury. Intensive medical management with high-intensity statin therapy before noncardiac surgery is

Table 2. Strategies to Prevent and Manage Perioperative Cardiovascular Events Under Investigation

Prevention of perioperative cardiovascular events:	
High-intensity statin	Lowering the Risk of Operative Complications Using Atorvastatin Loading Dose (LOAD; NCT01543555)
Ranolazine	Pathophysiology and Prevention of Perioperative Myocardial Injury (NCT01810796)
Ischemic preconditioning	Preconditioning Shields Against Vascular Events in Surgery (SAVES; NCT01691911) Prevention of Myocardial Injury in Non-cardiac Surgery (PIXIE; NCT02344797)
Combination therapy (ACEi, β-blocker, statin)	Optimization of Pre-surgical Testing With an Intensive Multifactorial Intervention to Minimize Cardiovascular Events in Orthopedic Surgery (OPTIMIZE-OS; NCT01837069)
Postoperative management of perioperative cardiovascular events	
Ticagrelor	Study of Ticagrelor Versus Aspirin Treatment in Patients With Myocardial Injury Post Major Non-cardiac Surgery (INTREPID; NCT02291419)
Dabigatran	Management of Myocardial Injury After Noncardiac Surgery Trial (MANAGE; NCT01661101)

ACEi indicates angiotensin-converting-enzyme inhibitor.

a particularly promising strategy to reduce cardiovascular events. Ongoing trials will refine our understanding of perioperative cardiovascular events and will determine management of myocardial injury after noncardiac surgery (Table 2).

Case Resolution

Preoperative cardiovascular risk stratification was performed. The patient had 1 RCRI risk factor, associated with a 0.9% risk of major perioperative cardiac complications; by the National Surgical Quality Improvement Program calculator he had a 0.74% risk of MI or cardiac arrest and a 0.4% risk of death. In light of the low RCRI score, β-blocker therapy was not initiated. Clopidogrel was discontinued 5 days before surgery, and aspirin and statin were continued in the perioperative period. The patient underwent an uncomplicated elective total knee replacement. On the first postoperative day, a 1-month course of low-molecular weight heparin was initiated for VTE prophylaxis. The patient was discharged home with no postoperative cardiovascular complications.

Conclusions

Prevention of perioperative cardiovascular events is an important consideration for general practitioners, cardiologists, anesthesiologists, and surgeons alike, but substantial gaps in knowledge remain. Until additional data are available, mitigation and management of perioperative cardiovascular risk requires careful, individualized assessment of cardiovascular disease and the surgery-specific thrombotic and bleeding risks.

Sources of Funding

Dr Berger was funded in part by the National Heart, Lung, and Blood Institute of the National Institutes of Health (HL114978), American Heart Association Clinical Research Program (13CRP14410042), and Doris Duke Charitable Foundation (2010055).

Disclosures

None.

References

1. Vascular Events In Noncardiac Surgery Patients Cohort Evaluation Study I, Devereaux PJ, Chan MT, Alonso-Coello P, Walsh M, Berwanger O, Villar JC, Wang CY, Garutti RI, Jacka MJ, Sigamani A, Srinathan S, Biccard BM, Chow CK, Abraham V, Tiboni M, Pettit S, Szczeklik W, Lurati Buse G, Botto F, Guyatt G, Heels-Ansdell D, Sessler DI, Thorlund K, Garg AX, Mrkobrada M, Thomas S, Rodseth RN, Pearse RM, Thabane L, McQueen MJ, VanHelder T, Bhandari M, Bosch J, Kurz A, Polanczyk C, Malaga G, Nagele P, Le Manach Y, Leuwer M, Yusuf S. Association between postoperative troponin levels and 30-day mortality among patients undergoing noncardiac surgery. *JAMA*. 2012;307:2295–2304
2. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P; POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*. 2008;371:1839–1847. doi: 10.1016/S0140-6736(08)60601-7.
3. Devereaux PJ, Mrkobrada M, Sessler DI, Leslie K, Alonso-Coello P, Kurz A, Villar JC, Sigamani A, Biccard BM, Meyhoff CS, Parlow JL, Guyatt G, Robinson A, Garg AX, Rodseth RN, Botto F, Lurati Buse G, Xavier D, Chan MT, Tiboni M, Cook D, Kumar PA, Forget P, Malaga G, Fleischmann E, Amir M, Eikelboom J, Mizera R, Torres D, Wang CY, VanHelder T, Paniagua P, Berwanger O, Srinathan S, Graham M, Pasin L, Le Manach Y, Gao P, Pogue J, Whitlock R, Lamy A, Kearon C, Baigent C, Chow C, Pettit S, Chrolavicius S, Yusuf S; POISE-2 Investigators. Aspirin in patients undergoing noncardiac surgery. *N Engl J Med*. 2014;370:1494–1503. doi: 10.1056/NEJMoa1401105.
4. Oberweis BS, Smilowitz NR, Nukala S, Rosenberg A, Xu J, Stuchin S, Iorio R, Errico T, Radford MJ, Berger JS. Relation of perioperative elevation of troponin to long-term mortality after orthopedic surgery. *Am J Cardiol*. 2015;115:1643–1648. doi: 10.1016/j.amjcard.2015.03.003.
5. Schneider GS, Rockman CB, Berger JS. Platelet activation increases in patients undergoing vascular surgery. *Thromb Res*. 2014;134:952–956. doi: 10.1016/j.thromres.2014.08.009.
6. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, Davila-Roman VG, Gerhard-Herman MD, Holly TA, Kane GC, Marine JE, Nelson MT, Spencer CC, Thompson A, Ting HH, Uretsky BF, Wijeysundera DN; American College of Cardiology; American Heart Association. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation*.2014;130:e278–e333.doi:10.1161/CIR.0000000000000106.
7. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA*. 2004;291:2092–2099. doi: 10.1001/jama.291.17.2092.
8. Schouten O, Boersma E, Hoeks SE, Benner R, van Urk H, van Sambeek MR, Verhagen HJ, Khan NA, Dunkelgrun M, Bax JJ, Poldermans D; Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. Fluvastatin and perioperative events in patients undergoing vascular surgery. *N Engl J Med*. 2009;361:980–989. doi: 10.1056/NEJMoa0808207.
9. Antoniou GA, Hajibandeh S, Hajibandeh S, Vallabhaneni SR, Brennan JA, Torella F. Meta-analysis of the effects of statins on perioperative outcomes in vascular and endovascular surgery. *J Vasc Surg*. 2015;61:519–532.e1. doi: 10.1016/j.jvs.2014.10.021.
10. Sanders RD, Nicholson A, Lewis SR, Smith AF, Alderson P. Perioperative statin therapy for improving outcomes during and after noncardiac vascular surgery. *Cochrane Database Syst Rev*. 2013;7:CD009971. doi: 10.1002/14651858.CD009971.pub2.
11. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med*. 2005;353:349–361. doi: 10.1056/NEJMoa041895.
12. Flu WJ, van Kuijk JP, Chonchol M, Winkel TA, Verhagen HJ, Bax JJ, Poldermans D. Timing of pre-operative Beta-blocker treatment in vascular surgery patients: influence on post-operative outcome. *J Am Coll Cardiol*. 2010;56:1922–1929. doi: 10.1016/j.jacc.2010.05.056.
13. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW Jr; American College of Chest Physicians. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(2 suppl):e278S–e325S. doi: 10.1378/chest.11-2404.
14. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet*. 2000;355:1295–1302.
15. Gómez-Outes A, Terleira-Fernández AI, Suárez-Gea ML, Vargas-Castrillón E. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ*. 2012;344:e3675.
16. McFalls EO, Ward HB, Moritz TE, Goldman S, Krupski WC, Littooy F, Pierpont G, Santilli S, Rapp J, Hattler B, Shunk K, Jaenicke C, Thottapurathu L, Ellis N, Reda DJ, Henderson WG. Coronary-artery revascularization before elective major vascular

surgery. *N Engl J Med*. 2004;351:2795–2804. doi: 10.1056/NEJMoa041905.
17. Wilson SH, Fasseas P, Orford JL, Lennon RJ, Horlocker T, Charnoff NE, Melby S, Berger PB. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J Am Coll Cardiol*. 2003;42:234–240.
18. Hawn MT, Graham LA, Richman JS, Itani KM, Henderson WG, Maddox TM. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. *JAMA*. 2013;310:1462–1472. doi: 10.1001/jama.2013.278787.
19. Wijeysundera DN, Wijeysundera HC, Yun L, Wąsowicz M, Beattie WS, Velianou JL, Ko DT. Risk of elective major noncardiac surgery after coronary stent insertion: a population-based study. *Circulation*. 2012;126:1355–1362. doi: 10.1161/CIRCULATIONAHA.112.102715.
20. van Kuijk JP, Flu WJ, Schouten O, Hoeks SE, Schenkeveld L, de Jaegere PP, Bax JJ, van Domburg RT, Serruys PW, Poldermans D. Timing of noncardiac surgery after coronary artery stenting with bare metal or drug-eluting stents. *Am J Cardiol*. 2009;104:1229–1234. doi: 10.1016/j.amjcard.2009.06.038.

Perioperative Management to Reduce Cardiovascular Events

Nathaniel R. Smilowitz and Jeffrey S. Berger

Circulation. 2016;133:1125-1130
doi: 10.1161/CIRCULATIONAHA.115.017787
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539