

REVIEW TOPIC OF THE WEEK

Cardiac Risk of Noncardiac Surgery

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ABSTRACT

Major perioperative cardiac events are estimated to complicate between 1.4% and 3.9% of surgeries. Because most surgeries are elective, there is the opportunity to implement strategies to reduce this risk. Accurate identification of patients at risk for such events will allow patients to be better informed about the benefit-to-risk ratio of procedures, and guide allotment of limited clinical resources, utilization of preventive interventions, and areas of future research. This review focuses on important features of the initial pre-operative clinical risk assessment, indications for diagnostic testing to quantify cardiac risk, and the methods and indications for pre-emptive therapies. (J Am Coll Cardiol 2015;66:2140-8)
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More than 50 million surgical procedures are performed annually in the United States (1). Pooled analyses estimate that 1.4% to 3.9% are complicated by a major perioperative cardiac event (2). The vast majority of surgeries are performed electively, allowing an interlude where strategies to reduce risk may be implemented. Accurate identification of patients at risk may not only help to better inform patients about the benefit-to-risk ratio of procedures, but also guide the allotment of limited clinical resources, utilization of preventive interventions, and areas of future research. Herein, we review important features of the initial pre-operative clinical risk assessment, indications for diagnostic testing to quantify cardiac risk, and methods and indications for pre-emptive therapies.

PRE-OPERATIVE CLINICAL RISK ASSESSMENT

CORONARY ARTERY DISEASE. The incidence of a major adverse cardiac event (MACE) of death or myocardial infarction (MI) perioperatively is first and foremost related to the baseline risk. Coronary artery disease (CAD) is estimated to affect 6.2% of the U.S. adult population (3). Higher rates of perioperative morbidity and mortality are associated with unstable

angina or recent MI (4). Timing of surgery after a recent myocardial event also impacts rates of perioperative MACE. Livhits et al. (5) demonstrated a marked increase in the post-operative incidence of MACE as the length of time from the myocardial event to surgery shortened. This risk was attenuated by prior successful coronary revascularization at the time of the cardiac event. On the basis of these data, American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend at least a 60-day interval between an acute coronary syndrome (ACS) and elective noncardiac surgery (6).

HEART FAILURE. Whereas an estimated 5.7 million Americans currently have heart failure (HF), this number is projected to grow to more than 8 million by 2030 (3). Actively decompensated HF with clinical features is a significant risk factor for perioperative MACE and is a component of many cardiac risk stratification indexes. van Diepen et al. (7) demonstrated that a history of HF increased perioperative risk, even in a currently compensated patient, finding significantly higher 30-day post-operative mortality rates in patients with nonischemic HF (9.3%), ischemic HF (9.2%), and atrial fibrillation (AF) (6.4%) than in those with stable CAD (2.9%). Diastolic dysfunction with and without systolic dysfunction is

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associated with a significantly higher rate of MACE, prolonged length of stay, and higher rates of post-operative HF (8). Current guidelines state that the effect of asymptomatic left ventricular (LV) dysfunction on perioperative outcomes is unknown, but note that a single-center prospective cohort study has reported evidence for increased perioperative cardiac risk in patients with asymptomatic LV dysfunction (9). Flu et al. (9) reported that in patients undergoing elective vascular surgery, the 30-day cardiovascular event rate was 49% in patients with symptomatic HF, 23% in those with asymptomatic systolic LV dysfunction, 18% in those with asymptomatic diastolic LV dysfunction, and 10% in those with normal LV function.

VALVULAR HEART DISEASE. Older studies found severe valvular heart disease to significantly increase the risk of perioperative MACE (10). Agarwal et al. (11) reported that patients with moderate or severe aortic stenosis undergoing nonemergency noncardiac surgery had a 30-day mortality rate double that of propensity score-matched patients without aortic stenosis (2.1% vs. 1.0%). Post-operative MI was almost 3 times as frequent in patients with aortic stenosis than in those without (3.0% vs. 1.1%; $p = 0.001$) (11). However, Tashiro et al. (12) reported that patients with truly asymptomatic severe aortic stenosis and those without aortic stenosis had similar MACE rates. These data were not incorporated into the recent ACC/AHA guidelines.

In patients with severe mitral regurgitation, Bajaj et al. (13) demonstrated worse 30-day composite outcomes (death and post-operative MI, HF, and stroke) than in patients without mitral regurgitation (22.2% vs. 16.4%; $p < 0.02$). Key predictors of adverse post-operative outcomes after noncardiac surgery included ejection fraction $<35\%$, ischemic mitral disease, and diabetes (13). Lai et al. (14) reported a 5-fold increase in-hospital mortality rate (9.0% vs. 1.8%; $p = 0.008$) in patients with moderate-to-severe and severe aortic regurgitation compared with case-matched controls without aortic regurgitation. In this study, key predictors of in-hospital death included LV ejection fraction $<55\%$ and creatinine >2 mg/dl (14). Because there are no trials regarding their perioperative care, current guidelines advise that patients with moderate-to-severe aortic regurgitation and severe aortic regurgitation could be monitored with invasive hemodynamics and echocardiography, in addition to being admitted to an intensive care unit setting in the post-operative period (6).

ARRHYTHMIAS. Although few studies have evaluated perioperative cardiac risk due to cardiac arrhythmias,

there appears to be little risk associated with asymptomatic arrhythmias. A consecutive, prospective study from the Veterans Affairs demonstrated no increased risk of perioperative MACE due to asymptomatic ventricular arrhythmias or AF (15). Whereas older studies (16) demonstrated an association with intra-operative and post-operative arrhythmias, but no increased risk of MI or cardiac death, more recent reports demonstrate increased perioperative cardiac risk from the presence of increased numbers of premature ventricular contractions or nonsustained ventricular tachyarrhythmia (17).

PULMONARY VASCULAR DISEASE. In patients with pulmonary vascular disease undergoing noncardiac surgery, mortality rates vary from 4% to 26%, and cardiac and/or respiratory failure rates from 6% to 42% (18,19). As such, current guidelines recommend continuation of pulmonary vasodilator therapy perioperatively (Class I) and pre-operative evaluation by a pulmonary hypertension specialist before major elective noncardiac surgery (Class IIa) (6).

PROCEDURE TYPE. The type of surgery the patient will undergo contributes substantially to the perioperative cardiac risk. Differing from prior versions, the 2014 guidelines characterize risk as either low or elevated. A low-risk procedure is defined as a procedure wherein the combined surgical and patient characteristics predict a risk of MACE $<1\%$. Generally, these surgeries are those with a less invasive approach, limiting fluid shifts and cardiac stress; procedures typical of this category include cataract surgery and endoscopy (19). Conversely, procedures with a $>1\%$ risk of MACE are considered to be elevated risk and include open and vascular procedures (20). It is thought that this risk may be attenuated in certain circumstances with a less invasive technique.

CALCULATION OF RISK. Several multivariate risk indexes may be helpful for pre-operative assessment. The Revised Cardiac Risk Index (RCRI) is, perhaps, the most well-known and simplest tool. It consists of 6 predictors of risk, including: high-risk surgery (defined as intraperitoneal, intrathoracic, or suprainguinal vascular); history of ischemic heart disease; history of congestive HF, history of cerebrovascular disease; pre-operative treatment with insulin; and pre-operative creatinine >2 mg/dl (16). The presence of 2 or more of these predictors carries an elevated risk level for post-operative major cardiac complication (21).

ABBREVIATIONS AND ACRONYMS

ACC	= American College of Cardiology
ACE	= angiotensin-converting enzyme
ACS	= acute coronary syndrome(s)
AF	= atrial fibrillation
AHA	= American Heart Association
CAD	= coronary artery disease
DAPT	= dual-antiplatelet therapy
DES	= drug-eluting stent(s)
ESC	= European Society of Cardiology
HF	= heart failure
LV	= left ventricle/ventricular
MACE	= major adverse cardiac event(s)
MET	= metabolic equivalent
MI	= myocardial infarction
PCI	= percutaneous coronary intervention
RCRI	= Revised Cardiac Risk Index

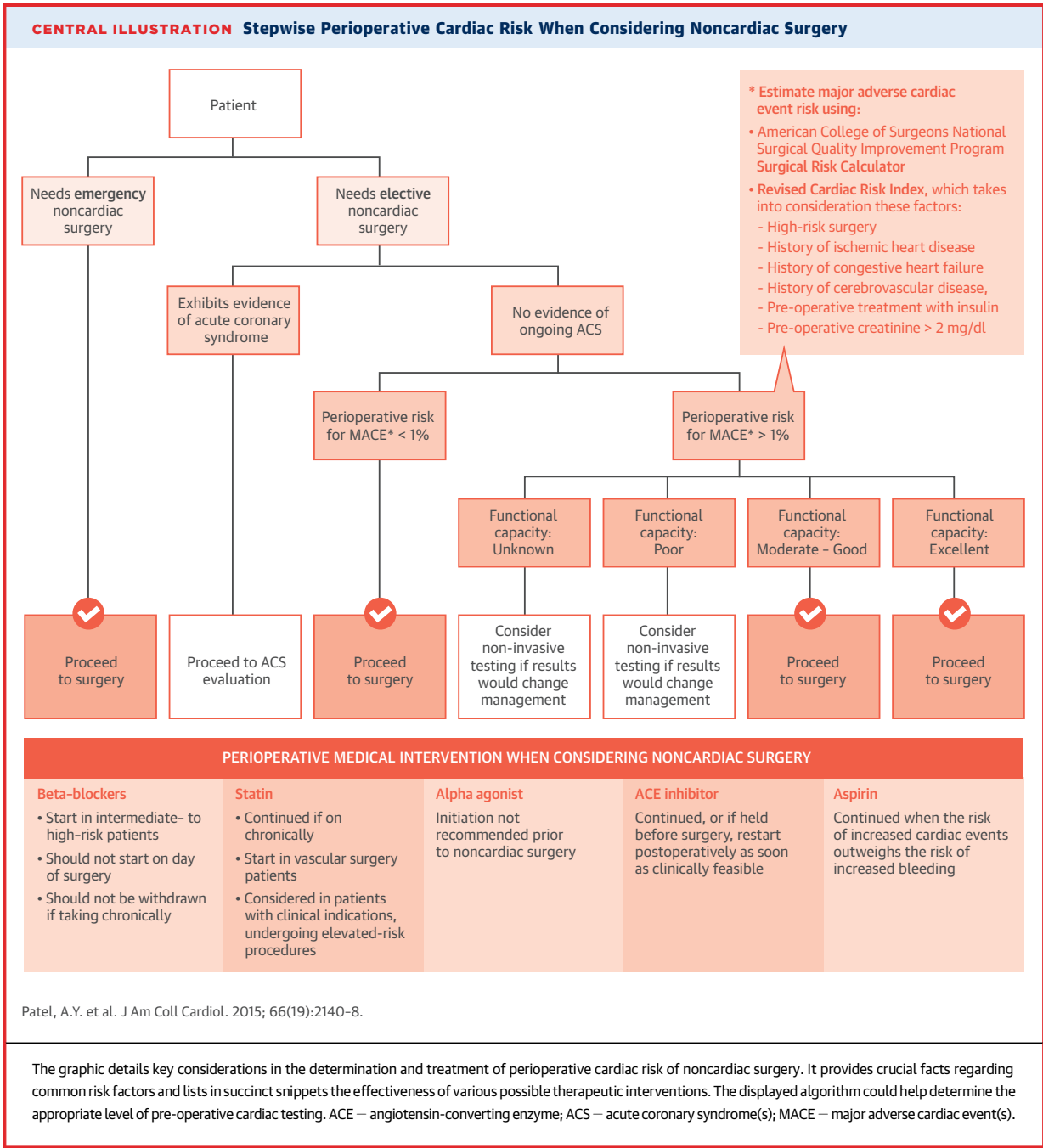
The American College of Surgeons created 2 newer risk indexes by utilizing prospectively collected data from over 1 million operations at more than 525 U.S. hospitals (22). The NSQIP Myocardial Infarction and Cardiac Arrest (MICA) risk calculator was reported in 2011, on the basis of a large, multicenter derivation and validation study (23). The NSQIP MICA adjusts odds ratios depending upon the surgical site and predicts the risk for cardiac arrest or MI. The derivation study showed evidence of increased discriminative power compared with the RCRI. The NSQIP Surgical Risk Calculator was developed in 2013 using the specific current procedural terminology code to provide surgery-specific risk calculation (22). The model includes 21 patient-specific variables and calculates the risk of 10 outcomes, including MACE and death. Although the NSQIP Surgical Risk Calculator has not been externally validated, it may provide the most precise prediction of surgery-specific risk. Current guidelines allow use of either the NSQIP MICA calculator, the NSQIP Surgical Risk calculator, or the RCRI as part of a pre-operative assessment.

PRE-OPERATIVE CARDIAC TESTING. Current guidelines propose a stepwise approach to perioperative cardiac assessment (**Central Illustration**) (6). If the surgery is an emergency (meaning that life or limb is threatened if the procedure is not initiated, typically within <6 h), the patient should proceed directly to the surgery without further cardiac testing. If the surgery is elective (meaning that the procedure could be delayed for up to 1 year) or time-sensitive (meaning that a delay >1 to 6 weeks will negatively affect outcomes), but the patient exhibits evidence of an ACS, then the patient should directly proceed with an ACS evaluation. Similarly, if a patient planned for elective or time-sensitive surgery experiences symptomatic arrhythmias, new or poorly controlled HF, and/or important valvular heart disease, then he or she should undergo an evaluation to properly characterize and optimally treat the underlying cardiac condition before noncardiac surgery.

If the proposed surgery is elective or time-sensitive and the patient does not have current ACS, then calculation of perioperative risk for MACE may be done on the basis of either an assessment of the type of surgery, and either the RCRI or NSQIP calculators. If the perioperative risk for MACE is <1%, the patient can generally proceed to surgery without further cardiac testing. Chen et al. (24) recently reported that pre-operative testing before cataract surgery (a typically low-risk procedure) is more strongly associated with provider preferences than patient characteristics, signifying that this patient population may provide an opportunity for improvement. If the perioperative

MACE risk is higher than 1%, a determination of functional capacity may be helpful for further assessing risk. “Excellent” functional capacity is designated as >10 metabolic equivalents (METs), typified by activities such as racquetball singles or fast running; “good capacity” is defined as 7 to 10 METs, achieved by activities such as jogging or skiing; “moderate capacity” (4 to 6 METs) would be demonstrated by activities such as bicycling, sexual activity, or tennis singles; and “poor capacity” is defined as <4 METs (walking, golf, or yard work). Perioperative and long-term cardiac risks are increased, particularly among patients unable to perform 4 METs during daily activities (25). A patient with a functional capacity >4 METs, can generally proceed directly to surgery, with acceptable risk. However, if the patient is being considered for high-risk surgery and the functional capacity is <4 METs, consideration of additional testing to evaluate for ventricular, coronary, and/or valve status may be warranted if it would modify management.

Prophylactic coronary revascularization exclusively to reduce perioperative cardiac events is not recommended, even in patients undergoing elective elevated-risk surgery (6). This Class III recommendation was driven primarily by the CARP (Coronary Artery Revascularization Prophylaxis) trial, which demonstrated no difference in mortality or post-operative MI in patients with stable CAD undergoing elective vascular surgery, regardless of whether they received pre-operative percutaneous coronary intervention (PCI), bypass surgery, or no revascularization (20). When coronary PCI is performed before noncardiac surgery, elective noncardiac surgery should typically be delayed 14 days after balloon angioplasty, 30 days after bare-metal stent implantation (26), and 365 days after drug-eluting stent (DES) implantation (27,28). The recent European Society of Cardiology (ESC) guidelines and recent data suggest that with newer-generation DES implantation, a 6-month duration of dual-antiplatelet therapy (DAPT) is not unreasonable when the need for noncardiac surgery is especially compelling (27,29-31). The ACC/AHA December 2014 Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes provides a related Class IIa recommendation: if the risk of morbidity from bleeding outweighs the anticipated benefit of a recommended duration of P2Y₁₂ inhibitor therapy after stent implantation, earlier discontinuation (e.g., <12 months) of P2Y₁₂ inhibitor therapy is reasonable (32). These guidelines are informed by data reported by Holcomb et al. (33). Analysis of their retrospective cohort study at Veterans Affairs medical centers demonstrated that the highest incremental risk of noncardiac surgery on



adverse cardiac events among post-stent patients is in the initial 6 months following stent implantation and stabilizes at 1.0% after 6 months. Most recently, the ISAR-SAFE (Intracoronary Stenting and Antithrombotic Regimen: Safety and Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) trial was unable to demonstrate any significant clinical outcome differences between 6 months or 12 months of DAPT in patients treated with second-generation DES (34). Additionally, the ITALIC (Is

There a Life for DES After Discontinuation of Clopidogrel) trial demonstrated no statistically significant difference in rates of bleeding or thrombotic events in patients treated with everolimus-eluting stents and either 6 months or 24 months of DAPT (35). Similarly, the SECURITY (Second Generation Drug-Eluting Stent Implantation Followed by Six- Versus Twelve-Month Dual Antiplatelet Therapy) trial demonstrated non-inferiority in cardiac death, MI, stroke, stent thrombosis, and bleeding for 6 months and 12 months of

TABLE 1 Major Changes in Recommendations From 2007 to 2014		
Recommendation	Change	New References
The 12-lead ECG		
Pre-operative resting 12-lead ECG is reasonable for Patients with known coronary heart disease or other Significant structural heart disease, except for low-risk surgery	Class I to Class IIa	(46)
Pre-operative resting 12-lead ECG may be considered for asymptomatic patients, except for low-risk surgery	Class IIa to Class IIb	(47)
Exercise Stress Testing		
Cardiopulmonary exercise testing may be considered for patients undergoing elevated risk procedures	Class III to Class IIb	(48-50)
Timing of elective noncardiac surgery in patients with previous PCI		
Noncardiac surgery should be delayed after PCI	New	(27,28,51-53)
Class I: 365 days after drug-eluting stent implantation		
Class I: 30 days after bare-metal stent implantation		
Class I: 14 days after balloon angioplasty		
Beta-blockade		
<i>Beta-blockers should be given to patients undergoing vascular surgery in whom pre-operative testing reveals ischemia</i>	Deleted (previously Class I)	
In patients with intermediate- or high-risk pre-operative tests, it may be reasonable to begin beta-blockade therapy before surgery	Class IIa to Class IIb	(54)
In patients with ≥3 RCRI factors, it may be reasonable to begin beta-blockade therapy before surgery	New (Class IIb)	(55)
Beta-blockers should not be started on the day of surgery	New (Class III)	(43)
Alpha-2 agonists		
Alpha-2 agonists are not recommended for prevention of cardiac events	Class IIb to Class III	(56)
Angiotensin-converting enzyme inhibitors		
Perioperative continuation of ACE inhibitors or ARBs is reasonable	New	(57,58)
ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ECG = electrocardiogram; PCI = percutaneous coronary intervention; RCRI = Revised Cardiac Risk Index.		

DAPT following second-generation DES implantation (36). The PARIS (Patterns of Non-Adherence to Dual Anti-Platelet Regimen In Stented Patients) registry reported that the reason for cessation of DAPT impacted the risk of MACE; in comparison to patients continued on DAPT, patients who were noncompliant or discontinued DAPT due to bleeding had an adjusted hazard ratio for MACE of 1.50 (95% confidence interval [CI]: 1.14 to 1.97; $p = 0.004$) (37). Importantly, patients who had their DAPT interrupted for a surgical procedure only demonstrated a trend towards increased MACE, with a hazard ratio of 1.41 (95% CI: 0.94 to 2.12; $p = 0.10$) (37). In their recent review, Montalescot et al. (38) concluded that safe interruption of DAPT after 6 months is possible in selected patients and that the total duration of DAPT beyond the initial 3 to 6 months should be driven by patient characteristics, including stent type, comorbidities, patient tolerance, and overall clinical profile. The balance between MACE and bleeding risk with respect to DAPT duration remains a debated topic and an area of active investigation (39-41).

ANCILLARY TESTING. The value of a pre-operative electrocardiogram is generally thought to depend upon the type of surgery. Current guidelines states

that it is reasonable for those with known heart disease (Class IIa), or those who are asymptomatic without known heart disease, but undergoing a moderate- or high-risk surgery (Class IIb) (6).

PERIOPERATIVE MEDICAL INTERVENTIONS

BETA-BLOCKADE. A recent systematic review from the ACC/AHA found that although perioperative beta-blockade started within 1 day of surgery reduced nonfatal MI, it significantly increased the risk of adverse events, including stroke and death (42). The POISE-1 trial (Perioperative Ischemic Evaluation Study), which initially raised concerns for increased stroke and death, has since been criticized for poor reflection of clinical practice. POISE-1 used a high dose of a long-acting beta-blocker and did not include a titration protocol before or after the procedure (43). Moreover, with the recent controversy regarding the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo) IV and V (44), the systematic review found insufficient data for the use of beta-blockade 2 or more days before surgery.

The guidelines continue to provide a Class I recommendation for continuation of beta-blockade therapy for patients on beta-blockers long-term, due

to a benefit seen in observational studies (45). Additionally, they provide a new Class IIb recommendation for initiating beta-blockade therapy perioperatively for patients with intermediate- or high-risk stress test results, or with ≥ 3 RCRI risk factors facing major surgery (Table 1) (46-58). However, those recommendations were on the basis of limited, observational data.

Since the guidelines were published, Friedell et al. (59) reported further findings in support of this recommendation. In their retrospective observational analysis of 326,489 patients at Veterans Affairs hospitals, 42% of patients undergoing noncardiac surgery received perioperative beta-blockade therapy. In patients who received beta-blockade therapy, 30-day mortality rates of 1% were patients with no cardiac risk factors, 1.7% for patients with 2 risk factors, and 3.5% for patients with 3 to 4 risk factors. In patients who did not receive beta-blockade therapy, 30-day mortality rates were 0.5% with no cardiac risk factors, 1.4% with 1 to 2 risk factors, and 6.7% with 3 to 4 risk factors (59). These findings provide further evidence for current guidelines, which support beta-blockade therapy for patients with high cardiac risk undergoing noncardiac surgery.

Beta-blockade definitively should not be initiated the day of surgery (43,60). ESC guidelines recommend use of a β_1 -selective agent, such as atenolol or bisoprolol, instead of metoprolol, because these agents have shown efficacy in trials, with a slow up-titration period (when possible, at least 1 week and up to 30 days) beginning with a low dose, such as 50 mg of atenolol. Dose adjustment should be done towards a goal resting heart rate between 60 and 70 beats/min and a systolic blood pressure >100 mm Hg (31). Patients most likely to benefit from judicious beta-blocker treatment usually already have an indication for such treatment, such as prior systolic HF, an MI within the past year, or known angina pectoris (55).

STATIN THERAPY. There is a Class I recommendation for patients on chronic statin therapy to continue their statin perioperatively (6). A recent small, randomized controlled trial found a reduction in MACE with atorvastatin therapy in patients undergoing vascular surgery (61). Additionally, observational data has found a 5-fold benefit in MACE rates with patients on statin therapy (62). If a patient has atherosclerotic cardiovascular disease, the recent 2013 guidelines on the treatment of blood cholesterol suggest initiation of statin therapy before surgery (63). Of note, the ESC guidelines differ slightly in that they recommend initiation of statins at least 2 weeks before vascular surgery and do not recommend initiating statins before any nonvascular surgery (31).

ALPHA AGONISTS. Current guidelines recommend against initiation of alpha-2 agonists in patients undergoing noncardiac surgery. The recent POISE-2 study, a large randomized, blinded, multicenter clinical trial, found that administration of clonidine did not reduce rates of perioperative death or nonfatal MI, but did increase rates of nonfatal cardiac arrest and hypotension (56).

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS. There are no randomized controlled studies regarding the impact of angiotensin-converting enzyme (ACE) inhibitors on perioperative cardiac risk. A large retrospective study found no statistically significant differences in perioperative MACE outcomes, but demonstrated an increased rate of intraoperative hypotension in patients on ACE inhibitors (57). Conversely, a smaller study found that discontinuation of ACE inhibitor therapy before surgery resulted in no major harm (64). As such, the current guidelines state (as a Class IIa recommendation) that continuation of ACE inhibitors perioperatively is reasonable and that if ACE inhibitors are held before surgery, it is reasonable to restart, as clinically feasible, post-operatively.

ANTIPLATELET THERAPY. It is a Class I recommendation for patients with recently implanted bare-metal stents or DES to continue DAPT, unless the relative risk of bleeding outweighs the benefit of prevention of stent thrombosis. Similarly, it is a Class IIb recommendation that it may be reasonable for patients who have not had previous coronary stenting, but are on a daily aspirin, to continue the aspirin therapy throughout the perioperative period. As such, continuation of aspirin perioperatively is reasonable, especially in patients with high-risk CAD or cerebrovascular disease, unless there is concern for increased bleeding risk due to the type of procedure (e.g., spinal, vitreoretinal, among others). However, on the basis of POISE-2, which found no benefit in either starting or continuing aspirin therapy in non-stented patients undergoing noncardiac surgery (65), current guidelines provide a Class III recommendation against initiating aspirin therapy pre-operatively because aspirin was associated with a higher risk of bleeding.

ANTICOAGULANTS. The benefits of anticoagulation perioperatively must be weighed on a case-by-case basis against the risks of bleeding in the particular surgery being planned. The most recent 2014 AHA/ACC/HRS Guidelines for the Management of Patients With Atrial Fibrillation do not endorse a specific recommendation for bridging or interrupting anticoagulation perioperatively (66). However, the 2014

ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery states that, in certain circumstances in which there is minimal to no risk of bleeding (such as cataract surgery or minor dermatologic procedures), it may be reasonable to continue anticoagulation perioperatively (6). For patients with mechanical mitral valves or a mechanical aortic valve and 1 additional risk factor (AF, previous venous thromboembolism, LV dysfunction, hypercoagulable state), bridging anticoagulation with unfractionated heparin may be appropriate when the risk of surgical bleeding is more than minimal (67). Since the publication of these 2 guidelines, the BRIDGE (Effectiveness of Bridging Anticoagulation for Surgery) trial demonstrated noninferiority between no bridging versus bridging with low-molecular-weight heparin perioperatively in patients with AF on warfarin long term (68). For patients requiring urgent reversal of vitamin K antagonism, fresh frozen plasma and prothrombin complex concentrates are preferred over vitamin K, due to the long lead time to effect with vitamin K supplementation (6). Idarucizumab, an antibody fragment, completely reversed the anticoagulant effects of dabigatran, a novel oral anticoagulant that functions via direct thrombin inhibition within minutes (69). For patients with normal renal function on novel oral anticoagulants for AF, discontinuation for 48 h before

the procedure is recommended (6). Control levels of activated partial thromboplastin time may suggest low serum concentration levels of anticoagulant for patients on long-term apixaban or rivaroxaban (66).

CONCLUSIONS

Cardiac risk in noncardiac surgeries is best tackled by a perioperative team approach. Close collaboration and shared decision-making among the patient, primary caregiver, cardiologist, surgeon, and anesthesiologist is key to ensuring proper implementation of current evidence-based guidelines. However, current evidence regarding much of what we do deeply lacks the rigor of multiple, prospective randomized controlled trials. As the U.S. healthcare system finds itself grappling with the goals of better patient care that is cost effective, further studies on the use of novel perioperative testing and interventions will be needed. Future research focusing on patient outcomes is needed to further clarify the proper care of these patients.

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