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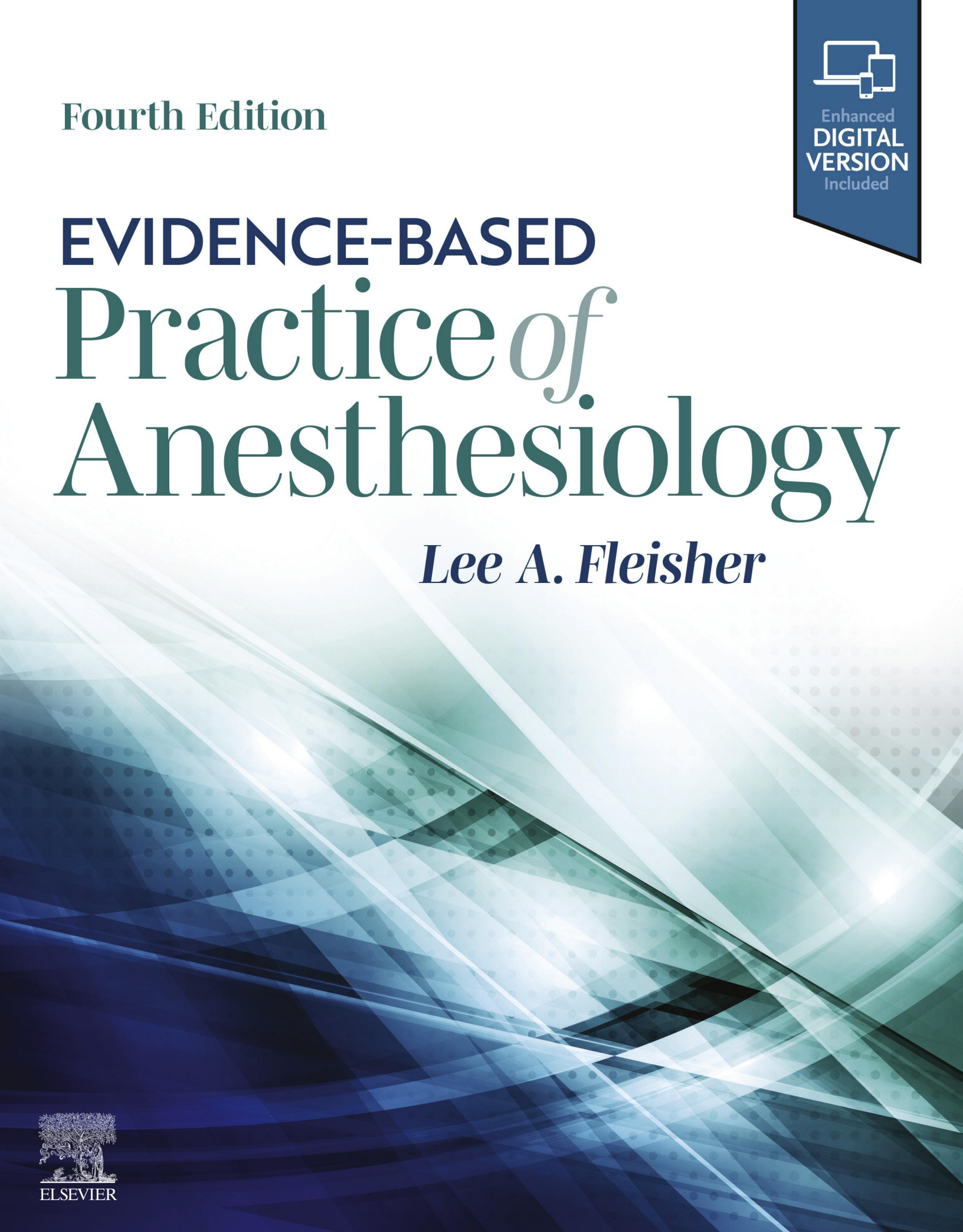
Lee A. Fleisher



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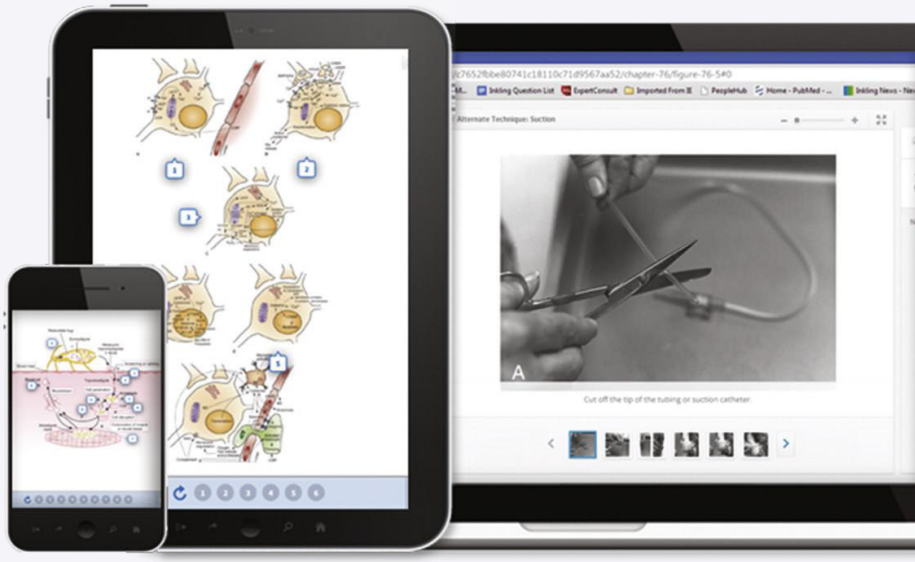

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Fourth Edition

EVIDENCE-BASED Practice *of* Anesthesiology

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To the numerous faculty, residents, and medical students of the Perelman School of Medicine at the University of Pennsylvania, who have inspired me to improve patient care through both the application and investigation of best practice during my 16 and a half years as the Chair of the Department of Anesthesiology and Critical Care.

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PREFACE

It has been 18 years since the publication of the first edition of *Evidence-Based Practice of Anesthesiology,* and I remain extremely pleased that anesthesiologists nurse anesthetists and anesthesiology assistants found the approach taken to critical questions in the first three editions useful in their practice. I am indebted to the many individuals who have written for this edition and approached the evidence in a standardized way. In editing the fourth edition, I maintained the approach and format of the earlier editions, updated important topics with ongoing controversy, and added many new topics for which there is increasing evidence on how best to practice. It is my hope that the field of anesthesiology and perioperative medicine will continue to grow with increasing high-quality investigations to expand our evidence base and help practitioners provide the highest quality of care to the individual patient.

I am indebted to several people who were critical in the publication of the previous editions and now the fourth edition of *Evidence-Based Practice of Anesthesiology.* I would like to particularly acknowledge my executive assistant, Eileen O'Shaughnessy, who helped me organize and invite authors for this and multiple other editions of *Evidence.* In addition to my publisher, I would like to thank Angie Breckon, who, as my developmental editor, ensured the quality of the final product. I hope that the fourth edition of this book will continue to provide the answers to many of your daily anesthesia questions.

Lee A. Fleisher, MD

FOREWORD

Dr. Lee A. Fleisher is currently the Chief Medical Officer and Director of the Center for Clinical Standards and Quality at Centers for Medicare and Medicaid Services (CMS). That means he is responsible for decisions by CMS regarding which procedures, drugs, and therapies should be paid for by the US federal government. His decisions involve the assessment of which treatments improve patient outcomes and whether the proof of benefit is adequate in the published trials. Without evidence, the assessment would involve beliefs and opinion but not science.

The COVID-19 pandemic documented the essential role for requiring evidence of benefit in trials that documented longer-lasting benefit and fewer complications. We are now seeing a decrease in COVID-19 deaths because randomized controlled trials documented the efficacy and significant benefit of vaccines and now pills that attack this virus. We are aware that COVID-19 has killed nearly 1 million US citizens and more than 5 million people worldwide in just 2 years. The death-rate is finally improving due to vaccines created—which were tested in clinical trials at record speed and shown to be of significant benefit.

Yet there are people who refuse to accept the evidence. Leaders in health care, at the federal government level and in other governments, as well as in hospitals and clinics, have been protecting our patients and our colleagues by accepting the evidence presented, requiring vaccinations of all employees, and using protective equipment. Hospitalization is occurring almost exclusively in unvaccinated individuals, more evidence of the benefit of the vaccines.

The pandemic has proved how important evidence in medicine is and how it can modify the course of a pandemic. The role of physicians, including anesthesiologists, has been to learn continuously by always reading the data presented, accepting the best evidence available, and changing practice to mirror the evidence.

Dr. Fleisher modeled the best behavior as our medical leader of CMS. He supported vaccination and evidence-based care. Anesthesiologists helped each hospital by utilizing the state-of-the-art techniques, proven to be beneficial in trials, and getting vaccinated to protect our patients, colleagues, and families.

We have survived the current pandemic by using evidence-based medicine.

We will improve our practice in anesthesia by using evidence-based data.

This book will help us improve our care of our patients, which is our most important goal.

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CONTENTS

1

Evidence-Based Practice Parameters: The Approach of the American Society of Anesthesiologists

Mark Grant, MD, PhD, Karen B. Domino, MD, MPH

CHAPTER OUTLINE

INTRODUCTION

Practice parameters are "strategies for patient management developed by the profession to assist physicians in clinical decision making."[1] The evidence-based practice parameters of the American Society of Anesthesiologists (ASA) include practice guidelines and practice advisories. Although both types of guidance employ similar approaches and methodologies, the evidence base supporting recommendations in practice advisories is limited in quantity, quality, and consistency. This chapter focuses on practice guidelines because they are the most evidence based, but the principles discussed apply equally to practice advisories.

The contemporary era in ASA practice parameter development began in 1993 with the publication of the difficult airway[2] and pulmonary artery catheterization[3] guidelines. In total, 14 practice guidelines and 8 practice advisories have been published along with numerous updates. In 2020, the number of citations to the guidelines indexed in the Web of Science approached 10,000.

CLINICAL PRACTICE GUIDELINES STANDARDS

Although practice guidelines date to as early as 1938,[4] it was not until 2011 that the National Academy of Medicine[a] released standards for developing trustworthy clinical practice guidelines.[5] Congress initiated the development of standards to improve the quality of guidelines. A companion set of standards was released simultaneously for systematic reviews—a requirement for a trustworthy practice guideline.[6]

The clinical practice guideline standards address eight areas: (1) transparency, (2) conflicts of interest, (3) development group composition, (4) systematic review conduct, (5) ratings for the strength of recommendations, (6) the articulation of recommendations, (7) external reviews, and (8) updates. Although all of the standards apply to guideline development, our focus is on the evidentiary foundations, which involves the synthesis of evidence informing recommendations (standards included in areas 4 through 6).

SYSTEMATIC REVIEWS AND GUIDELINES

The synthesis of evidence provided by a systematic review is the foundation of evidence-based guideline recommendations. Although systematic reviews can be complex undertakings, their conduct should be transparent, unbiased, reproducible, and devised to produce a valid synthesis of evidence. Guideline users should understand the approach adopted and the basis for decisions concerning the systematic review's conduct. The goals of an evidence synthesis are not simply to offer conclusions on whether interventions may, or may not, be more effective than the relevant comparator(s). The evidence synthesis must also quantify uncertainty in comparative effects to allow for the incorporation of patient preferences and values in recommendations. In this way, guideline recommendations can best inform decision making, improve patient care, and help create better health outcomes.

[a]Still known as the Institute of Medicine in 2011.

TABLE 1.1 PICOTS for Antiseptic-Treated Central Venous Catheters

Population	Patients undergoing elective insertion of a nontunneled central venous catheter for short-term use
Interventions	Antibiotic-coated catheters
	Chlorhexidine-silver sulfadiazine–impregnated catheters
	Silver-impregnated catheters
Comparators	Standard catheters
Outcomes	Catheter colonization
	Central-lineassociated bloodstream infection
	Catheter-related bloodstream infection
	Sepsis-related morbidity and mortality
Timing	Duration of catheter colonization ≤ 3 weeks
Setting	In-patient or other health care facilities where short-term central venous catheters are used

PICOTS, Population, interventions, comparators, outcomes, timing and setting.

CLINICAL QUESTIONS AND PICOTS (POPULATION, INTERVENTIONS, COMPARATORS, OUTCOMES, TIMING, AND SETTING)

The first steps in a guideline's systematic review are defining the PICOTS (population, interventions, comparators, outcomes, timing, and setting) and framing the questions to address.[7] Well-formulated questions facilitate and guide the review process—from searching and study selection together with the approach to evidence synthesis. The PICOTS and questions add transparency, reflecting the goals and thought processes of guideline developers.

Systematic review questions can address therapies, diagnoses, prognoses, the predictions of treatment response, and screenings. The different types of questions are generally answered by different study designs and approaches to evidence synthesis. For example, randomized designs are typically sought for therapeutic interventions, whereas observational studies most often form the evidence base for addressing diagnostic[8] and prognostic questions.

Table 1.1 illustrates the PICOTS derived from the 2020 central venous access guidelines,[9] which correspond to the therapeutic question: What is the effectiveness of antiseptic-treated catheters for reducing the incidence of catheter-related bloodstream infection and associated morbidity and mortality?

OUTCOMES AND EVIDENCE—IMPORTANCE, PREFERENCES, AND VALUES

The outcomes that patients experience and care about are health outcomes.[10] They vary in degree of importance to patients and for clinical decision making. Intermediate outcomes lead to health outcomes. Examples of intermediate outcomes include test results, test sensitivity and specificity, biologic parameters, and even the actions practitioners take. Intermediate outcomes do not always result in a health outcome; the strength of the link between the two determines the importance of intermediate outcomes and whether they can serve as a valid surrogate.[11] Evidence is considered direct when an intervention leads to a health outcome and indirect when it leads to an intermediate outcome. In the case of antiseptic-treated central venous catheters, catheter colonization is an intermediate outcome. It provides indirect evidence that colonization can, but does not always, result in clinical infections and consequences for patients.

Developing recommendations requires assigning levels of importance to outcomes and incorporating patient preferences and values for those outcomes. Safety outcomes are commonly encountered and are of utmost importance to patients and practitioners. In other instances,[12] such as the choice of anesthetic, patient preferences may vary.

STUDY SELECTION

The types of studies and designs included in the systematic review are determined by the questions, PICOTS, and evidence availability. Randomized clinical trials—individually or pooled in a meta-analysis—are often considered to provide the strongest and most convincing evidence. For this reason, if relevant randomized trials are identified, a review may exclude other study designs. Nevertheless, evidence from randomized designs is insufficient to address some questions. Two examples include safety outcomes or harms[13] because of infrequent events and diagnostic tests.[8] Although often asserted to the contrary, causal effects can be ascertained in well-conducted and analyzed nonrandomized studies.[14] Accordingly, deciding which types of studies might be relevant to guideline recommendations requires a clear rationale and justification.

DATA EXTRACTION AND MANAGEMENT

Accurate data extraction from studies, quality control, and careful data management enhance reproducibility and support valid evidence synthesis. Best practices include using standard review-specific data entry forms, using data verification or dual extraction of quantitative data, and maintaining data in analytical-friendly formats.

EVIDENCE SYNTHESIS

A single study is rarely sufficient to inform a guideline or policy recommendation.[15] Evidence is invariably required from multiple studies and therefore requires synthesizing. Evidence synthesis is the quantitative or qualitative analysis and summary of study results. It can range from a narrative description of study results to pairwise meta-analysis (a single intervention and comparator), network meta-analysis (multiple interventions or comparators), or complex modeling.

Regardless of the approach, the goal of synthesis is to summarize effects and quantify uncertainty (statistical and nonstatistical) to inform recommendations or other decisions.

Evidence synthesis proceeds by describing studies and the body of evidence, assessing individual study risk of bias (sometimes referred to as study quality), involving meta-analysis when appropriate, and appraising the strength of evidence for important outcomes.

DESCRIBING THE BODY OF EVIDENCE

A description of the body of evidence typically includes the study and patient characteristics, methods of outcome ascertainment, funding sources, and any other factors that might influence the interpretation of evidence. There are several reasons for this, including to gain an understanding of clinical heterogeneity among studies and the appropriateness of a meta-analysis, to list potential biases (e.g., losses to follow-up, variations in interventions, comparators, or outcomes), and to assess the generalizability of any conclusions. For example, Table 1.2 displays the characteristics of trials examining chlorhexidine-silver sulfadiazine–coated catheters included in the central venous access guidelines.[9]

META-ANALYSIS

A quantitative evidence synthesis using a meta-analysis requires consideration of the number of studies and their size, the degree of clinical heterogeneity (variation in PICOTS), the methodologic heterogeneity (variation in study conduct), how events are reported, and the event rates.[16] Although random effects models generally require five or more studies to be satisfactorily fitted,[17] two or three studies can be pooled in fixed effects models and are sufficient to conduct a meta-analysis and inform decision making.[18] Many factors are taken into account when interpreting meta-analyses, including the methods used to combine study results, statistical heterogeneity, small study effects, and potential publication bias.

STUDY-LEVEL RISK OF BIAS (CRITICAL APPRAISAL)

The certainty in a body of evidence depends largely on whether study results are believable and internally valid (i.e., their risk of bias). Approaches and tools for assessing risk of bias vary according to study design (e.g., randomized clinical trials,[19] nonrandomized studies of interventions,[20] diagnostic studies[21]). Although tools are generally design specific, similar domains are considered across designs, including biases in selecting participants, study performance, attrition, and detection of events, as well as other potential biases, such as research misconduct. Two reviewers generally evaluate the risk of bias independently, and the process can be automated for randomized trials.[22] Fig. 1.1 displays the risk of bias assessments for trials of chlorhexidine-silver sulfadiazine–impregnated catheters in the central venous access guideline using the Cochrane RoB 2.0 tool.[19]

STRENGTH OF EVIDENCE

The strength of evidence is the degree of certainty that an estimated effect and accompanying confidence interval (uncertainty) represents the range of true or plausible effects. Synonyms for the strength of evidence include the category of evidence,[23] certainty of the evidence,[24] and quality of evidence. That degree of certainty is judged by the quality, quantity, and consistency of evidence. Although there are many different frameworks for rating the strength of evidence,[25] all share the common purpose of informing decision making.

Two conceptual models underpin the strength of evidence frameworks: (1) evidence hierarchy and (2) certainty of evidence. The evidence hierarchy (pyramid) model's premise is that systematic reviews and meta-analyses of randomized designs provide the most convincing evidence, followed by individual randomized trials, observational studies, and then case series or case reports. The certainty of evidence model incorporates the evidence hierarchy insofar as it reflects study validity but defines the strength of evidence in terms of how convincing the accuracy of the range of estimated effects is now or will be in the future.

The requirements for frameworks to rate the strength of a body of evidence include a systematic assessment of the risk of bias, consistency of effects, precision, directness, and reporting bias; for bodies of evidence that include observational research, other domains are added: dose-response association, plausible confounding that would change the observed effect, and the strength of association.[5] The strength of evidence is a critical factor in determining the strength of a recommendation.

SUMMARIZING FINDINGS

Evidence-based recommendations require a clear and objective description of the body of evidence and synthesis. Absent a concise and informative summary, it may be difficult to consider the relevant aspects of a body of evidence, with decision makers defaulting to using global subjective judgment.[10]

FORMULATING GUIDELINE RECOMMENDATIONS

In addition to a well-conducted evidence synthesis, the guideline task force composition, conflicts of interest, and how recommendations are articulated must be considered. Task forces include content experts, clinicians, methodologists, and patient representatives. Conflicts of interest for task force members are disclosed and managed. The ASA imposes explicit conflict-of-interest disclosure and management policies, requiring that task force chairs and cochairs have no relevant conflicts of interest. Additionally, more than half of task force members must be free of potential conflicts of interest.

Finally, the process and intersections of evidence, task force, preferences and values, and task force recommendations are summarized in Fig. 1.2. It begins by defining the PICOTS and formulating the questions to be addressed by

TABLE 1.2 Characteristics of Trials Evaluating the Efficacy of Chlorhexidine-Silver Sulfadiazine–Coated Catheters for Preventing Catheter Colonization and Catheter-Related Bloodstream Infection

							Age in Years Mean, Median (SD) [IQR] {Range}				
Study	**Location**	**Centers**	**Dates**	**N[a]**	**CVCs**	**Analyzed**	**All**	**CSS**	**Control**	**Male (%)**	**Minimum CVC-days**
Bach 1996	Germany	1		233		Patient	>18				None
Ciresi 1996	US	1		191	251	Patient	56(2.2)			50%	None
Logghe 1996	Belgium	1	2/1993–3/1996	538	680	CVC		51(16)	50(15)	55%	None
Pemberton 1996	US	1		72		Patient		50(19)	48(19)		None
Van Heerden 1996	UK	1		54		Patient		45	52	60%	5
George 1997	UK	1		60	79	CVC	{16–90}				None
Maki 1997	US	1		158	403	CVC	48(18)				0.33
Tennenberg 1997	US	1	2/1993–11/1995	282		Patient	58(5)				None
Heard 1998	US	1	3/1994–6/1995	251	308	CVC	56(6)			≈60%	2
Collin 1999	US	1	6/1995–12/1995		237	CVC	47			69%	None
Hannan 1999	UK	1		228	351	CVC	63{30–86}				None
Marik 1999	US	1		75		Patient		63(10)	66(11)		1
Sheng 2000	Taiwan	1	11/1998–6/1999	204	235	CVC		61(18)	64(18)	61%	None
Van Vliet 2001	Nether-lands	1		94		Patient		67(8)	68(7)	70%	None
Theaker 2002	UK	1		181	232	CVC	62.5				None
Brun-Buisson 2004	France	14	6/1998–1/2002	366		Patient		58(18)	59(18)		3
Dunser 2005	Austria	1	1/2001–12/2002	190	325	CVC		62	60	69%	None
Jaeger 2005	Germany	1	3/2000–10/2000	106		Patient		49	45		None
Ostendorf 2005	Germany	1	1/2000–9/2001	184		Patient		53	51	62%	None
Rupp 2005	US	9	7/1998–6/2001	780		Patient		60	61	60%	None
Osma 2006	Turkey	1	9/2001–5/2003	133		Patient		49	48	53%	<3 expected
Camargo 2009	Brazil	1	7/2002–9/2003	109		Patient		73	74	56%	None
Mer 2009	South Africa	1	1996–1999	118		Patient		43	47	61%	None

[a]Number analyzed (not necessarily randomized). *CSS*, Chlorhexidine-silver sulfadiazine; *CVC*, central venous catheter; *IQR,* interquartile range; *SD*, standard deviation.

Trial	Outcome	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Bach 1996	CRBSI/colonization	?	+	+	+	+	?
Ciresi 1996	CRBSI/colonization	?	?	+	+	+	?
Pemberton 1996	CRBSI	?	+	−	+	+	−
Van Heerden 1996	Colonization	?	?	+	−	+	−
George 1997	Colonization	?	+	+	?	+	?
Logghe 1997	CRBSI	?	+	+	+	+	?
Maki 1997	CRBSI/colonization	+	?	+	+	+	+
Tennenberg 1997	CRBSI/colonization	+	+	+	?	+	?
Heard 1998	CRBSI/colonization	−	−	−	+	+	−
Collin 1997	Colonization	?	?	+	+	+	?
Hannan 1999	CRBSI/colonization	?	?	+	+	+	?
Marik 1999	CRBSI/colonization	?	+	+	+	+	?
Sheng 2000	CRBSI/colonization	?	+	+	+	+	?
Van Vliet 2001	Colonization	−	?	+	+	+	−
Theaker 2002	CRBSI/colonization	?	?	+	+	+	?
Brun-Buisson 2004	CRBSI/colonization	+	+	+	+	+	+
Ostendorf 2005	CRBSI/colonization	?	+	−	+	+	−
Rupp 2005	CRBSI/colonization	+	+	+	+	+	+
Dunser 2005	Colonization	?	?	+	+	+	?
Jaeger 2005	CRBSI/colonization	?	+	+	+	+	?
Osma 2006	CRBSI/colonization	?	?	+	+	+	?
Mer 2009	CRBSI/colonization	+	+	+	+	+	+
Camargo 2009	CRBSI/colonization	+	?	−	+	+	−

+ Low risk
? Some concerns
− High risk

Fig. 1.1 Individual study risk of bias assessments for trials of chlorhexidine-silver sulfadiazine–impregnated catheters. *CRBSI*, Catheter-related bloodstream infection.

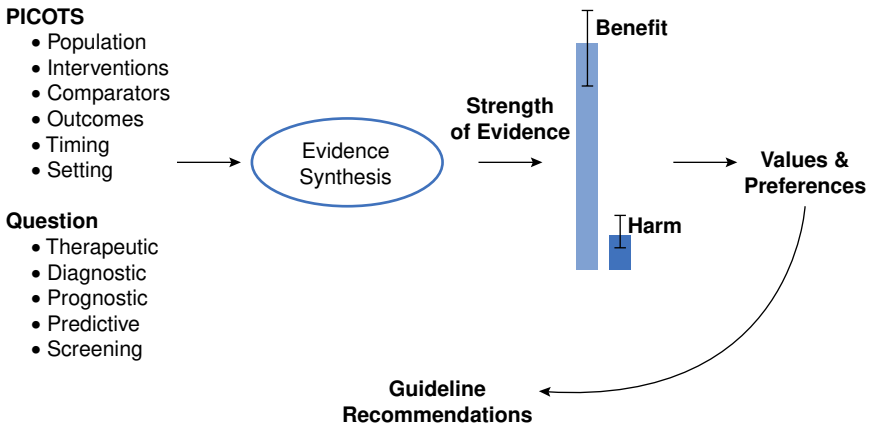

Fig. 1.2 Depiction of the evidence synthesis, values and preferences, and recommendation interface.

evidence. The evidence synthesis is then shaped and interpreted by the task force. The effect of interventions on benefits and harms are assessed; benefits and harms are then weighted according to how each is valued. Finally, guideline recommendations are crafted, including language indicating the strength of each recommendation. This is the essence of developing trustworthy evidence-based recommendations.

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2

Is a Preoperative Screening Clinic Cost-Effective?

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CHAPER OUTLINE

INTRODUCTION

Preoperative clinic visits have been shown to improve patient satisfaction, reduce unnecessary testing and consultation, and decrease length of hospital stay and in-hospital mortality postoperatively.[1–3] Optimization of a patient's medical condition before surgery has also been shown to decrease operating room (OR) cancellations and delays.[1] Furthermore, preoperative optimization aligns with the overarching goal of the Centers for Medicare and Medicaid Services (CMS) of providing comprehensive value-based care (VBC). Since the introduction of the Medicare Access and CHIP Reauthorization Act (MACRA) in 2015, CMS has steadily moved toward alternative payment models focusing on value-based payments and measurements and away from more individual fee-for-service payment models.[4] VBC is defined as a health care reimbursement model that is based on positive outcomes for patients relative to the cost.[5] Preoperative clinics and optimization strategies are examples of collaborative, multidisciplinary care pathways that create value. The preanesthetic assessment was initially instituted to improve OR efficiency and focused on strategies to reduce delays and cancellations on the day of surgery. Patients were often seen only a few days before surgery, limiting the ability to intervene on poorly controlled conditions. Since the mid-1990s, the focus of preoperative clinics and consultations has evolved, shifting toward optimization and management of modifiable risk factors and chronic illnesses. This has led to a push for earlier planning of patient perioperative care as soon as there is contemplation of surgery. There is evidence that suggests that up to 20% of patients seen in presurgical preoperative assessment clinics have modifiable risk factors that could reduce postoperative complications.[6,7] Preoperative consultations and clinics have a valuable role to play in a patient's surgical experience and outcomes.

PREOPERATIVE ASSESSMENT SETTINGS

The preoperative screening clinic is one example of a preoperative assessment alternative; others include a telephonic interview, an internet health screen, a primary care physician evaluation, and a mail-in health quiz. Frequently, a visit to a preoperative clinic is combined with another tool such as the health survey, and these results are used to identify patients requiring laboratory testing or a consultation with the anesthesiologist. Since the mid-1990s, preoperative testing clinics have gained in popularity. A survey of anesthesiology programs found the presence of a preoperative testing clinic in 88% of university and 70% of community hospitals in 1998.[8] Similar results were obtained after a survey in Ontario, Canada: 63% of 260 hospitals had preoperative clinics.[9] Options for multiple avenues of clinical care have allowed for further accessibility for patients. For example, a study was done evaluating remote preoperative patients in rural areas of Northern Territories in Australia, which showed positive perceptions by patients on technical quality, efficacy, patient experience, and patient preferences.[10] Additionally, the COVID-19 pandemic shifted many (if not all) preoperative assessment clinics to a virtual realm temporarily, and some have remained remote. This allowed institutions to consider once again how to navigate providing effective quality and comprehensive care.

CONSULTATIONS

In a patient with known or suspected cardiac diseases undergoing noncardiac surgery, there is still controversy on the best way to conduct the assessment. Cardiac consultations without a clear question and only "clearance" can be unnecessary and lead to delays, additional cost, and inconvenience to the patient and hospital.[11] Fischer et al. found that the introduction of the preoperative clinic led to a significant reduction

in the number of cardiology, pulmonary, and medical consultations.[12] After the introduction of stringent guidelines for consultation, Tsen and colleagues reduced the rate of cardiology consultations in patients undergoing noncardiac surgery from 1.46% (914 patients) to only 0.49% (279 patients; $p < .0001$), despite an increase in patient acuity over the 6-year study period. They also found that after the introduction of an electrocardiogram (ECG) educational program, they were able to reduce consultations for ECG abnormalities from 43.6% to 28.5% ($p < .0001$).[13]

Defining the role of the consultant is important in the preoperative setting. All consultations should provide a careful assessment of risk, and the success of a consultation is improved when the question is specific. An additional role of the consultant should be to advise on future health and additional postoperative strategies to reduce the patient's future risk, if possible.

COLLABORATIVE CARE

Brain Health

In 2015, the American Society of Anesthesiologists (ASA) proposed the Perioperative Brain Health Initiative to minimize the impact of preexisting cognitive deficits and optimize cognitive recovery for adults 65 and older undergoing surgery.[14] Postoperative delirium (POD) is a form of delirium that manifests in patients 1 to 3 days after their operation or procedure, with potentially long-standing effects on the patient and health care system overall.[15] The mechanism of POD has not been clearly described; however, there are multiple risk factors that are associated with its development. Previously reported common preoperative risk factors include age greater than 70 years, preexisting cognitive impairment (CI), use of benzodiazepines, and previous history of POD. The incidence of POD ranges from 5% to 15%. It is important to identify patients at risk for POD because it has been shown to increase in-hospital (and long-term) mortality rates.[16,17] POD is also associated with increased postoperative complications, longer length of hospital stay, and higher rates of discharge to an outside facility.[15] A substantial portion (approximately 20%) of elective surgical patients in the geriatric population without dementia have CI at baseline before surgery.[18,19] Studies have shown that preoperative cognitive screening of older surgical patients may be valuable for risk assessment and risk stratification, especially for identification and possible prevention of POD.[20] A Mini-Cog examination can be performed before surgery and the patient may need a referral for further evaluation by a primary care physician or geriatrician.[21,22] The Society of Perioperative Assessment and Quality Improvement (SPAQI) has made recommendation statements for various screening instruments for CI.[23] Many of these tests, such as the copy command clock-drawing test (CDT), Mini-Cog, and the mini-mental state exam (MMSE) show enough sensitivity and specificity for detecting CI. These tools can be used by laypeople or experienced examiners, are not very time consuming, and are freely available.

Frailty

Frailty is an age-related multifactorial state of decreased physiologic reserve that results in poor health outcomes, including falls, incident disability hospitalization, and mortality.[24] In the perioperative period, frail patients are at increased risk for postoperative complications and use a high amount of resources. Although frailty is not siloed to the geriatric population, it is most commonly seen in the older population. Identification of frailty in a patient allows for better preoperative optimization, can act as a catalyst for shared decision-making conversations, and may potentially decrease postoperative complications through identification of modifiable risk factors.[25] There are a number of frailty screening tools that are effective and feasible in practice. These include the Clinical Frailty Scale (CFS) and the FRAIL scale.[26] The screen enables the team to identify those who will benefit from a more comprehensive geriatric assessment by a geriatrician.

Preoperative Anemia

Preoperative iron deficiency anemia is the most common hematologic abnormality in patients undergoing major elective surgery.[27] The World Health Organization (WHO) defines anemia as a hemoglobin concentration of less than 13 g/dL in men and less than 12 g/dL in women.[28] Other causes of anemia include chronic disease, vitamin deficiencies, chronic renal failure, and hemoglobinopathies. Estimates of anemia in the surgical population range from 25% to 75% in orthopedic and colorectal surgeries, respectively.[7] In the preoperative clinic setting, there is an opportunity to optimize anemia to reduce the incidence of perioperative transfusions. Patients with preoperative anemia are at increased risk for 30-day mortality, and there is an independent risk factor for red blood cell (RBC) transfusion and postoperative morbidity.[29] In addition, reductions in perioperative transfusions can result in reduced costs for the blood bank and overall health care system. A program implemented at Duke for perioperative anemia screening and preoperative erythropoietin and/or iron therapy showed a financial model net value of more than US $2.5 million over 5 years.[30] Once anemia is identified in a patient in the preoperative process, further assessment of the type of anemia is warranted. This should include follow-up labs for testing for iron deficiency anemia, such as serum iron, transferrin levels, total iron binding capacity, and ferritin. Iron deficiency anemia can be treated with oral or intravenous (IV) formulations of iron. Oral iron takes longer to achieve restoration of iron stores and has side effects such as gastrointestinal upset. IV iron can increase hemoglobin up to 2.3 g/dL.[31] There are different formulations available and different dosing strategies. The simplest dosing available is a one-time dose of IV iron, which is most optimal at least 4 weeks before surgery.[30]

Chronic Pain and Surgery

Approximately 100 million US adults suffer from chronic pain. In the United States, chronic pain has resulted in lost productivity and treatment costs amounting to up to US $635 billion.[32] Anesthesia and surgery medical professionals often

encounter patients with active substance abuse disorders, patients in recovery, and patients who are prone to substance use disorders who require surgery and need effective analgesic plans. Ideally, a clear multidisciplinary plan should be created at the time surgery is booked for these patients. Preoperative communication is integral to setting realistic expectations for postoperative pain, developing opioid-sparing analgesic regimens and options for peripheral nerve blocks/regional anesthesia, and discussing concerns for relapse or diversion. Additionally, patients who are at high risk for developing chronic postsurgical pain (CPSP) can be identified in the preoperative clinic. Approximately 5% to 10% of patients develop CPSP 1 year after major surgery.[33] Patients at high risk for developing CPSP are those with posttraumatic stress disorder (PTSD), depression, anxiety, and pain catastrophizing. Inadequately controlled acute pain and excessive analgesic use have repeatedly been shown to delay recovery and hospital discharge after surgery.[33,34] These patients, in addition to those with known chronic pain, can be followed throughout their perioperative period by an acute pain service to allow for better management and should also ideally be seen by an acute pain physician preoperatively.

Shared Decision Making

Another essential element of VBC is providing patient-centered perioperative care. This includes making treatment decisions based on patient preferences and goals. This key component of patient autonomy is known as shared decision making (SDM). SDM involves discussions between the professional and the patient that bring knowledge, concerns, and perspective to the process of seeking agreement on a course of treatment. It allows the patient to participate in dialogue and convey their concerns and wishes. One survey showed that SDM enables patients to be better informed and feel less anxious about medical decisions.[35] Additionally, patients who felt their preoperative surgical decision making was led by their physicians were far more likely to feel conflicted about moving ahead with surgery than those who felt they had engaged in SDM. Additionally, involving patients in their own health care and giving regard to their goals could improve their satisfaction as well. This conversation can improve the appropriateness of care, which therefore becomes higher value of care for patients based on patient-centered outcomes.[36] Therefore, as the United States shifts away from a fee-for-service health care system and toward a VBC system, a multidisciplinary team can be involved to help facilitate SDM conversations for complex patients.

OPERATING ROOM CANCELLATIONS

When surgery is cancelled, it can mean multiple things for the patient, the hospital, and the surgeon; it can also be emotional for the patient depending on their disease process. In the past, OR cancellation/same day cancellation was and (still is) associated with cost because it involves a loss of OR time, which could have gone to another surgeon and patient. The patient also experiences anxiety and a loss of time and effort when they arrive at the day of surgery only to find out it was cancelled. Preoperative assessment clinics have been shown to reduce OR cancellations. The Perioperative Optimization of Senior Health (POSH) clinic at Duke did a study, which showed cancellation rates within the POSH program were lower than institutional cancellation rates for adults over age 65 who did not participate in POSH.[37] Ultimately, 7.3% of POSH-referred patients did not proceed to surgery. Patients who did not proceed to surgery were significantly older, more likely to have functional limitations, and had more severe comorbidities than those who did proceed to surgery. This ties back into our shifting health care system from volume to VBC where perioperative care is centered around patient outcomes. Another study at Brigham and Women's Hospital, found 147 of 16,955 cases were cancelled for reasons associated with their preoperative assessment before their operative date (approximately 1% of the sample).[38] Patients whose cases were cancelled had a higher ASA physical status and were older than noncancelled cases. They found that 9% of cases were cancelled because the patient judged the risks of the scheduled procedure to outweigh the clinical benefits. Another 4% were cancelled by the clinical team because preoperative clinical changes caused the risk to outweigh benefits. They also found 77% of the cancelled cases were at elevated risk per the American College of Cardiology/American Heart Association guidelines. Preoperative assessment clinics have been shown to be effective in implementing risk factor modification, which can decrease hospital costs by avoiding postoperative complications, long-term rehabilitation stays, and long hospital stays.

AREAS OF UNCERTAINTY

We have reviewed a complex, evolving care model in preoperative medicine. As the population ages and surgery becomes more common in patients with complex medical conditions and/or of advanced age, SDM and preoperative optimization are becoming increasingly important. VBC requires a focus on both patient outcomes and cost. A high-functioning preoperative optimization strategy, whether through a traditional clinic or virtual equivalent, can improve both short-term and long-term patient outcomes through optimization of chronic conditions, such as anemia, before the surgical episode and can also reduce the cost of unnecessary testing and delay or cancellations in the OR.

Nevertheless, there are still many questions to be answered regarding exactly how we can continue to evolve this VBC health system and, because this shift is relatively new, what the long-term implications are for patients, physicians, and the overall health care system. There are a lot of uncertainties on how individual departments can logistically come together to work toward patient goals and no clear-cut guidelines are out there to help navigate this system. It can also be difficult to place an exact number on the value gained through preoperative clinics.

AUTHORS' RECOMMENDATIONS

There is not one standard implementation method for a preoperative clinic; however, the following are suggestions for how to optimize a value-based preoperative clinic.

1. Use multidisciplinary teams for studied areas of benefit, such as by:
   a. Considering a geriatric pathway (including a cognitive and frailty assessment)
   b. Considering a perioperative anemia pathway
   c. Considering acute pain consults for chronic pain patients preoperatively
2. Ensuring the earliest possible preoperative clinic appointment is available once surgery is booked for complicated patients to ensure time for intervention and preparedness before surgery
3. Establishing patient screening for in-person versus virtual preoperative consultations
4. Discussing goals of care
5. Considering an appropriate consultation for a specialist if the anesthesiologist recommends it

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3

Which Patient Should Have a Preoperative Cardiac Evaluation (Stress Test)?

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CHAPTER OUTLINE

INTRODUCTION

Preoperative cardiovascular risk assessment attempts to prospectively identify at-risk patients and allows targeted management to reduce perioperative cardiac complications. These complications include both "demand" events, in which perioperative stress increases myocardial oxygen requirements to a level that cannot be met because of fixed obstructive coronary artery disease (CAD) or low perfusion pressure, and true "acute coronary syndromes" (ACS) with occlusive plaque rupture, likely due, in part, to perioperative inflammation and an associated prothrombotic state.[1,2]

A careful history and physical examination are the cornerstone for perioperative cardiovascular risk assessment. Epicardial obstructive CAD sufficient to cause demand-related biomarker release can be identified by cardiac stress testing and coronary angiography. Nevertheless, before pursuing these tests preoperatively, it is essential to determine whether that test will lead to a meaningful short- or long-term change in the management. This change in management includes not just the question of coronary revascularization but also decisions on the extent of surgery or the surgical approach, location of the surgery (i.e., outpatient or monitored facility), type of anesthesia, timing of the surgery, or consideration of nonsurgical alternatives.

Perioperative cardiovascular assessment has evolved to include risk prediction tools and biomarkers to identify at-risk patients and ischemia evaluation using stress testing, when indicated, to identify hemodynamically significant CAD followed by medical optimization or possible revascularization. Revolutionary changes in cardiovascular medical management, together with advances in surgical and anesthetic techniques, have significantly reduced operative morbidity and mortality rates; event rates have decreased from approximately 10% to 15% in intermediate-risk patients three decades ago to approximately 5% in contemporary "at-risk" patients (i.e., those with risk factors for or known CAD) and to approximately 1.5% in unselected noncardiac surgery patients.[1,3–5] Anesthesia-related deaths occur in less than 1 in 100,000 noncardiac procedures.[6] This reduction in risk likely attenuates any potential benefit of preoperative revascularization, and current guidelines do not recommend routine stress testing or revascularization in stable patients.[7–9] Consequently, the role of preoperative cardiac stress testing has been reduced to the identification of extremely high-risk patients, such as those with significant left main disease, for whom preoperative revascularization may provide a benefit independent of the noncardiac surgery.

ASSESSING CARDIAC RISK: OPTIONS/ EVALUATION STRATEGIES

As we integrate the available data into standard practice, the following key issues emerge:

1. Understanding risk factor implications, including risk prediction tools and biomarkers
2. Understanding absolute contraindications to nonemergent surgical procedures

3. Understanding medical treatment options independent of revascularization that can significantly affect patient outcome
4. Understanding the risks and benefits of revascularization in the preoperative period
5. Appropriate testing for ischemia evaluation

PERIOPERATIVE CARDIAC RISK STRATIFICATION: RISK PREDICTION TOOLS

Risk prediction tools can enable prospective quantification of perioperative cardiovascular risk and have been recommended by current guidelines (Table 3.1). In the Revised Cardiac Risk Index (RCRI), patients are divided into quartiles of predicted risk for in-hospital myocardial infarction (MI), pulmonary edema, ventricular fibrillation or primary cardiac arrest, complete heart block, or cardiac death based on six independent risk factors (https://qxmd.com/calculate/calculator_195/revised-cardiac-risk-index-lee-criteria).[10] RCRI is the simplest tool to use, and patients with at least two risk predictors are considered to have elevated risk. The MI or Cardiac Arrest (MICA) risk index and the American College of Surgeons Surgical Risk Calculator (ACS-SRC) were developed from the National Surgical Quality Improvement Program database and are accessible at https://qxmd.com/calculate/calculator_245/gupta-perioperative-cardiac-risk and https://riskcalculator.facs.org/RiskCalculator/index.jsp, respectively. The ACS-SRC is the most comprehensive, web-based tool. The *c*-statistic of these risk prediction tools varies from 0.76 to 0.80 for RCRI, 0.87 to 0.88 for MICA, and 0.80 to 0.94 for ACS-SRC.[10–12]

PERIOPERATIVE CARDIAC RISK STRATIFICATION: BIOMARKERS

Biomarkers such as troponin (see Chapter 62) and B-type natriuretic peptide (BNP; see Chapter 9) can improve preoperative cardiac risk stratification and have been recommended by the 2014 European Society of Cardiology/European Society of Anesthesiology (ESC/ESA) and the 2017 Canadian Cardiovascular Society (CCS) guidelines (see Table 3.1).[8,9] The Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION) investigators reported that patients with elevated postoperative troponins within 30 days of noncardiac surgery have an increased risk for 30-day mortality, nonfatal cardiac arrest, heart failure, and stroke.[13,14] These investigators defined myocardial injury after noncardiac surgery (MINS) as a rise and/or fall of troponin of presumed ischemic etiology within 30 days of noncardiac surgery that may or may not meet the criteria for the universal definition of MI.[13–16] The incidence of perioperative MIs has been reported to be 3% to 6%; it is estimated that approximately 93% of the episodes of MINS and 68% of the perioperative MIs would be unrecognized in the absence of troponin surveillance.[17] Consequently, the ESC/ESA and CCS guidelines (but not the 2014 American College of Cardiology/American Heart Association [ACC/AHA] guidelines) recommend postoperative troponin surveillance in high-risk patients.[7–9]

A meta-analysis including 2179 patients from 18 studies reported that preoperative BNP improved the risk stratification for death or nonfatal MI at 30 days (net reclassification index 20%) and at 180 days or more (net reclassification index 11%) after noncardiac surgery.[18] A prospective cohort study consisting of 10,402 patients reported that elevated N-terminal proBNP (NT-proBNP) (defined as >100 pg/mL) was significantly associated with vascular death and MINS at 30 days after noncardiac surgery and also improved cardiac risk prediction in addition to RCRI (net absolute reclassification improvement of 258 per 1000 patients).[19] In the METS (Measurement of Exercise Tolerance before Surgery) study, however, NT-proBNP was not predictive of 30-day MI or death.[20]

EVIDENCE THAT SPECIFIC HIGH-RISK CONDITIONS DEMAND PREOPERATIVE ASSESSMENT AND INTERVENTION

The ACC/AHA guidelines for preoperative cardiac assessment also define four "major" risk factors that preclude nonemergent surgical procedures: active/recent unstable coronary syndrome, decompensated heart failure (HF), significant arrhythmia, and severe valvular disease.[7]

Acute Coronary Syndrome

An active unstable coronary syndrome is, until proven otherwise, an ACS reflecting erosion or rupture of an atherosclerotic plaque. Patients with an ACS are at increased perioperative risk, and in such cases surgery should be delayed when possible. Retrospective electrocardiogram (ECG) analysis from the GUSTO-IIb (Global Use Of Strategies To Open occluded arteries in ACS) study demonstrated that mortality rates rise for 20 to 30 days after presentation, after which mortality rates stabilize.[21] Another study confirmed this high risk within the first 30 days but noted the significant risk for postoperative mortality and MI extended at least 2 months after an MI.[22] As such, the ACC/AHA guidelines recommend that at least 60 days should elapse after an MI, in the absence of a coronary intervention, before pursuing noncardiac surgery.[7]

Decompensated Heart Failure

Although treatments for HF have advanced significantly in the past decade, survival benefits have been more prominent in patients with mild to moderate disease than in those with advanced HF.[23] The 28-day case fatality rate in acute decompensated HF ranges from 9.2% to 12.1%.[24] These rates, which exceed the expected cardiovascular event rates for the vast majority of elective surgical procedures, would almost certainly increase significantly with the hemodynamic and systemic stress of surgery. Early multivariate risk factor analyses confirmed that decompensated HF was associated with an increased risk of perioperative morbidity and mortality.[4] Patients with nonischemic cardiomyopathy require optimization of the underlying pathology and careful monitoring of the volume status, cardiac medication adjustment, and monitoring for arrhythmias.

TABLE 3.1 Recommendations From Societies for Perioperative Cardiac Risk Assessment and Management

	2014 ACC/AHA and 2016 ACC/AHA focus update	2014 ESC/ESA	2017 CCS
Risk prediction tools	Recommend use of RCRI, MICA, or ACS-SRC for prediction of MACE (Class IIa/LOE: B)	Recommend use of RCRI, MICA, or ACS-SRC for prediction of MACE (Class I)	Favor RCRI over other cardiovascular risk prediction tools (Conditional recommendation; low-quality evidence)
Biomarkers	Uncertain usefulness of postoperative troponin surveillance or ECGs in asymptomatic patients at high risk for MI (Class IIb/LOE: B) BNP may be helpful in assessing patients with HF preoperatively or for diagnosing HF postoperatively in high-risk patients	May consider measuring BNP and hs-Tn perioperatively in high-risk patients (i.e., functional capacity ≤4 METS or RCRI >1 for vascular surgery, and >2 for nonvascular surgery or postoperative surgical Apgar score <7) (Class IIb/LOE: B)	Recommend daily troponins for 48–72 hours after noncardiac surgery and ECG immediately after the surgery in the recovery room if baseline risk of 30-day cardiovascular death or nonfatal MI is >5% (i.e., preoperative NT-proBNP ≥300 mg/L or BNP ≥92 mg/L or, if these biomarkers are not available, RCRI score ≥1, age 45–64 years with significant cardiovascular disease, or age ≥65 years) (Strong recommendation; moderate-quality evidence)
Beta-blockers	Continue beta-blockers if patient taking them chronically Do not initiate beta-blockers within 24 hours of surgery If RCRI ≥3, reasonable to start beta-blockers (Class IIb/LOE: B) Reasonable to start beta-blockers if intermediate- or high-risk myocardial ischemia noted in preoperative risk stratification tests (Class IIb/LOE: C)	Continue beta-blockers if patient taking it chronically Do not initiate beta-blockers within 24 hours of surgery May consider preoperative beta-blockers if ≥2 clinical risk factors or ASA ≥3 if high-risk surgery (Class IIb/LOE: B) and if known CAD or myocardial ischemia (Class IIb/LOE: B) - Atenolol or bisoprolol may be first choice (Class IIb/LOE: B)	Continue beta-blockers if patient taking it chronically Do not initiate beta-blockers within 24 hours of surgery
Statins	Continue statins perioperatively (Class I/LOE: B) Perioperative initiation of statins may be considered in patients undergoing elevated risk procedures in accordance with guideline-directed medical therapy (Class IIb/LOE: C) For patients undergoing vascular surgery, reasonable to initiate statins preoperatively (Class IIb/LOE: B)	Continue statins perioperatively (Class I/LOE: C) Favor statins with a long half-life (e.g., atorvastatin) or extended-release formulations (e.g., lovastatin) if oral intake not feasible in the immediate postoperative period For patients undergoing vascular surgery, initiate statins ideally ≥2 weeks before surgery (Class IIa/LOE: B)	Evidence too weak to make recommendation on initiation of statins Continue statins perioperatively (Strong recommendation; moderate-quality evidence)
Antiplatelet therapy	Initiation or continuation of aspirin not beneficial in patients without significant risk factors or known CAD (Class III/LOE: B) Continue aspirin in patients with coronary stents unless bleeding risk is exceptionally high Continue DAPT in patients with coronary stents unless the bleeding risk is prohibitive (Class I/LOE: C)	Continuation of aspirin should be individualized (Class IIb/LOE: B) Continue aspirin in patients with coronary stents unless bleeding risk is exceptionally high	Recommend against initiation of aspirin for prevention of perioperative cardiac events (Strong recommendation; high-quality evidence) Recommend against continuation of aspirin perioperatively except in patients with coronary stents or those undergoing carotid endarterectomy (Strong recommendation; high-quality evidence)

TABLE 3.1 Recommendations From Society Guidelines for Perioperative Cardiac Risk Assessment—cont'd

	2014 ACC/AHA and 2016 ACC/AHA focus update	2014 ESC/ESA	2017 CCS
ACEI/ARB	Reasonable to continue ACEI/ARB perioperatively If discontinued, reasonable to resume when feasible	Withhold ACEI/ARB 24 hours before noncardiac surgery unless the patient is stable and has left ventricular systolic dysfunction (Class IIa/LOE: C) Resume ACEI/ARB on postoperative day 2 if the patient is hemodynamically stable Initiate ACEI/ARB ≥1 week before noncardiac surgery in stable patients with left ventricular dysfunction (Class IIa/LOE: C)	Withhold ACEI/ARB 24 hours before noncardiac surgery (Strong recommendation; low-quality evidence)
Coronary revascularization	Recommend against routine preoperative coronary revascularization in stable patients before noncardiac surgery (Class III/LOE: C)	May be considered in stable patients before nonurgent carotid endarterectomy (Class IIb/LOE: B) but not in stable patients before low-risk surgery (Class III/LOE: C)	Recommend against routine preoperative coronary revascularization in stable patients before noncardiac surgery (Strong recommendation; low-quality evidence)
Timing of surgery after PCI	Postpone elective surgery for a minimum of 30 days after BMS-PCI and 12 months after DES-PCI (6 months after DES-PCI in 2016 focus update) (Class IIb) and for at least 12 months after ACS (Class I) If surgery cannot be postponed beyond 3 months after PCI and $P2Y_{12}$ inhibitor has to be interrupted perioperatively, continue aspirin perioperatively if the bleeding risk allows (Class IIb/LOE: C)	Postpone elective surgery for a minimum of 4 weeks after BMS-PCI and 6 months after new-generation DES-PCI, and for up to 1 year after ACS, irrespective of the revascularization strategy	No recommendation
Stress testing	Reasonable to forgo noninvasive testing with functional capacity >10 METS (Class IIa/LOE: B) or ≥4–10 METS (Class IIb/LOE: C) even if estimated to be at elevated risk Routine noninvasive stress testing not useful before low-risk noncardiac surgeries (Class III/LOE: B) May be reasonable to perform pharmacologic stress testing if elevated risk (≥1% risk of MACE) and poor or unknown functional capacity **if** it will impact decision making or perioperative care (Class IIb/LOE: C)	Routine noninvasive stress testing not useful before low-risk noncardiac surgeries (Class III/LOE: C) Recommend imaging stress testing with >2 clinical risk factors (RCRI) and poor functional capacity for high-risk surgery (Class I/LOE: C) May be considered if 1–2 clinical risk factors and poor functional capacity and high- or intermediate-risk surgery (Class IIa/LOE: C)	Recommend against stress testing (Strong recommendation; low-quality evidence) Recommend against exercise stress testing (Strong recommendation; low-quality evidence) Recommend against MPI and stress echocardiography (Strong recommendation; low- to moderate-quality evidence)
CPET	May be considered if unknown functional capacity and if planning high-risk procedure (Class IIb/LOE: B)	No recommendation	Not recommended (Strong recommendation; low-quality evidence)

ACC/AHA, American College of Cardiology/American Heart Association; *ACEI/ARB*, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; *ACS*, acute coronary syndrome; *ACS-SRC,* American College of Surgeon's Surgical Risk Calculator; *ASA*, American Society of Anesthesiologist's physical status score; *BMS*, bare metal stent; *BNP*, B-type natriuretic peptide; *CAD*, coronary artery disease; *CCS*, Canadian Cardiovascular Society; *CPET*, cardiopulmonary exercise testing; *DAPT*, dual antiplatelet therapy; *DES*, drug eluting stent; *ECG*, electrocardiogram; *ESC/ESA*, European Society of Cardiology/European Society of Anesthesiology; *HF*, heart failure; *hs-Tn*, high sensitivity troponin; *LOE*, level of evidence; *MACE*, major adverse cardiovascular event; *METS,* metabolic equivalents; *MI*, myocardial infarction; *MICA*, myocardial infarction and cardiac arrest; *MPI*, myocardial perfusion imaging; *NT-proBNP*, N-terminal-proBNP; *PCI*, percutaneous coronary intervention; *RCRI*, revised cardiac risk index.

Perioperative cardiac risk indices include HF as an independent prognostic variable for perioperative complications. Patients with acute HF may have significantly higher risk for perioperative mortality compared to those with CAD. Although symptomatic HF is associated with negative perioperative outcomes, the effect of asymptomatic left ventricular (LV) dysfunction is not known. LV ejection fraction (EF) less than 30% is an independent predictor of worse perioperative outcomes; mortality rates are better in patients with HF with preserved EF, but these rates are still higher compared with those without HF. Diastolic dysfunction with or without systolic dysfunction has also been associated with a higher risk for major adverse cardiovascular events (MACE), longer length of stay, and postoperative decompensated HF.

Arrhythmias and Conduction Disorders

In the perioperative context, "significant" arrhythmia refers to hemodynamically significant rhythm disturbances. Ventricular arrhythmias are of sufficient threat that even hemodynamically tolerated sustained ventricular arrhythmias should delay anything but emergent surgery. Nevertheless, nonsustained ventricular arrhythmias do not preclude surgical procedures and do not increase perioperative cardiovascular risk unless they result in hemodynamic compromise or occur in patients with structural heart disease or inherited conduction disorders.[7,25,26]

Uncontrolled atrial arrhythmias (i.e., with ventricular response rates exceeding approximately 100 beats per minute) place patients at increased risk for myocardial injury. Accordingly, rate control should be established before surgery. Although rate-controlled atrial arrhythmias do not preclude surgery, they are associated with an unmodifiable increase in perioperative risk and identify a sicker cohort of patients. With atrial arrhythmias, there is the ancillary issue of anticoagulation that needs to be addressed while balancing the risk for thromboembolism and bleeding.

Symptomatic bradycardia and high-grade atrioventricular conduction abnormalities are also considered significant arrhythmias in the context of perioperative risk. The presence of sinus node dysfunction and atrioventricular block require caution with perioperative beta-blockers; bifascicular blocks and isolated bundle branch blocks do not preclude the use of beta-blockers. Intraventricular conduction delays with no history of high-grade atrioventricular block or symptoms rarely progress to complete heart block perioperatively.

Valvular Disease

In general, regurgitant lesions are not a contraindication to elective surgery because such lesions are relatively tolerant of perioperative fluid shifts and anesthetic induction. In contrast, symptomatic or severe stenotic lesions are sensitive to changes in both preload and afterload and increase the risk for perioperative hemodynamic decompensation. It is recommended that patients with suspected moderate or higher-grade valvular stenosis or regurgitation undergo a preoperative echocardiogram if there was no prior echocardiogram in the past year or if there has been a significant change in the clinical status or physical examination since the last echocardiogram (Class I recommendation; level of evidence [LOE]: C).[7] Should the patient meet the indications for valvular replacement or repair based on the symptoms and severity, valvular intervention preoperatively before noncardiac surgery is effective in reducing the perioperative risk (Class I recommendation; LOE: C).[7] With advances in anesthetic and surgical techniques, patients with asymptomatic severe aortic stenosis (AS) or asymptomatic severe mitral or aortic regurgitation can undergo elevated-risk noncardiac surgeries with appropriate intra- and postoperative hemodynamic monitoring (Class IIa recommendation).[7] Patients with asymptomatic severe mitral stenosis can undergo elevated-risk noncardiac surgeries with appropriate intra- and postoperative hemodynamic monitoring if the morphology is not favorable for percutaneous mitral balloon commissurotomy (Class IIb recommendation; LOE: C).[7]

Although the decreasing incidence of rheumatic heart disease has made mitral valve stenosis a rare clinical finding, AS remains common. Several predictors of increased perioperative cardiac risk after noncardiac surgery in patients with AS have been proposed, including mean gradient greater than 45 to 50 mm Hg and/or aortic valve area less than 0.8 cm^2, LV systolic dysfunction, symptomatic AS, associated significant mitral regurgitation or other valvular disease, increase in mean gradient by 18 mm Hg or more during exercise, and significant CAD.[27] Efficacy of transcatheter aortic valve replacement (TAVR) in patients with AS undergoing noncardiac surgery is not established, but in patients with increased perioperative risk, TAVR can be considered on a case-by-case basis before elective noncardiac surgery.[7,27]

EVIDENCE FOR MODIFICATION OF PERIOPERATIVE RISK: ROLE OF MEDICAL TREATMENT

Beta-Blockers (see Chapter 14)

The role of so-called demand perioperative ischemia suggests that hemodynamic stress contributes to cardiovascular events.[2,3] Periods of greatest risk include peri-induction and the immediate postoperative period, presumably as lightened sedation allows for increasing sympathetic drive and resultant tachycardia.[2] Sympatholytic therapy with beta-blockers should blunt this response, minimizing myocardial demand, and current guidelines provide recommendations on their use in the perioperative period (see Table 3.1). The POISE (Perioperative Ischemic Evaluation) trial randomized 8351 patients planning to undergo noncardiac surgery to receive 100 mg of extended-release metoprolol succinate (or placebo) 2 to 4 hours before the surgery followed by a second dose within 6 hours of the surgery, and then initiate 200 mg of extended-release metoprolol succinate (or placebo) once daily starting 12 hours after the first postoperative dose for 30 days.[28] The metoprolol group had lower rates of cardiovascular death, nonfatal MI, and nonfatal cardiac arrest driven by a reduction in nonfatal MI, but there were more deaths and

strokes in this group compared with placebo. These results were similar to the conclusions in a subsequent systematic review.[29] The increased risk for death with metoprolol in the POISE trial was associated with clinically significant hypotension, bradycardia, and stroke. Sepsis or infection were the only causes of death that were significantly higher in the metoprolol group. The design of this trial where a significantly high dose of a long-acting beta-blocker was given immediately pre- and postoperatively may have contributed to the hypotension. A recent Cochrane review that included 83 randomized controlled trials with 14,967 participants undergoing noncardiac surgery reported that beta-blockers were associated with a reduced incidence of MI and atrial fibrillation or atrial flutter, an increased incidence of bradycardia and hypotension, an uncertain effect on 30-day all-cause mortality, and no difference in the rates of cerebrovascular events or ventricular arrhythmia.[30]

Statins

The 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors (also known as statins) have pleiotropic therapeutic effects on the cardiovascular system.[31] Although robust data from clinical trials are lacking, multiple observational studies have examined the perioperative outcomes of patients on statins, and in general, statins are associated with a reduced risk for perioperative mortality.[32–35] Current guidelines provide recommendations on statin use (see Table 3.1).[7–9,36,37]

Antiplatelet Therapy

There has been much uncertainty about the risks and benefits of aspirin in the perioperative period with noncardiac surgery. Perioperative antiplatelet therapy in patients with known CAD or at high risk for CAD requires a case-by-case discussion between the surgeon, anesthesiologist, cardiologist, and the postoperative team, carefully balancing the risk for thromboembolism and bleeding.[7] The POISE-2 trial randomized 10,010 patients planning to undergo noncardiac surgery to receive aspirin versus placebo.[38] Patients with recent coronary stents and those planning to undergo carotid endarterectomy, intracranial surgery, or retinal surgery were excluded. The 30-day risk for death or nonfatal MI was similar in the aspirin and placebo groups, but major bleeding was higher in the aspirin group. In contrast to the overall study results, a subgroup analysis of 470 patients with prior percutaneous coronary intervention (PCI) reported that aspirin decreased the risk for death or nonfatal MI compared with placebo without an increase in the risk for major or life-threatening bleeding, although the event rates were low.[39] In patients with coronary stents, aspirin should be continued throughout the perioperative period unless the anticipated bleeding risk is exceptionally high (e.g., neurosurgical procedures),[7,8] and dual antiplatelet therapy (DAPT) should be continued if the patient is at high thrombotic risk and the risk for bleeding is low (Class I recommendation; LOE: C).[7] Nevertheless, interruption of $P2Y_{12}$ inhibitors is recommended if the bleeding risk is high. When $P2Y_{12}$ inhibitors are interrupted, they should be resumed soon after the surgery (within 48 hours if possible), and patients should not be bridged with low-molecular-weight heparin.[8,40] Current guidelines provide recommendations on initiation and continuation of antiplatelet therapy in the perioperative period (see Table 3.1).[7–9,58]

Angiotensin-Converting Enzyme Inhibitors/ Angiotensin II Receptor Blockers (see Chapter 13)

Small clinical trials that studied the perioperative outcomes of patients on angiotensin-converting enzyme inhibitors/ angiotensin II receptor blockers (ACEI/ARB) have reported increased risk for intraoperative hypotension in patients on ACEI/ARB.[9,41–43] A systematic review confirmed this increase in hypotension in patients on ACEI/ARBs but found no increase in mortality or MACE.[44] Analysis of data from the VISION cohort made up of 14,687 patients aged 45 years or older undergoing noncardiac surgery reported lower risk for the composite of all-cause mortality, stroke or myocardial injury, and intraoperative hypotension among patients who held ACEI/ARB 24 hours before the surgery.[45] Current guidelines provide recommendations on withholding and resuming ACEI/ARB in the perioperative period although this issue remains controversial (see Table 3.1).[7–9]

Other Medical Therapies

A number of pharmacologic agents, including alpha-2 agonists (e.g., clonidine) (see Chapter 15), nitroglycerin, and calcium channel blockers (CCBs), have been studied but have shown only limited evidence of perioperative benefit, and perioperative initiation of these medications is not recommended. Results from the POISE-2 trial and a Cochrane review concluded that clonidine did not reduce 30-day mortality, MI, or stroke but increased the risk for nonfatal cardiac arrest, hypotension, and bradycardia.[46,47] Clonidine should, however, be continued in patients who are taking it chronically. The ACC/AHA and CCS guidelines recommend against perioperative initiation of alpha-2 agonists and CCBs for the prevention of cardiovascular events.[7,9] CCBs should be continued if the patient is taking them chronically, especially in those with a history of vasospastic angina or tachyarrhythmias. A Cochrane review concluded that nitroglycerin or isosorbide dinitrate did not improve mortality or cardiac complications in patients undergoing noncardiac surgery, but nitrates should be continued in patients taking them chronically.[48]

UNDERSTANDING THE RISKS AND BENEFITS OF REVASCULARIZATION IN THE PERIOPERATIVE PERIOD

The overarching emphasis of the ACC/AHA, ESC/ESA, and CCS guidelines is that the indications for preoperative coronary angiography are no different than in nonsurgical settings (e.g., those with left main disease or unstable CAD; see Table 3.1; see also Chapters 4 and 11).[7–9] The fact that a patient is scheduled for surgery, regardless of the degree of surgical

risk, should not affect the patient's need for assessment and possible revascularization.

Data defining the role of perioperative revascularization can be temporally stratified by the means of revascularization (coronary artery bypass graft [CABG], angioplasty, coronary stents). The CASS (Coronary Artery Surgery Study) database provided the first retrospective evidence of risk reduction with revascularization, showing reduced cardiovascular morbidity and mortality rates for at least 6 years after CABG.[49] Importantly, these data predate the use of the left internal mammary artery conduit, which has greater longevity,[50] which suggests that protective effects could be more durable in the current era. By the mid-1980s, percutaneous transluminal coronary angioplasty (PTCA) was a viable alternative to CABG. Retrospective review suggested that, compared with procedures used in historical controls, PTCA reduced perioperative cardiovascular morbidity and mortality rates,[51,52] and prospective randomized evaluation found that PTCA was as effective as CABG in lowering the perioperative risk.[53,54]

PCI employing bare-metal coronary stents to scaffold open lesions resulted in better coronary artery patency but increased the risk for stent thrombosis. Drug-eluting stents and DAPT decreased the risk for stent thrombosis but increased the risk for bleeding. Various society recommendations (see Table 3.1) differ somewhat in the timing of noncardiac surgery after PCI, and this remains a critical but controversial area that continues to evolve.[7,8,40,55–58]

The CARP (Coronary Artery Revascularization Prophylaxis) trial[59] was the first prospective randomized trial to study preoperative revascularization in patients with stable obstructive CAD and enrolled 510 patients scheduled for elective major vascular surgery (abdominal aortic aneurysm repair or lower extremity revascularization) in whom angiography revealed significant CAD amenable to revascularization. Patients were randomly assigned to optimal medical therapy with or without preoperative coronary revascularization (PCI or CABG). Significant (>50%) stenosis of the left main artery was an exclusion criterion, as was LVEF of less than 20% or severe AS. Most patients were taking aspirin and beta-blockers, and over half were on a statin. There was no significant difference in the rate of MI within 30 days of surgery or in the mortality at 2.7 years. Because revascularization itself is associated with morbidity and mortality, this study was unable to demonstrate a benefit of prophylactic preoperative revascularization over optimal medical therapy.

Results from several clinical trials (e.g., ISCHEMIA [International Study of Comparative Health Effectiveness with Medical and Invasive Approaches], COURAGE [Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation], and CARP) demonstrate that, for patients with stable CAD on optimal medical therapy, event rates may not change with the addition of PCI.[59–61] Taken together, the available evidence suggests that cardiac catheterization is best employed for two purposes: (1) to exclude life-threatening/critical CAD (e.g., critical left main disease) and (2) for relief of refractory symptoms.

ASSESSMENT OF ISCHEMIA – WHO NEEDS A STRESS TEST?

Who Not to Test

Functional capacity is predictive of both perioperative and long-term cardiac events.[7] In general, asymptomatic patients with excellent functional capacity preoperatively do not require further cardiovascular testing before proceeding with the planned procedure (see Table 3.1),[7–9] and their prognosis is good even in the presence of stable ischemic heart disease or risk factors. Routine noninvasive stress testing is also not useful for patients planning to undergo low-risk noncardiac surgeries.[7,8]

Although an exercise ECG (e.g., treadmill or bicycle ergometer) can assess functional capacity, if the patient is able to achieve the target heart rate, the test was probably not indicated. The risk for perioperative and long-term cardiac events is significantly higher in patients who have myocardial ischemia at low exercise workloads compared with high exercise workload.[8] While an exercise test may provide additional information on hemodynamics and/or arrhythmias, it cannot reliably indicate the anatomic location of the ischemic lesion, and it has inferior diagnostic performance compared with diagnostic imaging tests.[62,63] For these reasons, pharmacological stress testing with imaging is preferred, if there is an indication.

Who to Test and How to Test

Increased morbidity and mortality rates are seen in patients with *poor functional capacity,* and cardiac stress testing has been used for preoperative risk stratification of patients with known or suspected CAD planning to undergo nonemergent procedures. It may be reasonable to perform pharmacologic stress testing in patients at elevated risk (≥1% risk for MACE) with poor or unknown functional capacity **IF** it will impact decision making or perioperative care.[7]

Patients with poor functional capacity include those unable to achieve 4-METs (metabolic equivalents of tasks).[64] A simple marker for 4-MET capacity is the ability to climb a flight of stairs or walk on level ground at 4 mph.[7] The METS study, a multicenter, international, prospective cohort comprising 1401 patients, compared the subjective assessment of preoperative functional capacity by anesthesiologists with three objective measures: cardiopulmonary exercise testing (CPET), score on the Duke Activity Status Index (DASI) questionnaire, and serum NT-proBNP.[20] In this study, subjective assessment did not accurately identify patients with poor cardiopulmonary fitness (<4 METs) or predict postoperative morbidity or mortality, but the scores on the standardized DASI questionnaire predicted the primary outcome of 30-day MI or death. The authors of this study recommended against using subjective assessments for estimation of MACE perioperatively. A subsequent analysis from the METS study concluded there was increased risk for 30-day MI or death for every 1 point below 34 on the DASI score.[65] It has been proposed that a DASI score greater than 34 may indicate low risk and a DASI score of less than 25 may indicate elevated risk.[66] In the METS study, peak oxygen consumption of 14 mL/kg/min (consistent with

4-MET capacity) measured during CPET was predictive of noncardiac postoperative complications only.[65] In contrast to the METS study, a more recent larger study including 4560 patients at higher risk (age >65 years or >45 years with cardiovascular disease) found that self-reported inability to climb two flights of stairs predicted MACE and all-cause mortality at 30 days and 1 year.[67]

In patients with or without known CAD who are unable to exercise adequately but have an indication to perform stress testing, pharmacologic stress radionuclide myocardial perfusion imaging (MPI) or dobutamine stress echocardiography are the most common modalities used in the perioperative setting. Although the sensitivity and specificity for the detection of significant CAD by stress testing are adequate (70%–88%)[68] and the negative predictive value is high (>95%), these tests have an unacceptably low positive predictive value (15%–20%) for cardiac events.[69] Although a negative test may provide some reassurance, most patients, even with a positive test, will not have a postoperative cardiac complication. Diagnostic testing is most helpful when the pretest probability is intermediate and the results will influence management.[62] The presence of moderate to large areas of reversible ischemia (20%–50%), at least two reversible defects on stress testing, and ischemic symptoms at less than 60% of the age-predicted maximal heart rate have been associated with an increased risk for perioperative MI.[70–72] Smaller areas of reversible ischemia (<20%) may not be associated with increased cardiac events postoperatively,[71] and fixed defects predict long-term but not short-term cardiac events.

In patients with morbid obesity, stress radionuclide MPI with positron emission tomography is preferred because obtaining high-quality images may be challenging with either stress radionuclide MPI with single photon emission computed tomography (CT; using technetium-99m-sestamibi or tetrofosmin or thallium-201) or stress echocardiography. In patients with left bundle branch block or ventricular pacing, stress echocardiography or vasodilator stress radionuclide MPI should be considered. Stress echocardiography has the additional advantage of providing an assessment of LV function at rest, pulmonary hypertension, and valvular function. Dobutamine should be avoided in patients with severe hypertension, significant arrhythmia, hemodynamically significant LV outflow obstruction, and hypotension.[7,8] Stress radionuclide MPI with vasodilators should be avoided if the patient has critical carotid occlusive disease, bronchospasm (e.g., patients with chronic obstructive lung disease), significant hypotension, or high-grade heart block.[7]

The role of coronary computed tomographic angiography (CCTA) and coronary artery calcium score before noncardiac surgery is unclear.[7] Although CCTA may improve risk prediction, it may overestimate the risk, and the CCS guidelines recommend against using CCTA to improve preoperative cardiac risk prediction (Strong recommendation; moderate quality evidence).[9,73]

In patients with *unknown functional capacity,* CPET may be considered if planning a high-risk procedure per the ACC/AHA guidelines, but this has not been recommended by other guidelines (see Table 3.1).[7–9]

For patients with stable CAD, guideline-directed optimal medical therapy is adequate. In a nonsurgical setting, the ISCHEMIA trial found no difference in the risk for cardiovascular death, MI, hospitalization for unstable angina or HF, or resuscitated cardiac arrest among patients with moderate to severe ischemia on stress testing who were randomized to initial invasive or initial conservative optimal medical therapy.[60] Even in patients in whom coronary artery stenosis is noted on angiography, there has been increasing evidence to focus on the functional significance of the stenosis to guide decisions on PCI using fractional flow reserve instead of the anatomic severity of the stenosis alone. This additionally suggests that some degree of ischemia and coronary artery stenosis is tolerated, and the long-term incidence of MACE is not increased if optimal medical therapy is continued.[74–76] In the perioperative setting, however, significant hemodynamic perturbances, a proinflammatory and hypercoagulable state, or interruption of prior antithrombotics may influence the occurrence of postoperative cardiac events. Acute plaque rupture could occur in nonflow limiting coronary lesions, or cardiac events could occur as a result of mismatch in supply and demand. In situations where evaluation for ischemia is challenging, consultation with a cardiovascular specialist should be obtained.

AREAS OF UNCERTAINTY AND FUTURE DIRECTION

Differences in society guidelines highlight multiple areas of controversy and uncertainty. Several risk prediction tools have been proposed to support preoperative risk stratification and quantification of the risk. Although direct comparisons between risk prediction tools cannot be made, RCRI remains the simplest tool, and ACS-SRC remains the most comprehensive one. Either one or a combination of both have been used to estimate the risk and to facilitate discussion with the patient/caregiver.[77] Newer risk indices have been developed but require external validation before widespread use.

Assessment of functional capacity still remains the anchor for decisions on cardiovascular testing before noncardiac surgery, but how to best assess the functional capacity is being questioned (either subjectively using METS or objectively using CPET or DASI). If using DASI, the specific cutoffs will need to be externally validated. The use of biomarkers (NT-proBNP and troponin) is slowly increasing and may provide assistance along with risk prediction tools in deciding whether to pursue further preoperative cardiac testing or possibly change postoperative management strategies (e.g., monitoring, medical comanagement, troponin surveillance).

In general, preoperative noninvasive or invasive testing to assess for ischemia in patients undergoing moderate- to high-risk surgeries should be pursued only if that test or intervention would have been pursued irrespective of the surgery or if it will change management. Even in patients with evidence of moderate to severe ischemia, there is a move toward optimal medical therapy over revascularization, except in patients with left main disease or critical three-vessel disease.

The outcomes of patients with coronary stents have significantly improved with the newer generation stents and use of DAPT. Shorter durations of DAPT are being studied, and careful consideration should be given to the timing of noncardiac surgery after PCI and the duration of interruption of DAPT perioperatively. Unless the risk for bleeding is excessive, aspirin should be continued in the perioperative period in patients with coronary stents. Finally, guidelines will have to be updated to reflect the evolving data from new studies.

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4

Should Patients With Stable Coronary Artery Disease Undergo Prophylactic Revascularization Before Noncardiac Surgery?

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CHAPTER OUTLINE

INTRODUCTION

The preoperative assessment of a patient in need of elective noncardiac surgery is often a difficult task. There has been enormous controversy regarding the appropriate strategy for diagnosing and managing coronary artery disease (CAD) before elective noncardiac surgery because of the paucity of clinical trial data. Overall, elective surgical procedures in a population of general medical patients are associated with a very low risk for perioperative cardiac complications; the incidence of either myocardial infarction (MI) or death is less than 1%.[1,2] Although the risk increases with the age of the patient, the low risk for perioperative complications does not justify widespread cardiac testing among all groups of surgical patients.

Among patients undergoing vascular surgery, however, the perioperative risk for cardiac complications is high. Although the reasons relate, in part, to the hemodynamic stresses associated with aortic procedures, the prevalence of atherosclerotic heart disease in patients undergoing vascular surgery exceeds 50%,[3] and therefore may require special attention in the preoperative period. CAD remains the major cause of death after any vascular operation[4]; therefore consideration for preoperative coronary artery revascularization is a justifiable endeavor.

OPTIONS

As outlined by the American College of Cardiology/American Heart Association (ACC/AHA) Task Force recommendations before noncardiac operations,[5] the approach to assessing the potential cardiac risk associated with any patient scheduled for an elective noncardiac operation includes the nature of the operation, the risk for associated CAD, and the functional capacity of the patient (Fig. 4.1). Determining the probability that a patient has severe obstructive CAD is one key ingredient of the preoperative risk assessment and should be based initially on the clinical history coupled with the nature of the operation. This entails the understanding that patients with vascular and orthopedic operations have the highest risk for postoperative cardiac complications compared with other noncardiac operations.[6–9] Specifically, individuals in need of a vascular operation involving an abdominal approach for either an expanding abdominal aortic aneurysm or advanced claudication have the highest risk.[2] Although urgent and emergent vascular operations occur in at least 20% of screened patients undergoing vascular operations,[10] these individuals are rarely considered candidates for preoperative coronary angiography and their preoperative risk management will not be addressed. The initial evaluation requires an assessment of a prior history of cardiac problems or risk factors along with either classic angina or unusual symptoms such as shortness of breath or atypical chest pains. Attention should be given to clinical risk variables,[2,11] which include age greater than 70 years, angina, history of congestive heart failure, prior MI, prior stroke or transient ischemic attack (TIA), history of ventricular arrhythmias, diabetes mellitus (particularly insulin-dependent diabetes), and abnormal renal function (creatinine level greater than 2.0 mg/dL). The physical examination also provides insight into high-risk variables,[5,10] including a chronic debilitated state, increased jugular venous distention, edema, S_3 gallop, and significant aortic stenosis, and the 12-lead electrocardiogram (ECG) provides prognostic information related to the presence of abnormal Q waves or heart

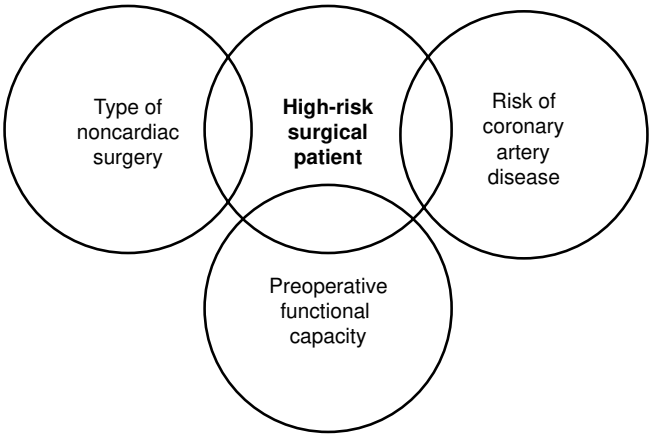

Fig. 4.1 Preoperative assessment.

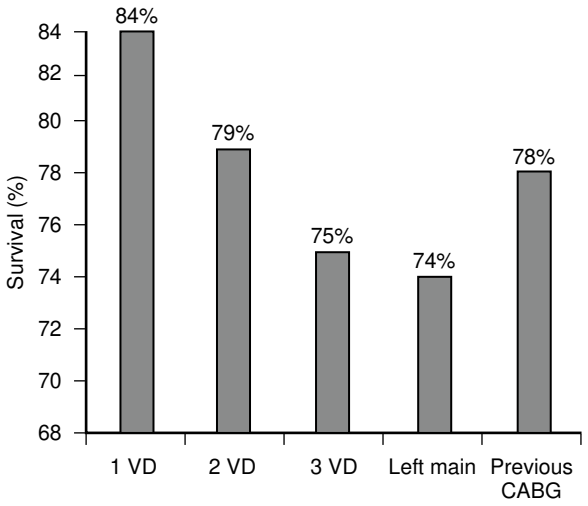

Fig. 4.2 Extent of coronary artery disease and survival 2.5 years after the vascular operation. *CABG,* Coronary artery bypass graft; *VD,* vessel disease.

rhythms. Although select clinical variables do predict perioperative cardiac morbidity and mortality risk, the optimal risk stratification tool for prediction of all complications in the postoperative period is controversial.[9] The final approach, therefore, is to determine whether, despite the absence of unstable clinical variables, there is sufficient concern to justify provocative stress testing preoperatively. Assessing the functional capacity of patients undergoing elective operations is an important ingredient in determining whether a patient can withstand the rigors of a prolonged operation. In those patients who are unable to achieve a 4-MET (metabolic equivalent of task) demand, a level compatible with routine daily activities, there is increased risk for postoperative events, and additional testing may be warranted.[12] Among patients with sufficient exercise capacity and an interpretable ECG, stress testing with an ECG alone may be a cost-effective means of risk stratification for low-risk patients who do not need additional cardiac workup.[13,14] Among those patients who cannot exercise or who have baseline ECG abnormalities, stress imaging tests have been recommended as the standard alternative for the preoperative detection of multivessel coronary artery disease.[6] The presence of multiple ischemic segments indicative of either multivessel CAD or left main disease is considered high risk and is associated with an increased risk for perioperative cardiac complications and reduced long-term survival.[15,16] Ultimately, a combined approach of using clinical variables associated with stress imaging tests is most cost-effective.[17] The role of adjuvant pharmacologic therapies cannot be overemphasized[18] and will be addressed in other chapters.

EVIDENCE

Role of Coronary Revascularization

Severe CAD is common among patients undergoing vascular surgery[3] and is a major determinant of long-term survival after vascular surgery.[4] Thus the role of coronary revascularization in the preoperative management of patients with stable coronary artery disease has been one of the most debated issues in the field of perioperative medicine. As part of the Coronary Artery Revascularization Prophylaxis (CARP) trial, we have learned from the registry and randomized cohorts undergoing preoperative coronary angiography that the extent and severity of CAD is an identifier of long-term survival after vascular surgery (Fig. 4.2).[19] This observation, coupled with outcome data from the Coronary Artery Surgery Study (CASS), which suggested better outcomes in patients with vascular disease who underwent coronary artery bypass surgery,[20] would support a plausible hypothesis that widespread identification and treatment of CAD should be an essential part of preoperative management. The paucity of prospective randomized data, however, has made it difficult for physicians to reach a consensus on the optimal strategy for those patients with CAD who are scheduled for elective noncardiac surgery. A survey conducted before the publication of the CARP trial showed that recommendations for preoperative revascularization deviated from the guidelines 40% of the time, and the chance of widely disparate opinions among the participating cardiologists was 26%.[21] Clearly, a large-scale trial was needed to test the long-term benefit of preoperative coronary artery revascularization before major noncardiac operations.

The CARP trial was the first randomized, multicenter study designed to assess the role of prophylactic revascularization in patients with CAD undergoing elective vascular operations.[10] Over a 4-year period involving 18 university-affiliated Veterans Affairs medical centers, 510 (9%) of 5859 screened patients were enrolled and randomly assigned to a preoperative strategy of either coronary artery revascularization or no revascularization before elective vascular surgery. The surgical indications were an abdominal aortic aneurysm in 169 (33%) or symptoms of lower extremity arterial occlusive disease, including severe claudication in 189 (37%) and rest pain in 152 (30%). Among the patients randomly assigned to a strategy of preoperative coronary artery revascularization,

TABLE 4.1 Clinical Studies Assessing the Role of Coronary Revascularization Before Major Vascular Surgery

	CARP Trial	DECREASE-V Pilot	Landesberg Study	Monaco Study
Study design	Multicenter, prospective	Multicenter, prospective	Single-center, retrospective	Multicenter, prospective
Treatment allocation	Randomized	Randomized	Nonrandomized	Randomized
Endpoint	Mortality rate at 2.7 yr	Mortality rate at 1 yr	Mortality rate at 3 yr	Major adverse cardiac events
Treatment effect	No benefit	No benefit, possible harm	Benefit in intermediate risk	Benefit
Total patients screened	5859	1880	624	672
Total patients randomized	510	101	N/A	208
Patients with three-vessel or left main disease	93	37	73	55
Mortality rate: no revascularization group	23%	23.1%	21.8%	Not reported
Mortality rate: revascularization group	22%	26.5%	14.6%	Not reported

CARP, Coronary Artery Revascularization Prophylaxis; *DECREASE,* Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography.

percutaneous coronary intervention (PCI) was performed in 141 (59%) and bypass surgery was performed in 99 (41%). The results of the study showed that procedural-related deaths associated with coronary artery revascularization occurred in only 1.7% of the patients, and no complications were related to cerebrovascular events, loss of limbs, or dialysis. The median times (interquartiles) from randomization to vascular surgery were 54 (28, 80) days in the coronary revascularization group, however, and 18 (7, 42) days in the no-revascularization group ($p < 0.001$). Within 30 days after vascular surgery, the mortality rate was 3.1% in the coronary revascularization group and 3.4% in the no-revascularization group ($p = 0.87$). An MI, defined by any elevation in troponins after vascular surgery, occurred in 11.6% of the revascularization group and in 14.3% of the no-revascularization group ($p = 0.37$). At a median time of 2.7 years after randomization, the mortality rates were 22% in the revascularization group and 23% in the no-revascularization group ($p = 0.92$; relative risk, 0.98; 95% confidence interval, 0.70–1.37). The conclusions from the CARP study are that, among patients undergoing elective vascular surgery, a strategy of preoperative coronary artery revascularization before elective vascular surgery does not improve outcome but rather may delay or even prevent the needed vascular procedure. Based on these data, coronary artery revascularization before elective vascular surgery among patients with stable ischemic heart disease is not supported.[10] Since the CARP trial was published, three other studies have reported outcomes in patients with CAD undergoing noncardiac surgery (Table 4.1).[22,23]

Landesberg and colleagues[24] have accumulated enormous experience over the past decade and have shown that preoperative stress imaging tests with thallium can identify patients with a worse postoperative outcome. They have also shown the utility of a clinical scoring system that, in conjunction with a high-risk preoperative thallium test, suggests improved outcomes with preoperative coronary artery revascularization.[23] The authors have implied that the CARP results are not generalizable because the trial was underpowered for high-risk coronary anatomy because of the low prevalence of patients with triple-vessel CAD and the exclusion of unprotected left main stenoses from randomization.[23] To address this potential limitation, however, Poldermans and colleagues[22] tested the benefit of a strategy of preoperative coronary artery revascularization in patients with high-risk stress imaging test results who were scheduled for vascular surgery. Their preliminary results showed a borderline unfavorable outcome with revascularization 1 year after vascular surgery (mortality rate at 1 year: revascularization, 26.5%; no revascularization, 23.1%; $p = 0.58$). In a subgroup analysis of the CARP trial, we found no evidence of clinical benefit among patients with multivessel CAD randomly assigned to prophylactic revascularization.[25] Monaco and colleagues[26] randomly assigned 208 high-risk patients undergoing vascular surgery to a "selective strategy" consisting of coronary angiography based on high-risk findings on noninvasive imaging or a "systematic strategy" that consisted of routine preoperative coronary angiography with coronary revascularization as needed. As expected, the revascularization rate was higher in the systematic strategy arm of the study (58% versus 40%). Although in-hospital cardiac complications were similar in the two groups, a reduction in major cardiac events (MACE), including mortality, was reported during long-term follow-up in favor of a systematic strategy (86% versus 69%). The authors presumed this was because of higher utilization rates of coronary revascularization in the systematic strategy arm.

So how should a clinician integrate the findings from these three studies into a unified approach in the preoperative period? Although the findings from Landesberg and colleagues[24] are informative for prognosis, the potential selection bias that favors any decision to undergo coronary artery revascularization in some patients is an important limitation on predicting late outcomes on retrospective analyses. Likewise, in the study by Monaco and colleagues, the decision to perform coronary revascularization was not randomized, and this could explain the disproportionate magnitude of the benefit (20% absolute and 50% relative risk reduction in MACE at 8 years) with only modest differences in utilization rates of coronary revascularization.

The study results of the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo)-V pilot study and the CARP trial do not support an aggressive strategy in the vast majority of patients with stable cardiac symptoms. One important exception to this general rule is worth mentioning. Patients with left main CAD were excluded from the randomization process in CARP, but their management and outcomes after vascular surgery were captured in the CARP registry.[19] This subset of patients consisted of 48 of 1048 patients undergoing preoperative coronary angiography before their intended vascular surgery (4.6%). Although their long-term survival rate appears to be improved with preoperative coronary artery revascularization (survival at 2.5 years for surgically and medically treated left main disease was 84% and 52%, respectively; $p < 0.01$), it is uncertain that the prevalence of such a small cohort before vascular surgery warrants widespread screening with expensive stress imaging tests.

OTHER INTERVENTIONS

Remote Ischemic Preconditioning

One potential strategy for reducing myocardial injury during surgery is ischemic preconditioning, which describes the cardioprotection obtained from the application of one or more nonlethal episodes of myocardial ischemia and reperfusion before the index myocardial ischemic event.[27] The cardioprotective effects of remote ischemic preconditioning (RIPC) have been extensively documented in animal models[28–30] and small, proof-of-concept human studies. The Cardiac Remote Ischemic Preconditioning Prior to Elective Vascular Surgery (CRIPES) trial was a prospective, randomized, sham-controlled, phase II clinical trial using RIPC before elective vascular surgery.[31] The RIPC protocol consisted of three cycles of 5-minute forearm ischemia followed by 5 minutes of reperfusion. The primary endpoint was the proportion of subjects with a detectable increase in cardiac troponin I (cTnI) and the distribution of such increases. Of the 201 patients, 47 (23.5%) had an increase in cTnI above the upper reference limit within 72 hours of the vascular operation, with no statistically significant difference between those patients assigned to RIPC (n = 22; 22.2%) versus the sham procedure (n = 25; 24.7%; $P = 0.67$). Among the cohort with increased cTnI, the median peak values (interquartile range) in the RIPC and control group were 0.048 (0.004–0.174) and 0.017 (0.003–0.105), respectively ($P = 0.54$). In summary, RIPC was not effective in reducing elevations in cardiac troponins after vascular surgery.

Antioxidants

Ubiquinone, or CoQ10, is a lipid-soluble benzoquinone, which protects membrane phospholipids from oxidative damage and reduces oxidative stress and inflammation.[32] In a randomized, double-blind study, CoQ10 administered for 3 days (400 mg/day) before vascular surgery reduced N-terminal pro hormone B-type natriuretic peptide (NT-Pro BNP) levels in the postoperative period (a known risk factor for adverse events, including myocardial injury) and reduced length of stay.[33] Additional studies are needed to determine whether this favorable effect on cardiac biomarkers translates into a reduction in long-term adverse cardiac events.

AREAS OF UNCERTAINTY

To improve the outcomes of high-risk patients undergoing elective operations, we must shift the paradigm from widespread identification and treatment of CAD in the preoperative phase to a more comprehensive identification and modification of risk factors in the postoperative phase. The utility of biomarkers during the perioperative period is intriguing and may prove valuable in identifying those patients at the highest long-term risk for adverse cardiac events. Among patients undergoing noncardiac operations, postoperative MI occurs primarily in those individuals with a prior history of CAD,[34] and the highest risk is related to surgery for an expanding abdominal aortic aneurysm.[2] Serial troponin assays have become the standard means of surveillance in the postoperative period because only a minority of patients with a documented MI will have symptoms.[35,36] The cost effectiveness of widespread measurements of biochemical markers after noncardiac surgery is unclear but potentially provides a beneficial effect in targeting those individuals with advanced CAD in need of revascularization. The incidence of perioperative MI among individuals undergoing a vascular operation approaches 20% and can be predicted by abnormalities on preoperative stress imaging with thallium.[36] Among those individuals with a perioperative MI, the mortality rate is increased nearly fourfold during a 6-month postoperative follow-up period[37,38] and may predict the long-term mortality rate, although this is not certain beyond the first postoperative year.[39] Among those patients undergoing their intended vascular operation within the CARP trial, a perioperative elevation of troponin I above the 99th percentile of normal was most common in patients undergoing abdominal aortic cross-clamp procedures and was associated with a worse long-term outcome.[40] The causative factors that relate to a new MI in the postoperative phase are not necessarily related to a severe stenosis within a coronary artery that has not been revascularized. Instead, postoperative ischemic myocardium can be a result of coronary arteries that have been completely occluded and have insufficient collateral flow or a new unstable coronary artery lesion.[41] Alternatively, the perioperative

phase can be associated with increased myocardial supply–demand mismatch, leading to subendocardial hypoperfusion without any change in the severity of the coronary artery stenoses.[42] Based on pathologic analysis from patients who have died of a perioperative MI, advanced CAD is present in the majority of patients; only a minority of individuals show intracoronary artery thrombus.[43,44] Clearly, more studies are needed to not only understand the biology of acute coronary artery syndromes after noncardiac surgery but also determine the optimal timing of revascularization, if that is deemed necessary. After the operations, it is imperative that therapies directed at secondary prevention be vigorously administered in suitable patients and should include antiplatelet agents, statins, beta-blockers, and possibly angiotensin-converting enzyme (ACE) inhibitors. Within the CARP study, the vast majority of patients in both treatment arms were using these medications 2 years after randomization, and this may have contributed to an improved outcome in patients not undergoing an initial strategy of coronary artery revascularization.[9] Other than ischemic heart disease, patients with other modifiable risk characteristics, including congestive heart failure, ventricular arrhythmias, and diabetes, need to be targeted in the postoperative period. Among the nonrandomized patients in the registry of the CARP study, these clinical variables were independent clinical variables that predicted the long-term mortality rate.[45]

GUIDELINES

Guidelines published by the ACC/AHA on perioperative cardiovascular evaluation and care define recommendations as follows.

Recommendations for Preoperative Coronary Revascularization With Coronary Artery Bypass Grafting or Percutaneous Coronary Intervention

All of the following Class I indications are consistent with the ACC/AHA 2004 Guideline Update for Coronary Artery Bypass Graft Surgery.

Class I

Coronary revascularization before noncardiac surgery is:

- Useful in patients with stable angina who have significant left main coronary artery stenosis. (level of evidence [LOE]: A)
- Useful in patients with stable angina who have three-vessel disease. (Survival benefit is greater when the left ventricular ejection fraction is less than 0.50.) (LOE: A)
- Useful in patients with stable angina who have two-vessel disease with significant proximal left anterior descending stenosis and either an ejection fraction less than 0.50 or demonstrable ischemia on noninvasive testing. (LOE: A)
- Recommended for patients with high-risk unstable angina or non–ST-segment elevation MI. (LOE: A)
- Recommended in patients with acute ST-segment elevation MI. (LOE: A)

Class IIa

- In patients in whom coronary revascularization with PCI is appropriate for mitigation of cardiac symptoms and who need elective noncardiac surgery in the subsequent 12 months, a strategy of balloon angioplasty or bare-metal stent placement followed by 4 to 6 weeks of dual antiplatelet therapy is probably indicated. (LOE: B)
- In patients who have received drug-eluting coronary stents and who must undergo urgent surgical procedures that mandate the discontinuation of thienopyridine therapy, it is reasonable to continue aspirin if at all possible and restart the thienopyridine as soon as possible. (LOE: C)

Class IIb

The usefulness of preoperative coronary revascularization is not well established.

- In high-risk ischemic patients (e.g., abnormal dobutamine stress ECG with at least five segments of wall-motion abnormalities). (LOE: C)
- For low-risk ischemic patients with an abnormal dobutamine stress ECG (segments 1–4). (LOE: B)

Class III

- It is not recommended that routine prophylactic coronary revascularization be performed in patients with stable CAD before noncardiac surgery. (LOE: B)
- Elective noncardiac surgery is not recommended within 4 to 6 weeks of bare-metal coronary stent implantation or within 12 months of drug-eluting coronary stent implantation in patients in whom thienopyridine therapy or aspirin and thienopyridine therapy will need to be discontinued perioperatively. (LOE: B)
- Elective noncardiac surgery is not recommended within 4 weeks of coronary revascularization with balloon angioplasty. (LOE: B)

AUTHORS' RECOMMENDATIONS

- To improve the outcomes of high-risk patients, clinicians must shift the paradigm of widespread screening and treatment of coronary artery disease (CAD) before the operation to a comprehensive strategy for modification of risks in the postoperative period.
- The optimal strategy for identifying and treating high-risk patients before elective noncardiac surgery should underscore the value of a conservative strategy that includes proceeding with a timely operation, if deemed appropriate. It also should ensure use of medical therapies that reduce secondary outcomes in patients with CAD, particularly regarding therapeutic doses of beta-blockers.
- Patients with an unprotected left main stenosis may be the only subset of patients with multivessel CAD that need special consideration before a vascular operation. This subset consists of less than 5% of individuals undergoing noncardiac operations and does not justify widespread stress imaging tests preoperatively so that such a small subset can be identified.
- Those individuals with evidence of a perioperative myocardial infarction, congestive heart failure, ventricular arrhythmias, and diabetes should be targeted and appropriately treated in the postoperative period.

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5

Reducing Risk for Perioperative Stroke

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CHAPTER OUTLINE

INTRODUCTION

Although strokes can and do occur at any age, the incidence of stroke doubles with every decade after the age of 45 years, with three-fourths of all strokes in the United States occurring in people over the age of 65 years.[1] People over 65 represented 13.1% of the population in the year 2010 but are expected to grow to be 20.6% of the population by 2030.[2] Furthermore, the population of those undergoing surgery is aging at a faster pace than the general population is.[3,4] Perioperative stroke is a potentially devastating complication of surgery that is associated with substantial morbidity and a 5- to 10-fold greater likelihood of in-hospital mortality.[5–7]

A perioperative stroke can occur intraoperatively or in the postoperative period and is commonly defined as a brain infarction of ischemic or hemorrhagic etiology with focal or global neurologic deficits that persists beyond 24 hours occurring within 30 days of the initial surgical procedure.[8–10] Further classification of perioperative stroke (most commonly applied in the cardiac surgery population) consists of three subtypes based on the timing of the clinical presentation: intraoperative, early postoperative, and late postoperative.[11] These subtypes have distinct risk factors and outcomes related to the mechanism of injury. The first is intraoperative stroke, which is diagnosed upon anesthesia emergence and is primarily caused by thromboembolism or hypoperfusion. The next is early postoperative stroke, which occurs within the first 7 days after the initial surgery and is generally caused by postoperative arrhythmias or hemodynamic factors. The third is late postoperative stroke, which occurs after 7 days but before 30 days after surgery and is commonly related to the general cerebrovascular risk profile of patients.[11,12]

The incidence of clinically recognized perioperative stroke varies widely with the type and timing of surgical procedure and the method of stroke detection.[13] Comprehensive reviews on this topic typically illustrate the representative incidences based on surgical procedure.[13,14] Surgical categories commonly include cardiac surgery (1.0%–8.7%),[15–19] carotid endarterectomy (1.8%–4.8%),[20,21] neurosurgery (0.5%–3.0%),[22,23] and noncardiac/noncarotid/nonneurologic procedures (0.1%–0.8%).[6,24–27] Certain surgeries in the latter category have a higher risk for perioperative stroke than others, such as thoracic, transplant, and major vascular surgery.[27] Furthermore, the incidence of clinically unrecognized stroke, termed "covert stroke," after noncardiac, noncarotid, and nonneurologic surgery may be as high as 7% in patients 65 years and older.[28] Underreporting of stroke and the high rate of covert strokes are thought to be related to a potential masking of deficits because of comorbid factors and insufficient neurologic evaluations. For example, the highest clinical incidence of stroke after surgical aortic valve replacement was reported to be 17% in the Determining Neurologic Outcomes from Valve Operations Study by Messé and colleagues, in which a neurologist assessed the study patients preoperatively and performed serial postoperative evaluations.[29] Within the same cohort, the incidence of stroke reported to the Society of Thoracic Surgery was 6.6%, and the overall rate of perioperative stroke after aortic valve replacement published by The Society of Thoracic Surgeons National Database Annual Reports was 1.3% to 1.5% over a similar time period.[29–31] Of note, 54% of the patients without clinical stroke in Messé's study had evidence of silent cerebral emboli found with diffusion-weighted magnetic resonance imaging (MRI). This variability in perioperative stroke incidence likely reflects the underlying surgical anatomy, the risk for vascular compromise and injury, the patient's overall preoperative health status, and the methods employed to detect stroke. As such, there are likely no simple solutions to prevent this complex perioperative complication. The problem has been approached by different specialties with a variety of preventive measures, including the development of predictive models, preprocedural optimum medical therapy, intraoperative neuromonitoring, novel approaches to the surgical procedure, and multidisciplinary postprocedural

care. Despite innovations and strategies, the incidence of perioperative stroke has remained a concern.

PATHOPHYSIOLOGY

Perioperative stroke after nonneurologic surgery is predominantly ischemic, rather than hemorrhagic, and the proposed mechanisms include thrombotic, embolic, lacunar, hematologic (hypercoagulable state), and hypoperfusion proces ses.[6,9,24,32–36] Intraoperative stroke during cardiac surgery is because of macroembolism from atherosclerotic aorta or cardiac chambers during manipulation in 70% to 80% of cases, and watershed stroke attributable to hypoperfusion and cases of mixed etiology make up the remaining 20% to 30%.[37–40] Early postoperative stroke after cardiac surgery is typically the result of emboli related to postoperative arrhythmias, specifically new-onset or preexisting atrial fibrillation (AF) or hypoperfusion insults related to hemodynamic factors such as low cardiac output syndrome and bleeding.[7,41] Late postoperative stroke is most commonly thromboembolic in nature and related to the general atherosclerotic risk profile of patients, including intracranial atherosclerotic disease, hypercoagulability, and AF.

The location of infarct and the distribution pattern often provide clues to the embolic origin of thromboembolic stroke, which are helpful in the perioperative period. Emboli originating from atherosclerotic plaque of the carotid bifurcation affect the anterior cerebral circulation, whereas emboli from plaque in the subclavian or vertebral arteries affect the posterior cerebral circulation. Intracardiac thrombi or a ruptured atheroma in the aortic arch may result in thromboembolic stroke in multiple vascular territories. Typically, the anterior circulation is involved in almost three-quarters of all instances of thromboembolic stroke among the general population, with occlusion of the middle cerebral artery or one of its branches accounting for approximately 90% of cases.[42–45] Posterior circulation infarcts occur far less often. Nevertheless, thromboembolic stroke occurs twice as often in the posterior circulation in cardiac surgery patients compared with ischemic infarcts that occur in the general population.[46] This is consistent with embolized atheromas of the distal ascending aorta, which are commonly manipulated (cannulation, cross-clamping, proximal aortic anastomoses) during coronary artery bypass grafting (CABG).[47] Additionally, intraoperative stroke has been reported to occur more commonly in the right hemisphere, which can be attributed to the high-velocity jet emerging from the aortic cannula.[8,48]

Stroke after noncardiac, noncarotid, nonneurologic surgery more often presents after a variable recovery time, in either the early or late postoperative period, and is less often evident on emergence from anesthesia, which suggests that intraoperative proceedings may be contributory rather than causal for stroke in these surgical patients.[49] The mechanisms for perioperative stroke in this population aside from AF-related embolic events, or fat or air embolism, may include surgery-mediated inflammatory responses and hypercoagulability. Although intraoperative hypotension is often assumed to be a major cause of stroke, data to support this mechanism are lacking, largely because hypotension during surgery is ill-defined and commonplace.[33,50–53] Although a prolonged period of time with a critically reduced blood pressure will certainly result in cerebral hypoperfusion and stroke, the temporal relationship between hypotension and infarction is difficult to establish perioperatively and blood pressure thresholds for cerebral ischemia likely vary by individual. Furthermore, hypotension and underresuscitation in the postoperative period may go unrecognized because most patients are less intensively monitored than during surgery.[14]

Stroke after neurologic surgery is most commonly ischemic in origin. Unlike patients undergoing nonneurologic procedures where stroke is predominantly arterial in nature, neurosurgical patients may suffer either arterial or venous cerebral infarctions. Arterial ischemia may result from traumatic laceration or from intentional sacrifice of an artery for either hemostasis, aneurysmal ligation, or surgical access. Venous infarcts may similarly result from traumatic laceration (i.e., when a major venous sinus is disrupted by the craniotomy or when a bleeding vein is coagulated to provide hemostasis). Venous occlusion may also occur with compression from intraoperative or postoperative cerebral edema, which compromises cerebral perfusion and prevents venous outflow.[54] The increased venous pressure further reduces effective drainage of affected brain tissue. This leads to increased cerebral blood volume and an even further reduction in cerebral perfusion pressure with subsequent oxygen deprivation and eventual infarction. Resection of tumors located near cerebral venous sinuses, especially parasagittal, convexity, parafalcine, or tentorial locations, increase the risk for venous injuries. Cerebral venous sinus thromboses frequently lead to hemorrhagic infarctions, which are driven by venous congestion and subsequent rupture of venules and capillaries. Cerebral venous infarction should be considered in cases of perioperative neurosurgical stroke (with or without hemorrhage) that do not correspond to a typical arterial territory.[55] Clinically significant intracranial hemorrhages complicate 0.5% to 6.9% of craniotomies, and both the hematoma location and etiology are dependent on the preoperative pathology.[56,57] Although most postoperative bleeds usually occur within the first 24 to 48 hours, the first 6 hours has been identified as a critical period within which an acute postoperative hematoma may become clinically evident.[58] The pathophysiology of postoperative intracranial hemorrhages varies and may be related to the underlying surgical anatomy, reperfusion injury, perioperative hypertension, cerebrospinal fluid loss, or hyperosmolar therapy leading to a parenchymal shift, or coagulopathy.[57,59]

OPTIONS/THERAPIES

The implication from the previous discussion of the pathophysiology of perioperative stroke is clear. An appreciable reduction in the incidence of stroke requires both universal and selective improvements by each surgical and anesthesiology subspecialty. Available techniques and methods to reduce

perioperative stroke include measures to be taken early in the preoperative setting, such as predictive modeling and identification of modifiable risk factors, as well as medication and surgical optimization. Intraoperative measures to reduce the risk for perioperative stroke are increasing and involve preoperative and intraoperative strategic decision making, sophisticated detection techniques and surgical expertise, and multimodality neuromonitoring. Lastly, identification of perioperative stroke requires collaboration among an interdisciplinary and multiprofessional perioperative team to initiate early therapy, such as embolectomy.

EVIDENCE

Preoperative Evaluation and Predictive Modeling

A number of cardiovascular risk stratification models have been developed to predict major perioperative complications after cardiac surgery (most commonly after CABG) using preoperative risk factors, including the Revised Cardiac Risk Index (RCRI),[60] the myocardial infarction (MI) or cardiac arrest (MICA) calculator,[61] and the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) Surgical Risk Calculator.[62] Nevertheless, stroke is not the primary endpoint in many of these tools, nor is it independent of other perioperative events in composite outcomes. The $CHADS_2$ (congestive heart failure, hypertension, age > 75 years, diabetes [all 1 point each]; previous stroke [2 points]) and the CHA_2DS_2-VASc ($CHADS_2$ plus vascular disease, age 65–74 years, and sex category [female sex; all worth 1 point]) scores are validated clinical tools to stratify stroke risk in patients with nonvalvular AF and are used to predict perioperative stroke risk in patients undergoing CABG.[63–66] Moreover, the CHA_2DS_2-VASc risk score has also been shown to predict perioperative stroke in patients undergoing various cardiac surgeries independent of the presence of AF.[67] Although the presence of any one risk factor for stroke is not considered an absolute contraindication for surgery, the models emphasize the additive effect that individual risk factors have on perioperative stroke risk.

A 2016 multivariate analysis of 94,546 patients in the ACS NSQIP database found 10 independent preclinical predictors for development of stroke and coma after neurosurgery.[22] These predictors were age, history of diabetes, inpatient status, ventilator dependence, and previous neurologic disease (impaired sensorium, coma greater than 24 hours, stroke with/without neurologic deficit, tumor involving the central nervous system, and hemiparesis). Six of the 10 independent predictors were indicators of preoperative neurovascular injury, which has been shown to be a major risk factor for perioperative stroke among all surgical populations.

Mashour et al. were the first to derive a perioperative stroke risk model for patients undergoing noncardiac, nonmajor vascular, and nonneurologic low-risk surgery using data on 523,059 patients in the ACS NSQIP database from 2005 to 2008.[26] They too identified 10 independent predictors of perioperative stroke, including age 62 years or older, MI within 6 months, acute renal failure, history of stroke, dialysis, hypertension, history of transient ischemic attack (TIA), chronic obstructive pulmonary disease, current smoker, and body mass index 35.0 to 40.0 kg/m^2. A more recent retrospective analysis of the same ACS-NSQIP database by Wilcox et al. from 2009 to 2010 compared the effectiveness of Mashour et al.'s model with other established cardiovascular risk stratification scores in patients undergoing both low- and high-risk noncardiac surgery, including neurosurgery.[68] They found that MICA and the ACS Surgical Risk Calculator were highly discriminative for perioperative stroke, whereas the $CHADS_2$, CHA_2DS_2-VASc, Mashour, and RCRI models demonstrated inferior risk discrimination. Stroke prediction among all models was less optimal in patients undergoing vascular surgery, which the authors postulate was related to surgical factors, including vascular manipulation and intraoperative hemodynamics as well as the greater burden of comorbid disease contributing to a more heterogeneous risk profile.

History of stroke or symptoms of cerebrovascular insufficiency, such as transient neurologic deficits, are strong predictors of perioperative stroke.[13] The etiology and treatment of ischemic stroke are often intimately related to cardiac disease, and risks associated with antithrombotic medication cessation in preparation for surgery increase the chance of recurrent stroke from AF or preexisting cerebrovascular disease. Further, cerebral blood flow autoregulation is impaired immediately after stroke, making penumbral tissue susceptible to pressure-passive blood flow. Therefore perioperative hemodynamic alterations and interruption of antithrombotic medication pose a substantial risk to patients with recent stroke. Prevention of reperfusion injury and maintenance of collateral circulation require tight blood pressure monitoring and control if surgery is required soon after an acute ischemic stroke. Currently, there is a lack of high-quality data regarding how soon anesthesia and surgery are safe after stroke. In a large Danish nationwide cohort, patients with prior stroke within 3 months of undergoing surgical aortic valve replacement had a 14.7-higher risk for recurrent ischemic stroke.[69] The risk reduced to 4.0- and 2.3-fold in patients with a prior stroke 3 to less than 12 months and 12 months or more, respectively, after the incident stroke. Jorgensen et al. analyzed the same Danish nationwide cohort and filtered for patients undergoing elective noncardiac surgeries.[25] They found a more time-dependent risk for recurrent stroke in this wider cohort, with a stepwise decline in risk for longer time distances between stroke and surgery up until 9 months, after which risk stabilized with persistent increased risk thereafter compared with patients without history of stroke.[25] Notably, incidence rates of perioperative stroke were 150-fold higher in patients with stroke less than 3 months before surgery compared with patients without stroke with an adjusted odds ratio of 67.6 for recurrent stroke, which was the same or higher for low-risk surgery and intermediate-risk surgery compared with high-risk surgery.

Although timing of surgery is one modifiable factor to reduce risk for recurrent stroke, preoperative screening may help identify other modifiable risk factors, such as diabetes,

smoking, and hypertension. Historically, carotid artery stenosis has also been considered a major modifiable risk factor in the development of stroke after cardiac procedures. It is unclear, however, if carotid artery disease is a direct etiologic factor or just a surrogate marker for diffuse atherosclerotic disease.[70] Carotid artery disease exacerbates cerebral hypoperfusion, especially in the presence of poor collateral circulation, and patients with severe carotid disease have a higher risk for stroke when hypoperfusion occurs during surgery. Perioperative hypotension in this group leads to cerebral ischemia because maximally dilated vessels distal to the carotid artery stenosis cannot respond to reductions in blood pressure or cardiac output. Further, carotid intraplaque hemorrhage triggered by mechanical and/or anticoagulant forces can result in intimal ulceration and plaque destabilization, creating a nidus for thromboembolism. Despite this, the European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) 2018 Guidelines on myocardial revascularization suggest screening only patients who are deemed high neurologic risk based on preoperative risk stratification tools or with recent history of stroke or TIA (< 6 months) with carotid artery duplex ultrasound.[71] This recommendation is based on the lack of evidence that prophylactic revascularization of unilateral asymptomatic carotid stenoses in CABG candidates reduces the risk for perioperative stroke. Further, carotid artery ultrasound screening detects only a minority of patients with postoperative stroke.[70] Therefore the American Heart Association (AHA) and the ESC/EACTS recommend restricting prophylactic carotid revascularization to patients with symptoms and significant stenosis (50%–99%) and for patients with severe bilateral carotid bifurcation stenosis.[11,71]

In cardiac surgery, aortic atherosclerosis is also an important risk factor for perioperative stroke. This risk is greatest in patients with large or mobile aortic arch atheromas, such as those that protrude more than 5 mm into the aortic lumen.[72,73] Although atheromas are more likely to occur at the site of new injury during aortic cannulation or surgical clamping, large or mobile atheromas are also risk factors for stroke in patients undergoing noncardiac surgery. A preoperative noncontrast computed tomography (CT) chest scan, specifically of the ascending aorta/arch, is recommended before myocardial revascularization in patients over 70 years of age and/or with signs of extensive generalized atherosclerosis to better assess risk stratification and guide the surgical strategy.[71,74]

Like large or mobile atheromas of the ascending aorta or aortic arch, intracardiac thrombus can also be a source of thromboembolism in surgical and nonsurgical patients and has been identified in 25% of all ischemic stroke and TIA patients.[75] The left atrial appendage (LAA) is the most common location for thrombus formation in patients with AF, but studies have shown that atrial cardiopathy, including LAA dysfunction and left atrial enlargement, in the absence of atrial arrhythmia, play a role in thrombus formation and may be associated with both embolic stroke of undetermined source (ESUS) and cardioembolic stroke.[76] Another concerning region of the heart is the left ventricular (LV) apex in patients with chronic heart failure and severe LV dysfunction and in patients with a recent acute MI. Thrombi in either the LAA or in the LV apex are more easily detected with contrast-enhanced cardiac MRI than traditional transthoracic and even transesophageal echocardiography (TEE). TEE is the current gold-standard technique for detecting thrombus of the left atrium or LAA, and intravenously injected ultrasound contrast agents enables LV assessment, yet its invasiveness and associated risk of complications, as well as the need for sedation, are clear barriers to routine screening.[77] Transthoracic echocardiography (TTE) is commonly used to exclude LV thrombus in patients with acute ischemic stroke, but it has low sensitivity in patients with severely impaired LV ejection fraction and in detecting other sources of thromboembolism, such as LAA thrombus, small valvular abnormalities, and aortic plaque.[78–80] Although newer technology, including speckle tracking TTE, allows for direct assessment of atrial function and can discriminate the presence of left atrial or atrial appendage thrombus, it is not routinely performed.[81] Cardiac CT angiography is another noninvasive approach that may be used in preoperative screening for intracardiac thrombus and has the added benefit of simultaneous evaluation of the coronary arteries for the presence of atherosclerotic disease. Nevertheless, it exposes patients to iodinated contrast and radiation, which cardiac MRI avoids.

In the case of a preoperative finding of severe aortic atherosclerosis before cardiac surgery, the use of techniques that minimize aortic manipulation should be considered, and the risk-benefit ratio of the operation should be reevaluated. In the case of LV thrombus, anticoagulation should be initiated.

Perioperative Optimal Medical Therapy and Surgical Optimization

Early and late postoperative strokes (after awakening from anesthesia but within 30 days) are most related to postoperative arrhythmias and cerebrovascular disease. Therefore, the main strategies to mitigate the risk for postoperative stroke include pharmacologic or nonpharmacologic AF prophylaxis, elimination of the LAA, and anticoagulation for prevention of clot formation.

A Cochrane database systematic review and meta-analysis of randomized trials assessing the effects of prophylactic interventions for prevention of postoperative AF or supraventricular tachycardia after cardiac surgery identified beta-blockers, amiodarone, sotalol, and magnesium as the most prescribed pharmacologic agents, and atrial pacing and posterior pericardiotomy as the most prevalent nonpharmacologic interventions.[82] When all interventions were taken together, prophylactic treatment was associated with a borderline significant reduction in postoperative stroke in the treatment group (1.5%) compared with the control group (2.3%; odds ratio [OR] 0.69; 95% confidence interval [CI] 0.47–1.01; $I^2 = 0\%$).

Because more than 90% of intracardiac thrombus accumulation occurs in the LAA, LAA closure is an alternative treatment to prevent strokes in high-risk patients with

nonvalvular AF.[83] The Left Atrial Appendage Occlusion Study (LAAOS III) was a recent multicenter, double-blind randomized trial involving patients with AF and a CHA_2DS_2-VASc score of at least 2 who were to undergo cardiac surgery for another indication and were instead assigned to concomitant surgical LAA occlusion or no occlusion.[84] The investigators found that the risk for ischemic stroke or systemic embolism was lower with concomitant LAA occlusion performed during the surgery than without it (4.8% versus 7.0%; hazard ratio [HR], 0.67; 95% CI 0.53–0.85; $P = 0.001$).

Preoperative cessation and/or reversal of antithrombotic agents may be necessary to avoid excessive bleeding during surgery and to prevent perioperative complications. In the elective, nonacute setting, time will allow for renal and hepatic clearance of many medications. The activated prothrombin time (aPTT) should be normalized and the international normalized ratio (INR) should be less than 1.4 before any surgical intervention. Holding vitamin K antagonists for several days (typically >5 days for patients taking warfarin) will reduce the anticoagulant effect and checking an INR level the morning of surgery is recommended to confirm the reversal.

In patients with significant hypercoagulability or existing clot burden requiring anticoagulation, the risks and benefits of "bridging" with a shorter-acting agent, such as unfractionated heparin or low-molecular-weight heparin, in the perioperative period are unclear and typically require careful calculations and comparisons of the thromboembolic and bleeding risks.[85] Major factors that increase perioperative thromboembolic risk are AF, prosthetic heart valves, and venous or arterial thromboembolism in the preceding 3 months. Patients with these risk factors are composed of heterogenous groups, and scores like the CHA_2DS_2-VASc and HAS-BLED (which stands for "hypertension, abnormal renal and liver function, stroke, bleeding tendency or predisposition, labile INRs [for patients taking warfarin], elderly [age greater than 65 years], and drugs or excessive alcohol use") incorporate additional important clinical variables for thromboembolic and bleeding risk stratification.[86] Nevertheless, no scoring system can substitute clinical judgment. For patients with a very high risk for thromboembolism, such as ischemic stroke within the previous 3 months, or in patients with nonvalvular AF who have had inadequate anticoagulation in the preceding month, attempts should be made to delay elective surgery, if possible, until risk has returned to baseline. If delaying is not possible or in patients with chronically elevated thromboembolic risk who are receiving warfarin, anticoagulation should be stopped as close to surgery as possible, with the use of a bridging agent for those on warfarin and a temporary inferior vena cava for selected individuals. The heparin bridge is typically prescribed to begin 3 days before the planned procedure (i.e., 2 days after stopping warfarin), when the INR has started to drop below the therapeutic range. Low-molecular-weight heparin may be discontinued 24 hours before the planned surgery, based on an elimination half-life of approximately 3 to 5 hours, and an infusion of therapeutic unfractionated heparin may be continued up until 4 to 6 hours before the procedure, based on its elimination half-life of approximately 45 minutes.

Increasingly, patients with thromboembolic risk are prescribed direct oral anticoagulants (DOACs) and parenteral direct-acting anticoagulants such as dabigatran, apixaban, edoxaban, and rivaroxaban. Unlike warfarin and other vitamin K antagonists (e.g., acenocoumarol, phenprocoumon, and fluindione), which work indirectly by blocking the function of vitamin K epoxide reductase complex in the liver, leading to depletion of the reduced form of vitamin K that serves as a cofactor for gamma ɣ-carboxylation of vitamin-K-dependent coagulation factors II, VII, IX, and X, these direct thrombin (factor II) and direct factor Xa inhibitors block major procoagulant activities involved in the generation of a fibrin clot.[87] Direct thrombin inhibitors such as bivalirudin, argatroban, desirudin, and dabigatran prevent thrombin from cleaving fibrinogen to fibrin by binding directly to thrombin, rather than by enhancing the activity of antithrombin, as heparin does. Direct factor Xa inhibitors, including rivaroxaban, apixaban, edoxoban, and betrixaban, prevent factor Xa from cleaving prothrombin to thrombin and bind directly to factor Xa. In planned procedures with high bleeding risk, omitting direct factor Xa inhibitors for 2 days before surgery regardless of kidney function and direct thrombin inhibitors for 2 days in patients with normal kidney function is recommended based on elimination half-lives of 9 to 14 hours for DOACs.[85] For patients with creatinine clearance of 30 to 50 mL/min receiving dabigatran, the same pharmacokinetic approach recommends omission to begin 4 days before surgery based on an elimination half-life of 18 to 24 hours in patients with impaired renal function.[88] Unlike cessation of vitamin K antagonists in patients with high thromboembolic risk, bridging is not necessary for the direct-acting anticoagulants.

Patients with a history of percutaneous coronary intervention (PCI) within the prior 12 months may be taking antiplatelet agents such as aspirin and platelet P2Y12 receptor blocking therapy to prevent coronary stent thrombosis. Based on the results of the large POISE-2 trial, it is recommended that patients treated with aspirin monotherapy for primary or secondary prevention of cardiovascular disease events hold such therapy for 5 to 7 days before surgery.[89] For patients taking dual antiplatelet therapy (DAPT) after PCI with stenting, cessation before the recommended duration of its use (at least 6 months after either bare metal stenting or drug-eluting stenting and 14 days after PCI using balloon angioplasty without stenting) is associated with an increased risk for adverse cardiovascular events such as MI, stent thrombosis, and death.[90] Deferring elective noncardiac surgery for 6 months after PCI with stenting to prevent interruption of DAPT is recommended, but with surgical interventions that cannot wait 6 months, the minimal duration of DAPT is 4 to 6 weeks after PCI with stenting and 48 hours after balloon angioplasty if possible.[91–93] For patients taking clopidogrel, ticagrelor, and prasugrel, it is recommended to hold therapy 5 days, 3 to 5 days, and 7 days before surgery, respectively, based on the manufacturer's package insert for each drug.

Intraoperative Decision Making

Intraprocedural techniques can help mitigate stroke risk. In cardiac surgery, modification of surgical techniques to avoid dislodgment of atheromatous debris has been guided historically by TEE performed by the anesthesiologist and manual palpation of the aorta by the surgeon. Detection of atheromatous burden within the ascending aorta guides the location of the cannula insertion, the position of aortic cross clamps, and the placement of vein grafts. Because TEE can be performed after intubation but before sternotomy, it offers more time to plan changes in surgical management than manual detection. Nevertheless, the air-filled trachea interposes the esophagus and aorta, which creates a blind spot that hinders visualization of the distal ascending aorta and its branches.[94] A meta-analysis of diagnostic accuracy studies comparing intraoperative imaging modalities demonstrated that the sensitivity of TEE in the detection of atherosclerosis of the ascending aorta was only 21%.[95] The sensitivity of digital palpation to assess atheroma in the aorta is similarly low, only 20.9%, and is associated with a greater risk for atheroma dislodgement.[96] Recently, epi-aortic ultrasound (EUS) techniques, with the direct application of an echocardiogram probe onto the aorta, have shown to be superior to both TEE and manual palpation in the detection and localization of aortic atherosclerosis.[96,97] Further, several studies, including a propensity score-matched analysis of 660 paired patients from the European Multicenter Study on CABG registry, showed that EUS was associated with significantly lower risk for stroke (0.6% vs. 2.6%, $P = 0.007$).[98,99] A modified TEE method, called the A-View (Aortic View) technique, has been developed to eliminate the aforementioned blind spot, in which a balloon positioned in the trachea and left main bronchus is inflated with saline to allow for visualization of the distal ascending aorta, aortic arch, and its branches, including the origins of the cerebral arteries.[100] This modified TEE approach has good overall diagnostic accuracy, with a sensitivity of 95% and specificity of 79%.[101] Compared with EUS, A-View TEE can be performed before incision, which allows more time for surgical strategizing. Risk of injury to the pulmonary tree, albeit rare, remains a major deterrent for more widespread use of the A-View TEE technique.

Surgical Techniques

In addition to surgical adjustments made upon intraoperative detection of atheromas, preemptive surgical strategies such as minimizing or eliminating aortic manipulation, single aortic cross-clamp techniques, and alternative cannulation sites are widely used to reduce stroke risk. Procedures such as off-pump CABG provide surgeons with more freedom to control the degree of aortic manipulation and are associated with less risk for intraoperative stroke compared with on-pump CABG.[102,103] Motallebzadeh et al. performed intraoperative emboli detection studies using transcranial Doppler (TCD) ultrasonography of the middle cerebral arteries and neurocognitive tests preoperatively and at set intervals up to 6 months after surgery among 212 patients randomly assigned to undergo on-pump or off-pump CABG.[104] They found reduced cerebral embolism with better neurocognitive scores at discharge in patients receiving off-pump CABG ($P < 0.001$ and $P = 0.001$, respectively) and only one nonfatal stroke in the off-pump group compared with three nonfatal strokes in the on-pump group within 30 days of surgery. Although the median number of embolic signals detected were far greater during on-pump CABG (1605) than during off-pump CABG (9), the highest rate of embolic signal detection during off-pump CABG occurred after removal of the side-clamp. Although aortic manipulation is reduced during off-pump compared with on-pump CABG, it is not eliminated and most centers, like the Motallebzadeh et al. study, routinely use aortic side-clamps to achieve proximal aortocoronary anastomosis. Of note, aortic clamping can be avoided completely with the use of clampless facilitating devices such as the Heartstring system or proximal anastomotic connectors. These techniques allow for proximal aortocoronary anastomosis without the use of a side clamp but still involve some aortic manipulation. An off-pump strategy using grafts off in situ arterial inflows allows for a no-touch aortic method.[105] Performed by experienced surgeons, these an-aortic or no-touch methods can reduce the incidence of stroke.[105,106] A network meta-analysis of 13 studies and 37,720 patients comparing clinical outcomes after an-aortic "no-touch" off-pump CABG, off-pump with the clampless Heartstring device, off-pump with partial clamp, and traditional on-pump CABG with aortic cross-clamping demonstrated an association between the degree of aortic manipulation and the incidence of perioperative stroke, with the most effective treatment for decreasing the risk for perioperative stroke being an-aortic off-pump technique.[47]

Neuroprotective modifications to aortic cannulas, such as filtration and suction systems, have been developed in an attempt to reduce embolic load during cardiac surgery. A multicenter randomized trial of patients with calcific aortic stenosis undergoing surgical aortic valve replacement evaluated the role of two cerebral embolic protection devices: the Embol-X (Edwards Lifesciences, Irvine, CA, USA), an intraaortic filtration device that captures emboli with a heparin-coated polyester mesh filter; and the CardioGard Cannula (CardioGard Medical Ltd, Or-Yehuda, Israel), a suction-based device that extracts both particulate and gaseous emboli.[107] The trial found no difference in clinical stroke among suction-based extraction nor intraaortic filtration versus controls (5.1% for suction-based extraction vs. 5.8% for control; and 8.3% for intraaortic filtration vs. 6.1% for control). Nevertheless, larger volume infarcts were more numerous in patients in the control group and a post-hoc analysis revealed numerically fewer patients with severe clinical stroke (National Institute of Health Stroke Scale score > 20) within the first 3 days after surgery among patients receiving a cerebral embolic protection device. Although these findings did not reach statistical significance, there was a significantly increased incidence of acute kidney injury (14 vs. 4, respectively; between-group difference, 2.7; 95% CI, 0.4–4.9) and a higher rate of cardiac arrhythmias (57 vs. 30, respectively; between-group difference, 7.2; 95% CI,

2.3–12.1) among patients in the intraaortic filtration group compared with the control group.

Ever since PCI with drug-eluting stents has emerged as an acceptable treatment for selected patients with left main coronary artery disease, numerous large randomized controlled trials have been undertaken to compare the periprocedural and long-term adverse events associated with percutaneous versus surgical revascularization techniques. These trials include the SYNTAX,[108] ERACI II,[109] ARTS,[110] MASS-II,[111] SoS,[112] PRECOMBAT,[113] FREEDOM,[114] VA CARDS,[115] BEST,[116] EXCEL,[117] and NOBLE.[118] Overall, PCI is associated with less intraoperative stroke than surgical myocardial revascularization; however, the presence of aortic atherosclerosis remains an independent risk factor for stroke among PCI patients, presumably secondary to catheter passage.[103,119] Moreover, the site of cardiac catheterization approach plays a role in perioperative stroke, with transradial intervention being the favored technique.[120] Pathologically, the abdominal and descending thoracic portions of the aorta as well as the aortic isthmus (portion of aorta just distal to the origin of the left subclavian artery) have the greatest plaque deposition.[121] Thus the radial intervention, and especially right-sided, avoids catheter contact with these anatomic locations and a large Japanese multicenter registry revealed that transradial intervention was indeed associated with a reduced risk for perioperative stroke compared with transfemoral intervention (0.1% vs. 0.4%; $P = 0.014$).[122] Additional causes of stroke associated with PCI are hypotension, air embolism, arterial dissection, and anticoagulation/antiplatelet therapy or hypertension causing hemorrhagic stroke. An 11-year statewide analysis from 2002 to 2012 comparing perioperative stroke rates after myocardial revascularization revealed the lowest rate with drug-eluting stent (DES; 0.5%), followed by bare-metal stent (BMS; 0.6%), off-pump CABG (1.3%), and on-pump CABG (1.8%).[103]

Intraoperative Blood Pressure Management

In general, hypoperfusion is believed to be an uncommon cause of perioperative stroke. Very few noncardiac perioperative strokes have been reported to be related to hypoperfusion. The term *hypoperfusion* can imply global hypoperfusion (i.e., resulting in bilateral watershed infarctions) or relative hypoperfusion through a preexisting stenosis (i.e., unilateral watershed infarction because of carotid stenosis). Gottesman et al. studied 98 patients who had MRI for a clinical stroke after cardiac surgery.[39] Watershed infarcts were identified in 68% of the diffusion-weighted imaging sequences of MRI and 37% of brain CTs. In fact, 48% of diffusion-weighted MRI scans demonstrated bilateral watershed infarcts (22% of CT scans). Patients with bilateral watershed infarcts were more likely to have undergone an aortic procedure than a simple CABG. Univariate and multivariate logistic regression revealed that patients with a decrease in mean arterial pressure (MAP) of at least 10 mm Hg from their preoperative baselines were more than four times more likely to develop bilateral watershed infarcts than patients with a small decrement or no decrement in blood pressure. Importantly, absolute intraoperative blood pressure was almost identical in the bilateral watershed infarct group compared with other infarct patterns. Watershed infarcts may be because of a mechanistic interplay of hypoperfusion and embolization.[123] A state of reduced perfusion (because of reduced MAP or because of carotid arterial narrowing) may prevent washout of microemboli showered during cardiac surgery and a subsequent settling of these particulates in watershed areas.

A recent consensus statement from the Perioperative Quality Initiative recommended targeting a MAP between 60 and 70 mm Hg in noncardiac surgery.[124] Findings from recent cardiac surgery studies support similar targets. A recent retrospective cohort study of 7457 patients undergoing CABG demonstrated a 16% increased risk for stroke for every 10 minutes that the MAP during cardiopulmonary bypass was less than 64 mm Hg.[125] They also showed that a 10% reduction of blood pressure below the preinduction level was associated with increased risk for stroke (adjusted OR 1.07; 95% CI 1.03–1.11; $P = 0.001$). The POISE trial randomly assigned 8351 patients with, or at risk for, atherosclerotic disease who were undergoing noncardiac surgery to receive extended-release metoprolol or placebo and found that although metoprolol reduced the incidence of MI, it increased the incidence of perioperative stroke and clinically significant hypotension.[126] The trial also showed that clinically significant hypotension increased the odds of stroke and mortality.

Intraoperative Neuromonitoring

Intraoperative neuromonitoring can identify changes in cerebral perfusion and guide subsequent interventions, such as increasing blood pressure or hemoglobin levels, reducing intracranial pressure, diverting cerebrospinal fluid, and reducing cerebral metabolic rate. Very brief episodes of hypoperfusion are relatively common during cardiac and noncardiac surgeries, but prolonged states of hypoperfusion will lead to ischemic stroke, with greater sensitivity in watershed areas of the brain. There is currently no device that can directly and noninvasively monitor cerebral perfusion. Nevertheless, devices that assess neurophysiological function (e.g., evoked potential recordings and electroencephalography [EEG]), monitor cerebral oxygenation (e.g., near-infrared spectroscopy and jugular venous bulb saturations), and record cerebral blood flow changes (e.g., TCD) serve as surrogate measures of cerebral perfusion pressure. Table 5.1 describes commonly used intraoperative neuromonitoring modalities and their reported diagnostic sensitivity and specificity for detecting clinical signs of ischemia.

Cerebral oximetry measures regional oxygen saturation of hemoglobin in arterial, venous, and capillary blood in the superficial frontal cortex ($rScO_2$) using near-infrared spectroscopy (NIRS) and can assess cerebral autoregulation when NIRS signals are continuously correlated with arterial pressure monitoring.[127,128] Cerebral oximetry monitoring may detect cerebral ischemia and NIRS has been increasingly used in a stand-alone fashion to measure $rScO_2$ changes (i.e., desaturations) from baseline during cardiac surgery, carotid

TABLE 5.1 Reported Sensitivity and Specificity of Intraoperative Neuromonitoring Techniques to Detect Clinical Signs of Cerebral Ischemia

Intraoperative Modality	Description	Reported Thresholds Associated With Clinical Signs of Ischemia	Sensitivity	Specificity
EEG	Summation of extracellular current fluctuations originating in superficial layers of the neocortex measured as distinct waves within beta (13–25 Hz), alpha (8–12 Hz), theta (4–7.5 Hz), or delta (0.5–4 Hz) rhythm frequency bands and recorded from electrodes on the scalp. Changes in EEG reflect abnormal CBF and disrupted metabolism and can be detected by recognition of specific patterns of activity through visual inspection of the frequency content and distribution of activity across the cortex. Reversible changes related to energy and ion-pump failure occur when CBF falls below 25–30 mL/100g/min and irreversible infarction occurs when CBF falls below 18 mL/100g/min.[156–158]	Alpha/delta ratio falling >10% below baseline in 6 consecutive recordings	100%[159]	76%[159]
		Single recording > 50% below baseline	89%[159]	84%[159]
		Decrease in amplitude of fast frequency by more than 50% or increase in theta or delta activity by more than 50%	28.57%[160]	90.33%[160]
Processed EEG	The bispectral index (BIS; Medtronic, Inc, Minneapolis, MN) and the patient state index (PSi; Masimo Corporation, Irvine, CA) are dimensionless numerical scales summated from electrical potentials of the superficial neocortex underlying surface electrodes embedded on an adhesive pad on the forehead and transformed into a number ranging from 0–100 (no electrical activity to awake).	Decrease in BIS number > 14% from baseline	81.8%[161]	89.7[161]
Somatosensory Evoked Potentials (SSEP)	Electrical activity response (compound action potential) of a sensory receptor or afferent nerve bundle in the PNS or CNS on the skin surface after repeated time-locked, controlled peripheral nerve stimulation resulting in an average waveform with peaks and troughs present at different time points relative to the stimulation. Waveform peaks are assigned a letter representing their polarity (**P**ositive or **N**egative) and an integer based on the post stimulus latency (in ms) at which they appear in a healthy population. Amplitudes represent the magnitude of the incoming afferent volley. Latency reflects the anatomic location along the somatosensory pathway impacted by the peripheral stimulus and both are thought to represent a combination of the PNS and CNS reception of the stimulus.[162] SSEP baseline amplitude is maintained when CBF is >16mL/100 g/min. 50% reduction in SSEP amplitude is observed when CBF is 12–16 mL/100 g/min.[163]	Decrease in amplitude to 50% of baseline or an increase in latency by more than 10% or an increase in CCT to more than 10 milliseconds	43–89%[139,147,160,164,165]	57–100%[139,147,160,164,165]
Transcranial Doppler Ultrasound	2-MHz pulsed Doppler ultrasound transducer on the scalp through specific acoustic windows where bone is thinner evaluates the ipsilateral cerebral blood flow velocity of intracranial arterial vessels at a depth of 45–60 mm.	Reduction of cerebral blood flow velocity > 50%	100%[147]	86%[147]
		Absolute cerebral blood flow velocity < 25 cm/s	100%[147]	69%[147]

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