SUPPLEMENT TO

PROCEEDINGS OF THE 4TH ANNUAL PERIOPERATIVE MEDICINE SUMMIT

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Overview

This enduring material is based on the 4th Annual Perioperative Medicine Summit, held February 5–7, 2009, in Miami Beach, Fla. The Summit's evidence-based lectures and panel discussions were audio recorded and transcribed, and the transcripts have been developed into the 20 articles in this proceedings publication. Both the Summit and enduring material are co-sponsored by the University of Miami Leonard M. Miller School of Medicine and the Cleveland Clinic Center for Continuing Education.

The goal of both the Summit and these proceedings is to help clinicians who provide perioperative care to incorporate the latest findings from clinical research into their practice so as to improve the quality and safety of their perioperative patient management.

Target Audience

Hospitalists, anesthesiologists, internists, and other health professionals engaged in perioperative management.

Objectives

At the completion of this activity, participants will be able to:

- Outline the various elements of the preoperative evaluation and communication techniques for the medical consultant
- Assess perioperative risk by applying the patient history, physical examination, and laboratory test results to evidence-based clinical prediction rules and guidelines for cardiovascular disease, pulmonary disease, thromboembolism, and delirium
- Define disease processes relevant to perioperative care
- Implement evidence-based therapies for perioperative care
- Integrate cost-effective perioperative testing in ambulatory and hospitalized patients
- Manage common postoperative medical complications
- Incorporate the latest findings from perioperative clinical research into their office or hospital practice

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Public reporting and pay-for-performance programs in perioperative medicine:
Are they meeting their goals?

ABSTRACT

Public reporting and pay-for-performance reimbursement are two strategies designed to stimulate hospital quality improvement. Information about the quality of hospital care (including surgical volumes and staffing, process-based measures, and mortality and other outcomes) is compiled on various Web sites, giving the public means to compare providers. While public reporting has been shown to foster quality-improvement activities by hospitals, its effects on clinical outcomes are less certain. Likewise, consumers' awareness and use of publicly available hospital and provider quality data have been low but appear to be increasing.

KEY POINTS

Public reporting programs have expanded in recent years, driven by national policy imperatives to improve safety, increased demands for transparency, patient "consumerism," and the growth of information technology.

Hospital-based pay-for-performance programs have had only a minor impact on quality so far, possibly because financial incentives have been small and much of the programs' potential benefit may be preempted by existing public reporting efforts.

These programs have considerable potential to accelerate improvement in quality but are limited by a need for more-nuanced process measures and better risk-adjustment methods.

These programs may lead to unintended consequences such as misuse or overuse of measured services, "cherry-picking" of low-risk patients, or misclassification of providers.

Continued growth of the Internet and social-networking sites will likely enhance and change the way patients use and share information about the quality of health care.

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Hospital quality measures and rankings are now widely available to the public online, but is public reporting of this information an effective strategy for improving health care? Using a case study of a hospital that suffered negative publicity as a result of a quality report, this article explores the use of public reporting of performance data and pay-for-performance reimbursement strategies to foster quality improvement in the US health care system.

CASE STUDY: A SURGICAL PROGRAM GETS A BAD REPORT—IN THE HEADLINES

In September 2005, *The Boston Globe* ran a prominent story reporting that the UMass Memorial Medical Center in Worcester, Mass., was abruptly suspending its elective cardiac surgery program.[1] The program's suspension came after state public health officials presented UMass Memorial with a detailed analysis showing that the hospital's mortality rate for coronary artery bypass graft surgery (CABG) patients was the highest in the state and almost double the average for Massachusetts hospitals.[1]

Key personnel from UMass Memorial described the events preceding and following the program's suspension in a journal article published in 2008.[2] In 2002, UMass Memorial hired a new chief of cardiothoracic surgery, who resigned in early 2005. A few months after that resignation, state public health officials alerted the hospital to the abovementioned CABG mortality data (from 2002 and 2003), which they said would soon be reported publicly. UMass Memorial then conducted an internal review of its data from the most recent years (2004 and 2005) and found that its risk-adjusted CABG mortality had actually worsened, at which point the hospital voluntarily suspended its cardiac surgery program.[2]

More news stories arose about UMass Memorial's program and its problems. The hospital hired consultants and senior surgeons from around the state and New England to completely review its cardiac surgery program. They concluded that "many essential systems were not in place" and made 68 key recommendations, including a complete overhaul of the hospital's quality-improvement structure. The prior cardiac surgeons departed.[2]

The cardiac surgery program resumed after a 6-week hiatus, with day-to-day supervision by two senior cardiac

surgeons from a Boston teaching hospital. A nationally recognized cardiac surgeon was brought on as chief of cardiac surgery in January 2006. In the 18 months after the program resumed, risk-adjusted CABG mortality rates declined substantially, but patient volume failed to return to presuspension levels and the hospital reported $22 million in lost revenue in fiscal year 2006 as a result of the suspension.[2]

This case raises a number of questions that help to frame discussion of the benefits and risks of public reporting of hospital quality measures:

- To what extent does public reporting accelerate quality improvement?
- How typical was the subsequent mortality reduction reported by UMass Memorial—ie, can public reporting be expected to improve outcomes?
- Was the effect on patient volume expected—ie, how much does public reporting affect market share?
- Would a pay-for-performance reimbursement model have accelerated improvement?
- Why do public reporting and pay-for-performance programs remain controversial?
- Do patients have a right to know?

WHAT HAS FUELED THE MOVE TOWARD PUBLIC REPORTING?

Drivers of public reporting

Massachusetts is one of a number of states that publicly report outcomes from cardiac surgery and other procedures and processes of care. Three basic factors have helped drive the development of public reporting (and, in some cases, pay-for-performance) programs:

- **National policy imperatives** designed to improve quality and safety and to reduce costs
- **Cultural factors** in society, which include consumerism in health care and the desire for transparency
- **The growth of information technology** and use of the World Wide Web, which has been a huge enabler of public reporting. Public reporting could be done prior to the Web era but would not have reached such a wide audience had the results been released in a book that had to be ordered from a government printing office.

The rationale for public reporting

In theory, how might public reporting and pay-for-performance programs improve quality? Several different mechanisms or factors are likely to be involved:

- **Feedback.** The basic premise of the National Surgical Quality Improvement Program, to cite one example, is that peer comparison and performance feedback will stimulate quality improvement.
- **Reputation.** Hospital personnel fear being embarrassed if data show that they are performing poorly compared with other hospitals. Likewise, in recent years we have seen hospitals with the best quality rankings publicly advertise their performance.
- **Market share.** Here the premise is that patients will tend to select providers with higher quality rankings and shun those with lower rankings.
- **Financial incentives.** Pay-for-performance programs link payment or reimbursement directly to the desired outcomes and thereby stimulate quality improvement without working through the above-mentioned mechanisms.

Approaches to quality measurement

Public reporting of hospital performance requires selection of an approach to measuring quality of care. Generally speaking, measures of health care quality reflect one of three domains of care:

Structural (or environmental) aspects, such as staffing in the intensive care unit (ICU), surgical volume, or availablity of emergency medical responders. An example of a structure-oriented reporting system is the Leapfrog Group's online posting of hospital ratings based on surgical volumes for high-risk procedures, the degree of computerized order entry implementation, and the presence or absence of various patient safety practices.[3]

Processes of care, such as whether beta-blockers are prescribed for all patients after a myocardial infarction (MI), or whether thromboprophylaxis measures are ordered for surgical patients in keeping with guideline recommendations. Examples of process-oriented reporting systems include the US Department of Health and Human Services' Hospital Compare Web site[4] and the Commonwealth Fund's WhyNotTheBest.org site.[5]

Outcomes of care, such as rates of mortality or complications, or patient satisfaction rates. An example of an outcomes-oriented reporting system is the annual report of institution-specific hospital-acquired infection rates put out by Pennsylvania[6] and most other states.

IS THERE EVIDENCE OF BENEFIT?

A consistent effect in spurring quality-improvement efforts

Nearly a dozen published studies have evaluated whether public reporting stimulates quality-improvement activities, and the results have shown fairly consistently that it does. A 2003 study by Hibbard et al is representative of the results.[7] This survey-based investigation measured the number of quality-improvement activities in cardiac and obstetric care undertaken by 24 Wisconsin hospitals that were included in an existing public reporting system compared with the number undertaken by 98 other Wisconsin hospitals that received either a private report on their own quality performance (without the information being made public) or no quality report at all. The study found

that the hospitals that participated in public reporting were engaged in significantly more quality-improvement activities in both of the clinical areas assessed than were the hospitals receiving private reporting or no reporting.

A mixed effect on patient outcomes

In contrast, the data on whether public reporting improves patient outcomes have so far been mixed. A 2008 systematic review of the literature identified 11 studies that addressed this issue: five studies found that public reporting had a positive effect on patient outcomes, while six studies demonstrated a negative effect or no effect.[8] Unfortunately, the methodological quality of most studies was poor: most were before-and-after comparisons without controls.

One of the positive studies in this review examined the effects of New York State's pioneering institution of provider-specific CABG mortality reports (provider profiling) in 1989.[9] The analysis found that between 1987 and 1992 (during which time provider profiling was instituted), unadjusted 30-day mortality rates following bypass surgery declined to a significantly larger degree among New York Medicare patients (33% reduction) than among Medicare patients nationwide (19% reduction) ($P < .001$).

In contrast, a time-series study from Cleveland Health Quality Choice (CHQC)—an early and innovative public reporting program—exemplifies a case in which public reporting of hospital performance had no discernible effect.[10] The study examined trends in 30-day mortality across a range of conditions over a 6-year period for 30 hospitals in the Cleveland area participating in a public reporting system. It found that the hospitals that started out in the worst-performing groups (based on baseline mortality rates) showed no significant change in mortality over time.

DOES PUBLIC REPORTING AFFECT PATIENT CHOICES?

How a high-profile bypass patient chooses a hospital

When former President Bill Clinton developed chest pain and shortness of breath in 2004, he was seen at a small community hospital in Westchester County, N.Y., and then transferred to New York-Presbyterian Hospital/Columbia University Medical Center for bypass surgery.[11] Although one would think President Clinton would have chosen the best hospital for CABG in New York, Presbyterian/Columbia's risk-adjusted mortality rate for CABG was actually about twice the average for New York hospitals and one of the worst in the state, according to the most recent "report card" for New York hospitals available at the time.[12]

Why did President Clinton choose the hospital he did? Chances are that he, like most other patients, did not base his decision on publicly reported data. His choice probably was heavily influenced by the normal referral patterns of the community hospital where he was first seen.

Surveys show low patient use of data on quality...

The question raised by President Clinton's case has been formally studied. In 1996, Schneider and Epstein surveyed patients who had recently undergone CABG in Pennsylvania (where surgeon- and hospital-specific mortality rates for cardiac surgery are publicly available) and found that fewer than 1% of patients said that provider ratings had a moderate or major impact on their choice of provider.[13]

The Kaiser Family Foundation regularly surveys the public about its knowledge and use of publicly available hospital comparison data. In the latest Kaiser survey, conducted in 2008,[14] 41% of respondents said they believe there are "big differences" in quality among their local hospitals, yet 59% said they would choose a hospital that is familiar to them rather than a higher-rated facility. These findings may be explained, in part, by a lack of awareness that data on hospital quality are available: only 7% of survey participants said they had seen and used information comparing the quality of hospitals to make health care decisions in the prior year, and only 6% said they had seen and used information comparing physicians.

...But a trend toward greater acceptance

Although consumers' use of publicly reported quality data remains low, their recognition of the value of such data has grown over time. Kaiser has conducted similar public surveys dating back to 1996, and the period from 1996 to 2008 saw a substantial decrease (from 72% to 59%) in the percentage of Americans who would choose a hospital based on familiarity more than on quality ratings. Similarly, the percentage of Americans who would prefer a surgeon with high quality ratings over a surgeon who has treated friends or family more than doubled from 1996 (20%) to 2008 (47%).[14]

What effect on market share?

Studies on the effects that public reporting has on hospital market share have been limited.

Schneider and Epstein surveyed cardiologists in Pennsylvania in 1995 and found that 87% of them said the state's public reporting of surgeon- and hospital-specific mortality rates for CABG had no influence or minimal influence on their referral recommendations.[15]

Similarly, a review of New York State's public reporting system for CABG 15 years after its launch found that hospital performance was not associated with a subsequent change in market share, not even among those hospitals with the highest mortality rate in a given year.[16] Interestingly, however, this review also showed that surgeons in the bottom performance quartile were four times as likely as other surgeons to leave practice in the year following

their poor report, which is one of the most prominent outcomes associated with provider profiling reported to date.

PAY-FOR-PERFORMANCE PROGRAMS

Evidence on the impact of pay-for-performance programs in the hospital setting is even more limited than that for public reporting.

Some evidence has come from the CMS/Premier Hospital Quality Incentive Demonstration, a pay-for-performance collaboration between the Centers for Medicare and Medicaid Services (CMS) and Premier, Inc., a nationwide alliance of hospitals that promotes best practices.[17] The demonstration calls for hospitals that rank in the top quintile or decile for performance to receive a 1% or 2% Medicare payment bonus for five clinical focus areas: cardiac surgery, hip and knee surgery, pneumonia, heart failure, and acute MI. Performance ratings are based primarily on process measures as well as a few clinical outcome measures. Results from the first 21 months of the demonstration showed a consistent improvement in the hospitals' composite quality scores in each of the five clinical areas.[17]

It is important to recognize, however, that this improvement occurred against the backdrop of broad national adoption of public reporting of hospital quality data, which makes it difficult to tease out how much of the improvement was truly attributable to pay-for-performance, especially in the absence of a control group.

To address this question, my colleagues and I evaluated adherence to quality measures over a 2-year period at 613 hospitals participating in a national public reporting initiative,[18] including 207 hospitals that simultaneously took part in the CMS/Premier Hospital Quality Incentive Demonstration's pay-for-performance program described above. We found that the hospitals participating in both public reporting and the pay-for-performance initiative achieved only modestly greater improvements in quality than did the hospitals engaged solely in public reporting; the difference amounted to only about a 1% improvement in process measures per year.

In another controlled study, Glickman et al compared quality improvement in the management of acute MI between 54 hospitals in a CMS pay-for-performance pilot project and 446 control hospitals without pay-for-performance incentives.[19] They found that the pay-for-performance hospitals achieved a statistically significantly greater degree of improvement compared with control hospitals on two of six process-of-care measures (use of aspirin at discharge and smoking-cessation counseling) but not on the composite process-of-care measure. There was no significant difference between the groups in improvements in in-hospital mortality.

Why have the effects of pay-for-performance initiatives so far been so limited? It may be that the bonuses are too small and that public reporting is already effective at stimulating quality improvement, so that the incremental benefit of adding financial incentives is small. In the case of my group's study,[18] another possible factor was that the hospitals' baseline performance on the quality measures assessed was already high—approaching or exceeding 90% on 5 of the 10 measures—thereby limiting our power to detect differences between the groups.

CONTROVERSIES AND CHALLENGES

Many issues continue to surround public reporting and pay-for-performance programs:

- Are the measures used to evaluate health care systems suitable and evidence-based? Do they truly reflect the quality of care that providers are giving?
- Do the programs encourage "teaching to the test" rather than stimulating real and comprehensive improvement? Do they make the system prone to misuse or overuse of measured services?
- How much of the variation in hospital outcomes can be explained by the current process-of-care measures?
- Should quality be measured by outcomes or processes? Outcomes matter more to patients, but they require risk adjustment to ensure valid comparisons, and risk adjustment can be difficult and expensive to conduct.
- How much is chance a factor in apparent performance differences between hospitals?
- How much is patient selection a factor? Might public reporting lead to "cherry-picking" of low-risk patients and thereby reduce access to care for other patients?

Unidirectional measures can lead to misuse, overuse

In 2003, the Infectious Diseases Society of America updated its guidelines on community-acquired pneumonia to recommend that patients receive antibiotics within 4 hours of hospital admission. This recommendation was widely adopted as an incentive-linked performance measure by CMS and other third-party payers. Kanwar et al studied the impact of this guidelines-based incentive in a pre/post study at one large teaching hospital.[20] They found that while significantly more patients received antibiotics in a timely fashion after publication of the guidelines (2005) versus before the guidelines (2003), almost one-third of patients receiving antibiotics in 2005 had normal chest radiographs and thus were not appropriate candidates for therapy. Moreover, significantly fewer patients in 2005 had a final diagnosis of pneumonia at discharge, and there was no difference between the two periods in rates of mortality or ICU transfer. The researchers concluded that linking the quality indicator of early antibiotic use to financial incentives may lead to misdiagnosis of pneumonia and inappropriate antibiotic use.

Of course, antibiotic timing is not the only quality mea-

sure subject to overuse or misuse; other measures pose similar risks, including prophylaxis for deep vein thrombosis, glycemic control measures, and target immunization rates.

More-nuanced measures needed

We must also consider how well reported quality measures actually reflect our objectives. For example, an evaluation of 962 hospitals' performance in managing acute MI found that the publicly reported core process measures for acute MI (beta-blocker and aspirin at admission and discharge, ACE inhibitor at discharge, smoking-cessation counseling, timely reperfusion) together explained only 6% of the variance among the hospitals in risk-adjusted 30-day mortality.[21] This underscores how complicated the factors affecting mortality are, and how existing process measures have only begun to scratch the surface.

How much of a role does chance play?

Another issue is the role of chance and our limited power to detect real differences in outcomes, as illustrated by an analysis by Dimick et al of all discharges from a nationally representative sample of nearly 1,000 hospitals.[22] The objective was to determine whether the seven operations for which mortality is advocated as a quality indicator by the Agency for Healthcare Research and Quality are performed often enough to reliably identify hospitals with increased mortality rates. The researchers found that only for one of the seven procedures—CABG—is there sufficient caseload over a 3-year period at the majority of US hospitals to accurately detect a mortality rate twice the national average.

Although CMS is highly committed to public reporting, the comparative mortality data available on its Hospital Compare Web site are not very useful for driving consumer choice or motivating hospitals to improve. For example, of the nearly 4,500 US hospitals that reported data on 30-day mortality from MI, only 17 hospitals were considered to be better than the national average and only 7 were considered worse than the national average.[4]

CASE REVISITED: LESSONS FROM THE UMASS MEMORIAL EXPERIENCE

Returning to our case study, what can the UMass Memorial experience teach us, and how well does it reflect the literature about the usefulness of public reporting?

Did public reporting accelerate quality improvement efforts? Yes. Reporting led to the suspension of cardiac surgery and substantive reorganization, which is consistent with the literature.

Was the mortality reduction typical? No. An optimist's view would be that the drastic actions spurred by the media coverage had strong effects. A skeptic might say that perhaps UMass Memorial did some "cherry-picking" of patients, or that they got better at coding procedures in a way that reflected more favorably on the hospital.

Were the declines in patient volumes predictable? No. So far, the data suggest that public reporting has its greatest effects on providers rather than on institutions. This may change, however, with the introduction of tiered copayments, whereby patients are asked to pay more if they get their care from lower rated institutions.

Would financial incentives have accelerated improvement? It is too early to tell. The evidence for pay-for-performance programs is limited, and the benefits demonstrated so far have been modest. But in many ways the alternative is worse: our current system of financing and paying for hospital care offers no financial incentives to hospitals for investing in the personnel or systems required to achieve better outcomes—and instead rewards (through supplemental payments) adverse outcomes.

Did prospective patients have a right to know? Despite the limitations of public reporting, one of the most compelling arguments in its favor is that patients at UMass Memorial had the right to know about the program's outcomes. This alone may ultimately justify the expense and efforts involved. Transparency and accountability are core values of open democratic societies, and US society relies on public reporting in many other realms: the National Highway Traffic Safety Administration publicizes crash test ratings, the Securities and Exchange Commission enforces public reporting by financial institutions, and the Federal Aviation Administration reports on airline safety, timeliness of flights, and lost baggage rates.

FUTURE DIRECTIONS

In the future, we can expect more measurement and reporting of health care factors that patients care most about, such as clinical outcomes and the patient experience. It is likely that public reporting and pay-for-performance programs will address a broader range of conditions and comprise a larger number of measures. CMS has outlined plans to increase the number of publicly reported measures to more than 70 by 2010 and more than 100 by 2011. My hope is that this expansion of data, along with improved data synthesis and presentation, will foster greater use of publicly reported data. Further, the continued evolution of the Web and social networking sites is very likely to enhance public awareness of hospital performance and change the ways in which patients use these data.

DISCUSSION

Question from the audience: I'm concerned about what seems to be a unilateral effort to improve quality. There are many components of health care delivery beyond those you've described, including the efforts of patients, insurers, employers, and the government. The reality is that patients don't plan for illness, insurance companies often deny care, more and more employers are providing

less coverage or no coverage, and Medicare is on the road to insolvency. Is the battle for quality winnable when all these other components of delivery are failing?

Dr. Lindenauer: You make good points. But from the standpoint of professionalism, I think we have a compelling duty to constantly strive to improve the quality of care in our hospitals and practices. I have presented strategies for potentially accelerating improvements that providers are trying to make anyway. Public reporting and financial incentives are likely to be with us for a while, and their use is likely to grow. But as you said, they address only part of the problem confronting American health care.

Question from the audience: For the savvy health care consumer, is there one particular Web site for hospital or provider comparisons that you would especially recommend? Do you actually recommend using such Web sites to patients before they undergo certain procedures?

Dr. Lindenauer: I think the Hospital Compare site from the Department of Health and Human Services is the key Web site. The California Hospital Assessment and Reporting Taskforce (CHART) has a good site, and the Commonwealth Fund's WhyNotTheBest.org is an interesting newcomer.

However, even the most ardent advocates for public reporting wouldn't say the information available today is sufficient for making decisions. There's still an important role for getting recommendations from other doctors who are familiar with local hospitals and providers.

I'm optimistic that the changes that are coming to these Web sites will provide a better user experience and make it harder to ignore the results of public reporting. Today we can say, "Hospital A is better at discharge instructions or smoking cessation counseling." But we all can appreciate how weak those kinds of measures are because their implementation is subject to local interpretations. Once risk-adjusted outcomes and more-meaningful process measures are available, I'd be surprised if more patients weren't willing to base their decisions on published comparisons.

DISCLOSURES

Dr. Lindenauer has indicated that he has no financial relationships with commercial interests that have a direct bearing on the subject matter of this article.

This article was developed from an audio transcript of Dr. Lindenauer's lecture at the 4th Annual Perioperative Medicine Summit. The transcript was edited by the *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness, and was then reviewed, revised, and approved by Dr. Lindenauer.

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Cardiac risk stratification for noncardiac surgery:

Update from the American College of Cardiology/American Heart Association 2007 guidelines

ABSTRACT

The American College of Cardiology and American Heart Association updated their joint guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery in 2007. The guidelines recommend preoperative cardiac testing only when the results may influence patient management. They specify four high-risk conditions for which evaluation and preoperative treatment are needed: unstable coronary syndromes, decompensated heart failure, significant cardiac arrhythmias, and severe valvular disease. Patient-specific factors and the risk of the surgery itself are considerations in the need for an evaluation and the treatment strategy before noncardiac surgery. In most instances, coronary revascularization before noncardiac surgery has not been shown to reduce morbidity and mortality, except in patients with left main disease. The timing of surgery following percutaneous coronary intervention (PCI) depends on whether a stent was used, the type of stent, and the antiplatelet regimen.

KEY POINTS

In addition to patient-specific factors, preoperative cardiac assessment should account for the risk of cardiac morbidity related to the procedure itself. Vascular surgery confers the highest risk, with reported rates of cardiac morbidity often greater than 5%.

Continuation of chronic beta-blocker therapy is prudent during the perioperative period.

Coronary revascularization prior to noncardiac surgery is generally indicated only in unstable patients and in patients with left main disease.

Nonurgent noncardiac surgery should be delayed for at least 30 days after PCI using a bare-metal stent and for at least 365 days after PCI using a drug-eluting stent.

Discontinuing antiplatelet therapy in patients with coronary stents may induce a hypercoagulable state within approximately 7 to 10 days.

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In patients undergoing noncardiac surgery, preoperative intervention for a cardiac condition is rarely needed simply to reduce the risk of the surgery unless such intervention is indicated separate from the preoperative context.

This is the overriding message of the 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery issued by the American College of Cardiology (ACC) and American Heart Association (AHA),[1] for which I was privileged to chair the writing committee. This article outlines current best practices in cardiac risk stratification for noncardiac surgery, highlighting key recommendations from the ACC/AHA 2007 perioperative guidelines.

PURPOSE OF THE PREOPERATIVE CARDIAC EVALUATION

Provide clinical judgment, not clearance for surgery

A proper cardiac evaluation prior to noncardiac surgery involves a comprehensive patient assessment that draws on clinical findings, the clinical experience of the consulting physician (typically a cardiologist or internist), and an assessment of the literature. The purpose is not to give medical clearance for surgery but rather to provide informed clinical judgment to the anesthesiologist and the surgical team in terms of the following[1]:

- The patient's current medical status
- Recommendations regarding the management and risk of cardiac problems during the perioperative period
- The patient's clinical risk profile, to assist with treatment decisions that may affect short- or long-term cardiac outcomes.

Order tests only when results may change management

The consulting physician's clinical judgment is critical in determining the need to order any specific tests. In general, a test to further define cardiac risk is valid only when its results could change the planned management and lead to a specific intervention. Potential interventions that may result from knowledge gained through testing include:

- Delaying the operation because of unstable symptoms

- Coronary revascularization
- Attempting medical optimization before surgery
- Involving additional specialists or providers in the patient's perioperative care
- Modification of intraoperative monitoring
- Modification of postoperative monitoring
- Modification of the surgical location, particularly when the procedure is scheduled for an ambulatory surgical center.

The cardiac evaluation should result in an estimation of cardiac risk. If the consulting physician's estimation of risk is not clearly above or below the threshold for a potential intervention, then further testing may be indicated to further define the need for interventions (ie, reaching the threshold for action).

WHAT TO WORRY ABOUT FIRST: HIGH-RISK CONDITIONS THAT REQUIRE EVALUATION AND TREATMENT

In a recommendation categorized as a Class I, Level B endorsement,* the ACC/AHA 2007 perioperative guidelines specify four active cardiac conditions for which an evaluation and treatment are required before noncardiac surgery[1]:

- **Unstable coronary syndromes**, including unstable or severe angina or recent myocardial infarction (MI). These syndromes should be the first and most important consideration. Unstable angina is a hypercoagulable state, as is recent MI. The hypercoagulability of these conditions is compounded by the hypercoagulability induced by the perioperative setting itself. As a result, the rate of perioperative MI or death in the setting of unstable angina is as high as 28%.[2] In the case of unstable coronary syndromes, delaying surgery is appropriate if the risks of the surgery are deemed greater than its potential benefits.
- **Decompensated heart failure**, defined as New York Heart Association functional class IV disease or worsening or new-onset heart failure.
- **Significant arrhythmias**, defined as high-grade or Mobitz II atrioventricular block, third-degree atrioventricular heart block, symptomatic ventricular arrhythmias, supraventricular arrhythmias with uncontrolled ventricular rate, symptomatic bradycardia, and newly recognized ventricular tachycardia.
- **Severe valvular disease**, defined as severe aortic stenosis and symptomatic mitral stenosis.

* The ACC/AHA 2007 perioperative guidelines make recommendations by classifying the magnitude of benefit versus risk (I = the intervention should be undertaken; IIa = the intervention is reasonable to undertake; IIb = the intervention may be considered; III = the intervention should not be undertaken) and assigning a level of supporting evidence (A = highest level of evidence; B = limited evidence; C = very limited evidence).

CARDIAC RISK STRATIFICATION: INITIAL PATIENT ASSESSMENT

Clinical risk factors and functional capacity

The Revised Cardiac Risk Index of Lee et al[3] remains the general paradigm for stratifying cardiac risk before noncardiac surgery. This validated index consists of six independent predictors of cardiac complications:

- High-risk surgery (intraperitoneal, intrathoracic, or suprainguinal vascular procedures)
- Ischemic heart disease
- History of congestive heart failure
- History of cerebrovascular disease
- Insulin therapy for diabetes mellitus
- Preoperative creatinine level greater than 2.0 mg/dL.

The more predictors a patient has, the greater the risk of perioperative complications. Thus, the Revised Cardiac Risk Index is a good tool for establishing a baseline risk level for use in determining whether a preoperative or perioperative intervention is likely to make a difference in the patient's surgical outcome. For the purpose of the algorithmic approach to testing, the surgical procedure is not considered a risk factor. Additionally, type 2 diabetes mellitus is also considered a risk factor.

Another important determinant of risk is the patient's functional capacity. A study of 600 patients undergoing major noncardiac procedures found that poor self-reported exercise capacity, defined as an inability to walk four blocks or climb two flights of stairs, was associated with significantly more perioperative complications than was good exercise capacity.[4] Simple instruments such as the Duke Activity Status Index[5] can be used to estimate the patient's functional capacity.

Procedure-specific risk

In addition to patient-specific factors, surgery-specific cardiac risk can be important, especially in patients with more than two clinical risk factors. The ACC/AHA 2007 perioperative guidelines identify three categories of surgery-specific risk[1]:

- **Vascular surgery** (the highest-risk category and also the most extensively studied), which has been associated with cardiac morbidity rates of greater than 5% in many reports. Examples include aortic and other major vascular surgery, as well as peripheral vascular surgery.
- **Intermediate-risk surgery**, for which reported cardiac morbidity rates range from 1% to 5%. Examples include intraperitoneal and intrathoracic procedures, carotid endarterectomy, head and neck surgery, orthopedic surgery, and prostate surgery.
- **Low-risk surgery**, for which reported cardiac morbidity rates are generally below 1%. Examples include endoscopic and superficial procedures, cataract surgery, breast surgery, and ambulatory surgery. Patients undergoing these procedures do not generally require

further preoperative cardiac testing.[1]

Of course, some variability exists within each risk level as a result of institutional differences in surgical volume and expertise as well as in preoperative evaluation and other processes of care. Endovascular surgery is considered intermediate risk from a perioperative perspective but is in the same risk category as vascular surgery from a 1-year perspective.

Risk stratification promotes good perioperative outcomes

Appropriate risk stratification can make the day of surgery among the safest times for patients undergoing outpatient procedures. A retrospective analysis of Medicare claims from the late 1990s for more than 500,000 elderly patients undergoing low-risk procedures in various outpatient settings found that the mortality rate was only 1 in 50,000 on the day of surgery but increased substantially over the following 7 days and 30 days.[6] This was likely a reflection of the diligence applied to managing patient-specific risk factors before proceeding to outpatient surgery.

HEART RATE CONTROL

Chronic beta-blockade can obviate need for cardiac testing

The DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Strees Echo) II trial assessed the value of cardiac testing before major vascular surgery in intermediate-risk patients (ie, with one or two cardiac risk factors) receiving chronic beta-blocker therapy begun 7 to 30 days prior to surgery.[7] Among the study's 770 intermediate-risk patients, the primary outcome—cardiac death or MI at 30 days—was no different between those randomized to receive stress testing or no stress testing. The investigators concluded that cardiac testing can safely be omitted in intermediate-risk patients if beta-blockers are used with the aim of tight heart rate control.

Continue ongoing beta-blocker therapy, start in select high-risk patients

The ACC/AHA 2007 perioperative guidelines recommend continuing beta-blocker therapy in patients who are already receiving these agents (Class I, Level C). For patients not already taking beta-blockers, their initiation is recommended in those undergoing vascular surgery who have ischemia on preoperative testing (Class I, Level B). The guidelines designate beta-blockers as "probably" recommended (Class IIa, Level B) for several other patient subgroups with high cardiac risk, mainly in the setting of vascular surgery.[1]

Notably, the guidelines were written before publication of the Perioperative Ischemic Evaluation (POISE),[8] which questioned the risk/benefit profile of perioperative beta-blockade in patients with or at high risk of atherosclerotic disease (see the Poldermans–Devereaux debate on page S84 of this supplement), and therefore may require revision (an update is scheduled for release in November 2009).

LIMITED ROLE FOR CORONARY REVASCULARIZATION

Until recently, no randomized trials had assessed the benefit of prophylactic coronary revascularization to reduce the perioperative risk of noncardiac surgery. The first large such trial was the Coronary Artery Revascularization Prophylaxis (CARP) study, which randomized 510 patients scheduled for major elective vascular surgery to undergo or not undergo coronary artery revascularization before the procedure.[9] The study found that revascularization failed to affect any outcome measure, including mortality or the development of MI, out to 6 years of follow-up. Notably, the CARP population consisted mostly of patients with single-, double-, or mild triple-vessel coronary artery disease, so the study was limited in that it did not include patients with strong indications for coronary artery bypass graft surgery (CABG).[7]

A reanalysis of the CARP results by the type of revascularization procedure—CABG or percutaneous coronary intervention (PCI)—revealed that patients undergoing CABG had lower rates of death, MI, and additional revascularization procedures compared with those undergoing PCI, despite the presumably more extensive disease of the CABG recipients.[10]

Benefit apparently limited to left main disease

Further analysis of patients in the CARP trial who underwent coronary angiography found that one subgroup—patients with left main disease—did experience an improvement in survival with preoperative coronary revascularization.[11]

In a subsequent randomized pilot study, Poldermans et al found no advantage to preoperative coronary revascularization among patients with extensive ischemia who underwent major vascular surgery.[12] While this study was not adequately sized to definitively address the value of preoperative revascularization in these high-risk patients, its results are consistent with those of the CARP trial.

In a retrospective cohort study of patients who underwent noncardiac surgery, Posner and colleagues found that rates of adverse cardiac outcomes among patients who had recent PCI ($\leq$ 90 days before surgery) were similar to rates among matched controls with nonrevascularized coronary disease.[13] Patients who had had remote PCI (> 90 days before surgery) had a lower risk of poor outcomes than did matched controls with nonrevascularized disease, but had a higher risk than did controls without coronary disease.[13]

Proposed approach to management of patients with prior PCI

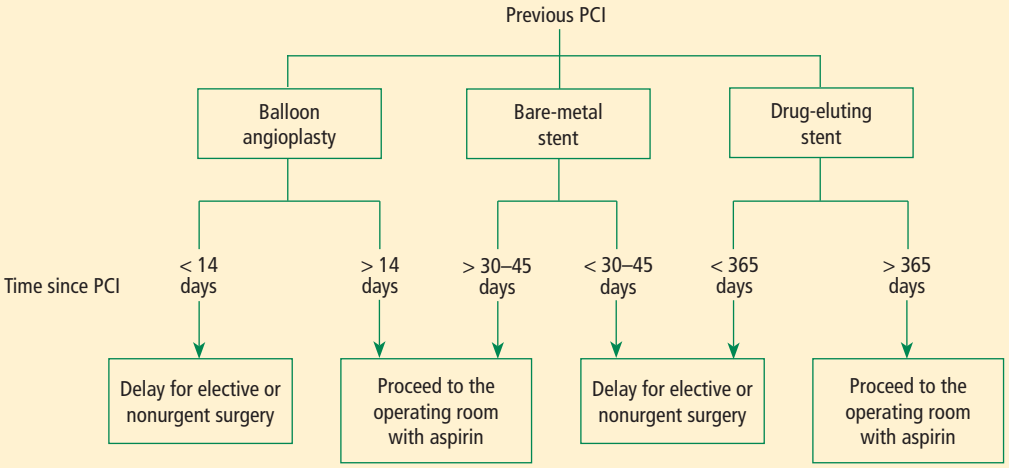

FIGURE 1. Recommended timing of noncardiac surgery following percutaneous coronary intervention (PCI) depends on whether a stent was placed and the type of stent used.[1]

PATIENTS WITH CORONARY STENTS: STENT TYPE AND TIME SINCE PLACEMENT ARE KEY

The lack of benefit from prophylactic PCI prior to noncardiac surgery also applies to PCI procedures that involve coronary stent placement. For instance, a propensity-score analysis found no benefit from prophylactic PCI (using stents in the vast majority of cases) in patients with coronary artery disease in terms of adverse coronary events or death following aortic surgery.[14]

In patients who have undergone prior PCI, noncardiac surgery poses special challenges, especially in relation to stents. Restenosis is a particular concern with the use of bare-metal stents, and development of stent thrombosis is a particular risk with the use of drug-eluting stents.[15] The use of drug-eluting stents requires intensive antiplatelet therapy for at least 1 year following stent implantation to prevent stent thrombosis.[16]

Time interval to surgery after bare-metal stent placement

The effect of prior PCI with bare-metal stents on outcomes following noncardiac surgery was examined in a recent large retrospective study by Nuttall et al.[17] The incidence of major cardiac events was found to be lowest when noncardiac surgery was performed more than 90 days after PCI with bare-metal stents. Using patients who had a greater than 90-day interval before surgery as the reference group, propensity analysis showed that performing surgery within 30 days of PCI was associated with an odds ratio of 3.6 for major cardiac events. The odds ratio was reduced to 1.6 when surgery was performed 31 to 90 days after PCI. These findings suggest that 30 days may be an ideal minimum time interval, from a risk/benefit standpoint, between PCI with bare-metal stents and noncardiac surgery.

Time interval to surgery after drug-eluting stent placement

A recent retrospective study by Rabbitts et al examined patients who had noncardiac surgery after prior PCI with drug-eluting stents, focusing on the relationship between the timing of the procedures and major cardiac events during hospitalization for the surgery.[18] Although the frequency of major cardiac events was not statistically significantly associated with the time between stent placement and surgery, the frequency was lowest—3.3%—when surgery followed drug-eluting stent placement by more than 365 days (versus rates of 5.7% to 6.4% for various intervals of less than 365 days).

ACC/AHA recommendations

Recommendations on the timing of noncardiac surgery in patients with prior PCI from the ACC/AHA 2007 perioperative guidelines **(Figure 1)** are consistent with the findings of the above two retrospective studies,[17,18] although the guideline writers concede that these recommendations are based on expert opinion and lack high-quality supportive evidence.[1] Indeed, stent thrombosis has been known to occur during operations performed 18 months or more after drug-eluting stent placement, so vigilance is always in order.

Timing of antiplatelet interruption

Results from a prospectively maintained Dutch registry[19] are consistent with the findings reviewed above: patients who underwent noncardiac surgery less than 30 days after bare-metal stent implantation or less than 6 months after drug-eluting stent implantation (early surgery group) had a significantly elevated rate of major cardiac events compared with patients in whom the interval between stenting and noncardiac surgery was longer (late surgery group). Notably, this report also

found that the rate of major cardiac events within the early surgery group was significantly higher in patients whose antiplatelet therapy was discontinued during the preoperative period than in those whose antiplatelet therapy was not stopped.[19]

A hypercoagulable state develops within 7 to 10 days after interruption of antiplatelet therapy, at which time the patient is vulnerable to thrombosis. In general, surgery should not proceed during this time without antiplatelet coverage.

From my perspective, giving ketorolac or aspirin the morning of surgery may be beneficial for patients whose antiplatelet therapy has been stopped 7 to 10 days previously, although no data from randomized trials exist to support this practice. Theoretically, it is reasonable to stop antiplatelet therapy 4 to 5 days before surgery in patients with an increased risk of bleeding without exposing them to the hypercoagulability that would set in if therapy were stopped earlier.

A FRAMEWORK FOR CARDIAC EVALUATION

The ACC/AHA 2007 perioperative guidelines include an evidence-based algorithm for determining which patients are candidates for cardiac testing as part of preoperative cardiac assessment.[1] As presented in **Figure 2**, this stepwise approach takes into account the urgency of the surgery, the presence or absence of active cardiac conditions, the type of surgery and its risk level, and the patient's functional capacity and cardiac risk factors.[1,20]

The following are among the algorithm's key recommendations:

- Patients requiring urgent noncardiac surgery should proceed to the operating room with perioperative surveillance (Class I, Level C).
- Patients with active cardiac conditions who are undergoing nonurgent surgery should be evaluated and treated per ACC/AHA guidelines before proceeding to the operating room is considered (Class I, Level B).
- Patients scheduled for a low-risk procedure can proceed to surgery without testing (Class I, Level B).
- Patients scheduled for intermediate-risk surgery or vascular surgery are to be assessed by functional capacity and clinical risk factors. Proceeding with planned surgery is appropriate in patients with good functional capacity (Class IIa, Level B). In patients with poor or unknown functional capacity undergoing vascular surgery who have three or more clinical risk factors, testing should be considered if the results would change management (Class IIa, Level B).
- Patients with one or more clinical risk factors undergoing intermediate-risk surgery and those with fewer than three clinical risk factors undergoing vascular surgery may proceed to planned surgery with control of heart rate to diminish the stress response perioperatively (Class IIa, Level B), or they may undergo noninvasive testing, but only if the results would change management (Class IIb, Level B).
- Patients undergoing intermediate-risk or vascular surgery who have poor or unknown functional capacity but no clinical risk factors may proceed to surgery without testing (Class I, Level B).

DISCUSSION

Question from the audience: The POISE study showed a 30% reduction in nonfatal MI with routine perioperative beta-blockade but an overall increase in mortality. Since most MIs occur immediately postoperatively and sepsis occurs a bit later, would you consider continuing beta-blocker therapy for a few days to prevent an MI but then stopping it before sepsis develops?

Dr. Fleisher: I've had discussions with sepsis experts about the link between beta-blocker therapy and sepsis and death in POISE, and the belief is that beta-blockers do not cause sepsis. I think that a septic patient on acute high-dose beta-blocker therapy can't respond appropriately because of an inability to increase cardiac output. I believe we should titrate beta-blockers more closely. Information on preoperative dose titration in POISE is not available because of the way the trial was designed. Sepsis developed in only 53 of the 8,351 patients randomized in the study.

I would not start an acute beta-blocker protocol just to get a patient through surgery. I would start a perioperative hemodynamic protocol with the goal of maintaining the patient's heart rate at lower than 80 beats per minute. Because I don't believe that beta-blockers cause sepsis, if I initiated a beta-blocker preoperatively, I would not stop it at 2 days.

Question from the audience: Is there a time period during which a patient with a bare-metal stent could have back surgery or knee replacement surgery while not on aspirin?

Dr. Fleisher: The guidelines say that if a patient is on aspirin, it should be continued indefinitely. The issue is one of risk versus benefit. For back surgery, if bleeding is a concern, stopping aspirin for 6 or 7 days after the 30-day period following PCI is not unreasonable, but I would not stop it during the first 30 days following PCI.

Question from the audience: I don't assess for vascular surgery but rather for the Whipple procedure [radical pancreatoduodenectomy], and I use the Revised Cardiac Risk Index to assess the number of risk factors. I believe the Whipple procedure is a high-risk operation, but it appears to be considered an intermediate-risk operation by the ACC/AHA guidelines. Is my approach to risk assessment appropriate?

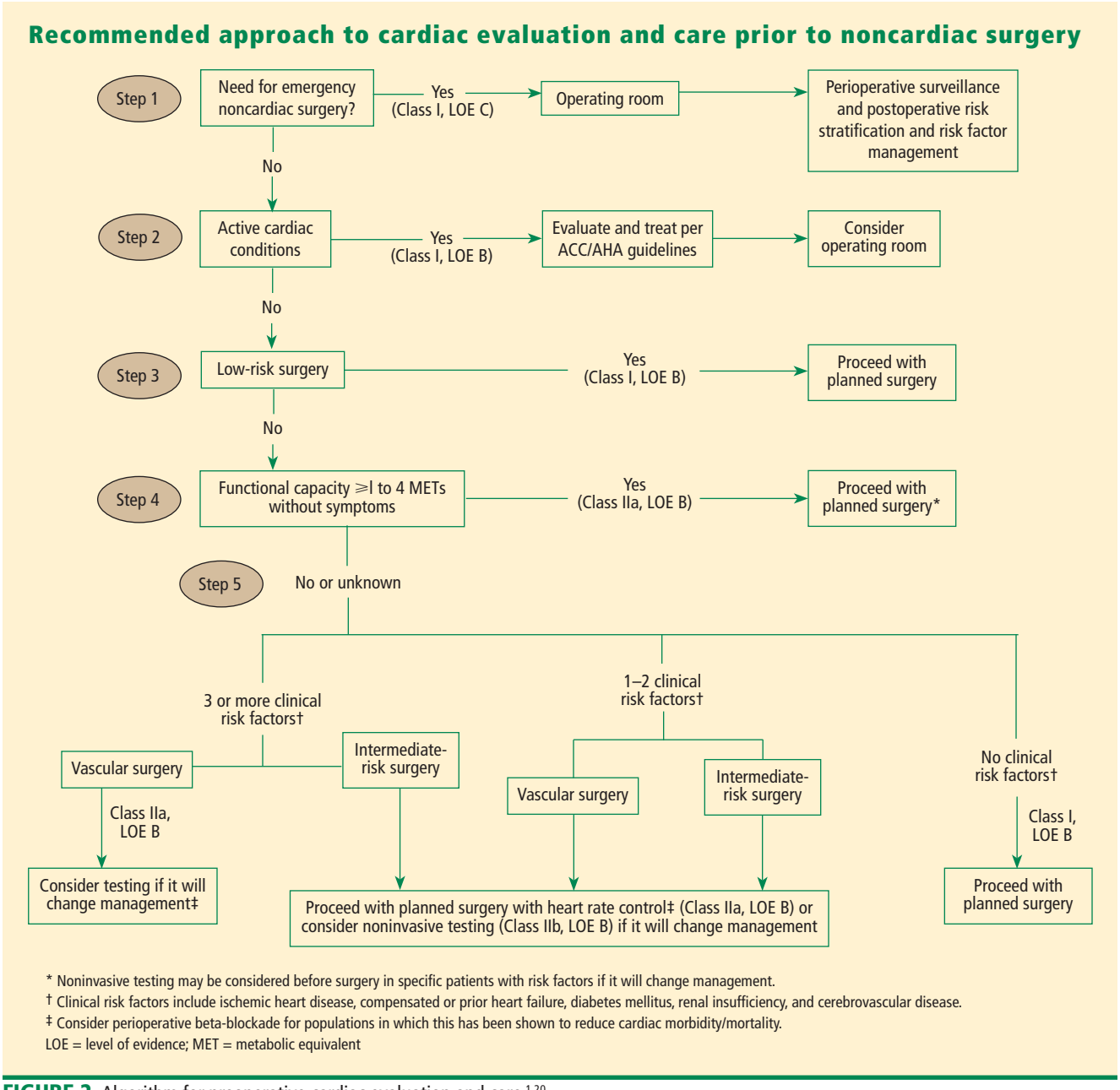

FIGURE 2. Algorithm for preoperative cardiac evaluation and care.[1,20]

Dr. Fleisher: If the rates of morbidity and mortality with the Whipple procedure are low at your institution, you might risk worsening your outcomes by applying someone else's paradigms to your institution. There's a big difference in risk between a surgeon who does a Whipple in 5 hours with 0.5 to 1.0 U of blood loss and a surgeon who does a 12-hour Whipple with 20 U of blood loss, necessitating a stay in the intensive care unit for multiple days. You need to consider the risk associated with your institution and specifically with the surgeon.

Question from the audience: Peripheral vascular disease is considered a coronary heart disease risk equivalent, so why is it not one of the criteria in the Revised Cardiac Risk Index?

Dr. Fleisher: The criteria are not hard and fast. The index was devised at one institution, Brigham and Women's Hospital, in about 4,000 patients, and it has been used

differently. It assigns 1 point to ischemic heart disease. It would not be inappropriate to assume that any atherosclerotic class of disease is equivalent to ischemic heart disease for risk purposes.

Question from the audience: You mentioned a 4-day window for withholding clopidogrel. Do you factor into the decision the duration of therapy? Some cardiologists go beyond the 1-year recommendation to continue clopidogrel after stenting because they believe there is still benefit.

Dr. Fleisher: The key is to confer with the cardiologist who implanted the stent, who knows the stenosis for which the stent was implanted. A problem we've had for years is that a practitioner will stop the antiplatelet agent without having spoken to the surgeon or the anesthesiologist. As an anesthesiologist, I need to know that someone has done a risk/benefit assessment of whether to continue antiplatelet agents in a given patient.

Question from the audience: The Revised Cardiac Risk Index of Lee et al[3] includes the type of surgery in its total point system while the ACC/AHA guidelines do not. Can you explain the discrepancy?

Dr. Fleisher: We on the writing committee for the ACC/AHA 2007 perioperative guidelines made a decision to pull out the type of surgery and use the other five risk factors of Lee et al. It was a consensus of the committee because we believed that the complexity of the surgery itself is a separate consideration for risk. That's why we included the medical risk factors and considered the surgical factors separately.

DISCLOSURES

Dr. Fleisher has indicated that he has no financial relationships with commercial interests that have a direct bearing on the subject matter of this article.

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Perioperative care of the elderly patient: An update*

ABSTRACT

Elderly patients pose unique challenges perioperatively. They are more likely than younger surgical patients to be mentally and physically compromised at baseline, which increases the risk of delirium and postoperative cognitive dysfunction. Postoperative cognitive risk can be predicted, however, and effective strategies exist to reduce this risk. Elderly patients are also at increased risk of a precipitous postoperative decline in physiologic reserve, which can lead to organ failure. General recommendations for the perioperative care of elderly patients include avoiding drugs that raise the risk of delirium, ensuring adequate caloric and fluid intake, getting the patient out of bed and into physical therapy as soon as possible, and early planning for discharge. An elderly patient's postoperative cognitive risk and its impact on quality of life should be factored into the decision whether to undergo surgery. Family conferences are recommended to address the many questions and challenges that surgery in an elderly person can pose.

KEY POINTS

Postoperative cognitive dysfunction and delirium are distinct conditions, though both are common in the elderly. Postoperative cognitive dysfunction may persist for weeks to months and may not be obvious, whereas delirium, a disorder of attention and cognition, is easier to detect clinically.

Major predictors of postoperative delirium are severe illness, baseline dementia, dehydration, and sensory impairment.

Drugs that raise dementia risk include anticholinergics, benzodiazepines, meperidine, tricyclic antidepressants, first-generation antihistamines, and high-dose H_2-receptor blockers.

Early performance of hip fracture surgery in the elderly (ie, within 24 hours of admission) has not been shown to lower mortality but appears to improve other outcomes.

Identifying and managing frail elderly patients is important. Signs of frailty are minimal activity, generalized muscle weakness, slowed performance, fatigue, and weight loss.

Acute hospital care is fast becoming acute geriatric care: people aged 65 years or older are only 13% of the population but account for 44% of days of care in nonfederal hospitals and 38% of discharges.[1] In general, the elderly have longer hospital stays, incur greater costs, and have a higher risk of adverse outcomes than do their younger counterparts.[2]

Among the most common surgical procedures for patients older than 65 are percutaneous coronary intervention with stenting, coronary artery bypass graft surgery, and open reduction internal fixation for hip fracture; the latter is the most common operation in patients aged 85 years or older.[3]

Elderly patients frequently pose many challenges perioperatively that are not often seen in younger patients. Dementia, frailty, impaired ability to care for oneself, and malnourishment may be present at baseline and are likely to worsen postoperatively. The elderly are at increased risk of acute delirium and cognitive impairment postoperatively, which often complicates recovery and discharge placement.

This article uses a case study to review perioperative problems commonly encountered in elderly surgical patients, particularly those undergoing hip surgery. As the case is presented, I will review strategies to assess risks and prevent and mitigate postoperative cognitive dysfunction and other barriers to recovery.

CASE: AN 82-YEAR-OLD WOMAN WITH HIP FRACTURE

An 82-year-old woman is admitted to undergo open reduction internal fixation for hip fracture. She has a history of osteoarthritis, systolic hypertension, and visual impairment (20/70). Her medications include a beta-blocker, a thiazide diuretic, analgesics as needed, and a multivitamin. She was independent in all activities of daily living before the fracture. She is a social drinker and does not smoke. She has no known cardiovascular, lung, or renal disease.

Her laboratory test results are as follows:

- Blood urea nitrogen (BUN), 24 mg/dL
- Creatinine, 1.0 mg/dL
- Hemoglobin, 12.8 g/dL
- Albumin, 3.8 gm/dL
- Normal levels of thyroid-stimulating hormone and vitamin B_{12}.

Thus, her lab results are normal except for the BUN:creatinine ratio being a bit high, at 24:1 (normal is 10:1, with ratios greater than 18:1 being associated with an increased risk of delirium[4]).

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ASSESSING COGNITIVE RISK: POSTOPERATIVE COGNITIVE DYSFUNCTION VS DELIRIUM

Question: Which of these statements about this patient is most correct?

A. *She is at high risk (> 40%) of postoperative cognitive dysfunction*
B. *Her risk of postoperative delirium is 5% to 10%*
C. *Postoperative delirium cannot be prevented*
D. *Preoperative haloperidol (1.5 mg/day for 3 days) will reduce the risk of delirium by 25%*

The best answer is A. Postoperative cognitive dysfunction is different from delirium, though it is part of a spectrum of cognitive impairment that may occur after surgery and even persist for a prolonged period. The patient's risk of postoperative delirium is actually a bit higher than 10% (see "Estimating the risk of delirium" below). Some evidence shows that postoperative delirium can be prevented, at least in hip fracture patients. Kalisvaart et al found that preoperative treatment with low-dose haloperidol reduced the duration and severity of delirium in elderly patients following hip surgery but did not reduce its incidence.[5]

Cognitive dysfunction often follows surgery

Postoperative cognitive dysfunction has long been recognized and was first described in patients after cardiac surgery, especially following coronary artery bypass graft procedures. In the last several years, we have recognized that it also occurs in patients who undergo noncardiac surgery. Postoperative cognitive dysfunction, which may persist for weeks to months, may not be obvious but can be detected by standard neuropsychological testing.[6]

Postoperative cognitive dysfunction is different from the "emergence delirium" that may immediately follow surgery and that is often associated with the wearing off of anesthesia. It is also distinct from "incident delirium," which sometimes occurs over the first few postoperative days (discussed below).

Postoperative dysfunction is especially persistent in the elderly

A recent study found cognitive dysfunction to be common at hospital discharge after major noncardiac surgery in adults of all ages: rates at discharge were 36.6% in patients aged 18 to 39 years, 30.4% in those aged 40 to 59, and 41.4% in those 60 or older.[7] Notably, however, the oldest group was most likely to have persistent symptoms. Three months after surgery, 12.7% of patients aged 60 or older continued to have postoperative cognitive dysfunction, which was more than double the rates in the young and middle-aged patient groups (5.7% and 5.6%, respectively).[7]

Although the cause of postoperative cognitive dysfunction is not well understood, predisposing factors in addition to advanced age include metabolic problems, lower educational level, and previous cerebral vascular accident.[7] When elective surgery is considered by elderly patients, the decision should take into account their risk of postoperative cognitive dysfunction and the impact it may have on their quality of life.

PREDICTING AND PREVENTING DELIRIUM

Delirium is easily recognized

Delirium is a common complication of surgery. Unlike postoperative cognitive dysfunction, delirium is easy to detect clinically. It is a disorder of attention and cognition and classically presents as an acute change in mental status accompanied by the following[8]:

- Fluctuation in awareness
- Memory impairment
- Inattention (inability to stay on task, distractibility)
- Disorganized or illogical thinking
- Altered level of consciousness—ie, hyperalertness (agitation, pulling out intravenous lines, etc) or hypoalertness ("quiet delirium").

Estimating the risk of delirium

Marcantonio and colleagues developed a model to predict the likelihood that delirium will develop in patients undergoing elective surgery.[9] The model assigns points to various risk factors as follows:

- Age ⩾ 70 years (1 point)
- History of alcohol abuse (1 point)
- Baseline cognitive impairment (1 point)
- Severe physical impairment (reduced ability to walk or perform daily activities) (1 point)
- Abnormal preoperative blood levels of electrolytes or glucose (1 point)
- Noncardiac thoracic surgery (1 point)
- Abdominal aortic aneurysm surgery (2 points).

The study to validate this model found that a score of 0 points is associated with only a 2% risk of developing postoperative delirium. A score of 3 or more points is associated with a 50% risk of postoperative delirium. A score of 1 or 2 points (as for the patient in our case study) is associated with an 11% risk, according to this Marcantonio model.[9]

Additionally, well-designed cohort studies of medical patients[10] have identified four major independent predictors of incident delirium:

- Severe illness (eg, high fever, complicated infections)
- Baseline dementia
- Dehydration (high BUN:creatinine ratio)
- Sensory impairments (particularly visual).

Kalisvaart et al conducted a prospective cohort study to determine whether these risk factors in medical patients are applicable to elderly patients undergoing hip surgery.[11] They found that the incidence of delirium was low (4%) in hip surgery patients with none of these factors, increased to 11% in patients with one or two of these factors, and increased to 37% in patients with three or four factors.

These findings suggest that hip surgery patients (like our case patient) may be at greater risk of postoperative delirium than is reflected in the Marcantonio model discussed above,[9] which was validated in a study of patients undergoing elective (not emergent) surgery.

Several drug classes raise dementia risk

Anticholinergic medications and other drugs with anticholinergic properties, ie, benzodiazepines and the opioid agent meperidine, also raise the risk for delirium. In general, the older an elderly patient is, the less appropriate these agents are. Many drugs that are not typically recognized as anticholinergics may have potent anticholinergic activity, including tricyclic antidepressants, first-generation antihistamines (eg, diphenhydramine), and high-dose H_2-receptor blockers (particularly cimetidine); these agents too should be avoided in elderly patients.[12]

Strategies to reduce postoperative delirium risk

How can we lower the risk of postoperative delirium in elderly hip fracture patients? Marcantonio et al[13] randomized 126 patients undergoing hip fracture repair to receive usual care alone or supplemented with the following additional measures:

- Supplemental oxygen during surgery
- Optimization of electrolytes and blood glucose preoperatively
- Discontinuation of high-risk medications
- Adequate nutritional intake (by parenteral route if necessary)
- Encouragement to get out of bed on the first postoperative day
- Treatment of severe pain.

The incidence of delirium was reduced from 50% in the usual-care group to 32% in the intervention group, and the incidence of severe delirium was reduced even more, from 29% to 12%, respectively.[13]

OTHER BEST PRACTICES IN PERIOPERATIVE HIP FRACTURE MANAGEMENT

In a systematic literature review to identify best practices for perioperative management of elderly patients with hip fracture, Beaupre et al[14] found the following measures to be among those with the strongest evidence of benefit:

- Use of spinal or local anesthesia rather than general anesthesia
- Use of pressure-relieving mattresses to prevent pressure ulcers
- Perioperative administration of antibiotics
- Deep vein thrombosis prophylaxis.

The review concluded that providing nutritional supplementation also is probably helpful although the evidence is not robust. Additionally, it was unclear whether minimizing the delay between hospital admission and surgery has any impact on mortality.[14]

Is early surgery better?

Early studies suggested that the sooner a hip fracture patient goes to surgery, the lower the mortality, but this has not been supported in well-controlled trials: no difference in mortality has been found whether the patient's conditions are first optimized to reduce the risk of surgery or if the operation commences within 24 hours.

Although mortality does not appear to be affected, avoiding delay of hip fracture repair yields improvement in other outcomes. In a well-designed prospective cohort study, Orosz et al found that medically stable patients with hip fracture (mean age, 82 years) who underwent surgery within 24 hours had fewer days of pain and less intense pain postoperatively than those whose surgery was delayed beyond 24 hours.[15] The early-surgery group also had a 1.94-day reduction in average length of stay compared with the late-surgery group.

A role for clinical pathways

To determine how the application of evidence-based perioperative practices affects actual outcomes in elderly hip fracture patients, Beaupre et al used a pre/post study design to evaluate the impact of an evidence-based clinical pathway at their institution.[16] Though there were no differences in in-hospital mortality or the overall costs of inpatient care in elderly hip surgery patients before and after pathway implementation, the patients undergoing surgery after pathway implementation were significantly less likely to have postoperative delirium, heart failure, pressure ulcers, and urinary tract infections compared with those undergoing surgery before implementation. The outcomes benefits of this type of multimodal intervention are likely to extend to abdominal surgical procedures as well.

CASE CONTINUED: POSTOP DAY 2—PATIENT IS CONFUSED AND CRYING IN PAIN

On the second postoperative day, our patient appears weak and slightly confused. She is not eating and is crying in pain. Her neurological exam is normal.

Question: Which is the most appropriate next step?

A. Increase physical therapy
B. Begin an antidepressant
C. Insert a nasoenteric feeding tube
D. Increase doses of analgesics

The best answer is D. With no prior history of depression, an antidepressant would probably not be useful. It is premature to recommend nasoenteric feeding. Because pain hampers physical therapy, an increase in physical therapy would likewise be premature. Because we know the patient is in pain, the correct answer perhaps seems obvious. But keep in mind that relieving pain also has many other positive ramifications: intense pain can be a cause of delirium or at least worsen its symptoms, and pain relief is a prerequisite for the physical therapy that this patient needs.

Strategies for pain control

In general, the treatment of choice for postoperative pain is low-dose morphine sulfate (eg, 1–4 mg every 2 hours, titrated as needed). Acetaminophen can be given safely to virtually all patients. Patient-controlled analgesia is reasonable for select patients but not for older patients with cognitive impairment. Nonsteroidal anti-inflammatory drugs might be helpful in younger patients and even in robust elderly patients, but they must be used very cautiously in the older population because of the risk of gastric ulcers and bleeding, acute kidney injury, fluid retention, and exacerbation of congestive heart failure.

POSTOP DAY 3: PATIENT REPORTS LONG-STANDING FATIGUE

On postoperative day 3, the patient is weak and complains of fatigue. She says that before the fracture, she was experiencing mild weight loss, fatigue, and reduced activity.

Question: What is the most likely reason for her symptoms before the fracture?

A. Frailty
B. Occult heart failure
C. Adverse drug reaction to her beta-blocker
D. Clinical depression

The best answer is A. Occult heart failure is a reasonable second choice, as it is very common in older patients and the diagnosis is easy to miss unless florid pulmonary edema or associated symptoms (eg, chest pain) are present. But this patient had no history of heart disease and was only on medications for hypertension. An adverse drug reaction, such as to the beta-blocker, is unlikely and would probably not cause weight loss. The patient had no history of depression, so clinical depression is unlikely. That said, all the choices are reasonable to consider in elderly patients reporting fatigue and weakness.

Frailty is important to recognize

It is important to identify frailty and to aggressively manage frail patients postoperatively. Although frailty is not clearly defined, Fried et al[17] identified five clinical features that correlate with its underlying pathophysiology:

- Minimal physical activity (ie, "doing less")
- Generalized (not focal) muscle weakness
- Slowed performance (eg, walking short distances takes longer)
- Fatigue or poor endurance
- Unintentional weight loss.

The presence of three or more of these features meets the criteria for frailty and is associated with increased risk for mortality over the next 3 years with or without surgery,[17] although surgery probably increases the risk.

Frailty is believed to be a failure over time of the homeostatic mechanisms that keep our organ systems functioning in the face of a stress. Decline in the ability of organ systems to maintain normal function is probably caused by inflammation, chronic disease, and normal aging, and has been termed *homeostenosis*. As a person ages and physiologic reserves are reduced, adding a stress such as surgery or severe infection can result in organ failure—usually multiple-system organ failure. In any intensive care unit, one is likely to see elderly patients who were admitted with one medical or surgical problem and soon end up having renal, liver, or brain dysfunction as well.

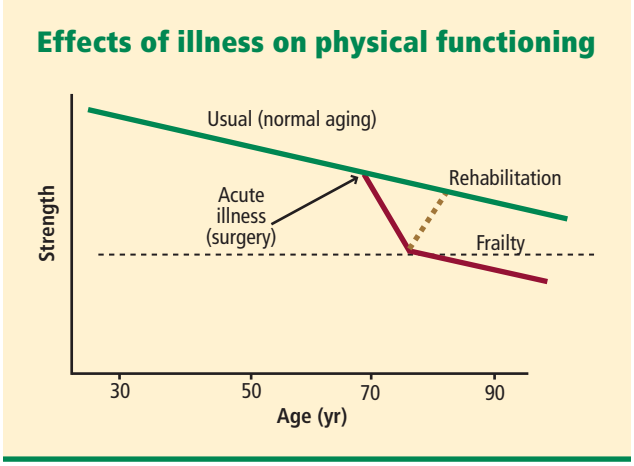

FIGURE 1. Strength throughout the adult life span. Whereas strength normally declines gradually during aging, an acute illness or surgery can cause a precipitous decline in strength. If the decline is too severe, the threshold of frailty is crossed.

Looked at another way, strength normally declines gradually during aging. An acute illness or surgery causes a precipitous decline in strength, and if it is too severe, the threshold of frailty is crossed **(Figure 1)**. Early mobilization and early and persistent physical therapy can help patients regain strength, thereby preventing frailty.

Physical therapy immediately after hip fracture surgery is associated with significantly better locomotion 2 months later.[18] A number of exercises are effective: range-of-motion exercises, low-impact aerobic activities, and exercises starting with low-intensity resistance (using bands, tubes, and weights) and progressing as tolerated to high-intensity resistance (with machines and pulleys) for an extended period of time.

Nutrition supplementation

Malnourishment can contribute to frailty, yet evidence for the benefits of supplementing nutrition is not strong, as noted above. However, meta-analyses of studies of nutritional interventions with meal supplementation (usually canned supplements) show that meal supplementation can improve mortality risk and reduce morbidity such as pressure ulcers in hospitalized elderly patients.[19,20] The patients most likely to benefit are those who are undernourished at baseline and aged 75 years or older.

CASE CONTINUED: WHAT HAPPENS POST-DISCHARGE?

Following surgery, our patient wonders, "Where will I go next? What will my lifestyle be like?"

These are important questions to consider when first evaluating whether an elderly patient should undergo surgery. In the case of hip fracture, standard thinking is that without surgery, the patient will never recover the ability to independently walk and perform activities of daily living. But we also must recognize the considerable risks of surgery in the elderly population, particularly those aged 75 years or older.

Comprehensive discharge planning

Early and intensive discharge management enhances quality of life and may help reduce hospital costs. A good model of care involves collaboration of orthopedic surgeons, hospitalists, general internists, geriatricians, and dietitians to address procedures, diet and nutrition, mobility and activities of daily living, and pain medications.[21] A case manager such as a social worker should start addressing care transition the day after surgery—planning ahead is imperative.

Following hip surgery, patients are routinely sent to skilled nursing facilities as soon as possible so they can start intensive physical therapy. Patients with significant functional impairment or who had delirium are more likely to require a prolonged hospital stay.

Naylor et al examined the effectiveness of comprehensive discharge planning in a study that randomized hospitalized patients (including surgical patients) 65 years or older to either usual discharge planning or intensive discharge planning with advanced practice nurses beginning early in hospitalization.[22] The intervention group was followed by home care nurses for up to 4 weeks and had continuous telephone access to the nurses. Patients who received the intervention had a significantly lower risk of hospital readmission, and those who were readmitted had significantly shorter hospital stays. The total cost of care was also significantly lower in the intervention group.

Family conferences aid decision making

Family conferences can be very useful for working through the many questions and challenges that surgery in an elderly person can pose, including whether the patient should undergo the operation, postoperative management, and postdischarge placement.[23] For patients with an uncertain prognosis because of unclear or multiple concurrent diseases, a family conference can help clarify the goals of therapy, inform the family about likely outcomes, and help determine the patient's wishes and values. Such issues should be revisited as the postoperative course proceeds.

Family conferences also provide a good opportunity to review advanced directives, the need for life support, and possible transfers to intensive care. Family conferences can also help resolve conflicts in care management, as family members may not agree with the need for surgery, how aggressive treatment should be, or where to send the patient for rehabilitation. Differences among family members on these questions are especially common with elderly patients. Working out such issues will improve patient care, especially when done early in the hospitalization.

DISCUSSION

Question from the audience: In our preoperative clinic, we are trying to intervene to reduce delirium and postoperative cognitive dysfunction. How can we quickly screen for the most important predictors and act to reduce the risk?

Dr. Palmer: The most important risk factor for delirium is age, which obviously can't be changed. Ask patients about alcohol use and depression. Check on nutritional status and begin supplementation if indicated. Discontinue high-risk medications. Check on electrolytes and their state of hydration; ideally, an electrolyte imbalance can be corrected preoperatively. In addition, other than in patients with end-stage renal disease, try to keep the hemoglobin above 7.5 g/dL, which appears to be associated with better outcomes and less risk of delirium.

It's also important to remind the family to bring in the patient's visual aids, hearing devices, and cane or walker so that they're available right after the operation.

Intraoperative factors that are important for preventing delirium include maintaining good blood pressure levels, giving supplemental oxygen, minimizing the time under general anesthesia, and using local anesthesia if possible.

Question from the audience: How strong is the evidence for using spinal anesthesia as opposed to general anesthesia in preventing postoperative cognitive dysfunction and delirium, especially in the setting of hip fracture repair?

Dr. Palmer: The evidence is fairly soft. For patients undergoing either hip or knee arthroplasty who were randomized to receive either spinal (or local) or general anesthesia, the risk of delirium was similar, but complications such as prolonged bed rest, pressure ulcers, and catheter-related urinary tract infections were somewhat reduced in the spinal/local group.[14] The relative risk of developing postoperative cognitive dysfunction is unclear—no randomized controlled trials have been conducted to answer that question.

Question from the audience: How do you use antipsychotic drugs, especially with the concerns from epidemiologic studies about an increased risk of death?

Dr. Palmer: No antipsychotic agents, including haloperidol, have a specific Food and Drug Administration–approved indication for treating agitation, dementia, or delirium. In general, they should not be used without a clear indication. That said, the usual off-label use is for patients who are severely agitated and are at risk of harming themselves or others. In an ICU setting, where

patients have multiple lines, the use of these agents can be considered for a very agitated patient. Alternatives exist, but antipsychotics like haloperidol have the advantage that they can be given in small increments very rapidly and achieve good control of severe agitation.

Antipsychotic agents should only be used with great caution and for the shortest duration needed. As delirium resolves, they should be tapered fairly rapidly over a few days and ideally should be discontinued by the time of hospital discharge.

None of the antipsychotic agents—including those in the first generation and the newer atypical agents—is free of this risk of increased mortality. The mechanism is not understood; it may be torsades de pointes or hypotension leading to stroke or sudden cardiac death.

Question from the audience: What is the most efficient way to assess cognitive and physical functioning preoperatively?

Dr. Palmer: There may be a documented history of dementia, or family members may tell you if there has been memory loss or some decline in the patient's self-care abilities. For patients without dementia, you can ask them directly if they can perform basic activities of daily living, such as getting out of bed or dressing. To assess higher-level function, ask if they can manage their own medications, pay bills, or handle their finances. If not, they might have cognitive impairment and are at higher risk for postoperative delirium. These are rather sensitive measures. There are instruments to assess this more precisely, but few clinicians have time to use them.

Quick bedside tests can help assess for delirium postoperatively. We see if patients are "alert and oriented times three" ("Do you know who you are, where you are, and the date?"). We test for attention by asking them to repeat a random string of numbers spoken 1 second apart in monotone; people who are delirious and many patients with severe dementia can't repeat more than three numbers. A patient who is alert and oriented, has a good attention span (more than three numbers in correct order), and has no history of dementia probably doesn't have delirium or dementia.

For physical function, ask if they can walk, get out of bed to a chair, and ambulate. If they don't give clear answers, observe them get out of bed or a chair, walk 10 feet, and return to bed. If they can do that with good balance, especially within 10 to 15 seconds, they probably have reasonably normal mobility and are at lower risk for postoperative complications such as falls with injury.

DISCLOSURES

Dr. Palmer has indicated that he has no financial relationships with commercial interests that have a direct bearing on the subject matter of this article.

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The role of testing in the preoperative evaluation

ABSTRACT

Preoperative laboratory and electrocardiographic testing should be driven by the patient's history and physical examination and the risk of the surgical procedure. A test is likely to be indicated only if it can correctly identify abnormalities and will change the diagnosis, the management plan, or the patient's outcome. Needless testing is expensive, may unnecessarily delay the operation, and puts the patient at risk for unnecessary interventions. Preoperative evaluation centers can help hospitals standardize and optimize preoperative testing while fostering more consistent regulatory documentation and appropriate coding for reimbursement.

KEY POINTS

Age-based criteria for preoperative testing are controversial because test abnormalities are common in older people but are not as predictive of complications as information gained from the history and physical exam.

Pregnancy testing is an example of an appropriate preoperative test because pregnancy is often not detectable by the history and physical exam and a positive result would affect case management.

Routine ordering of preoperative electrocardiograms is not recommended because they are unlikely to offer predictive value beyond the history and physical exam and are costly to an institution over time.

Routine and aged-based preoperative tests are no longer reimbursed by the Centers for Medicare and Medicaid Services.

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Routine presurgical assessment of patients with a standard battery of tests not only is wasteful but can lead to more unnecessary expense, delay, and even risk to the patient and physician. Any abnormal tests results, even if likely to be clinically unimportant to the upcoming surgery, will need to be followed up to rule out a significant abnormality that may have later implications. This review will outline strategies for making decisions about which tests are clinically useful for preoperative assessment of a given patient and also discuss the value of preoperative evaluation centers in promoting appropriate preoperative testing.

PREOPERATIVE EVALUATION SHOULD BE CLEARLY DIRECTED

Most patients scheduled for surgery at Brigham and Women's Hospital are assessed by the staff at our preoperative evaluation center. We take a medical history and conduct a physical examination, review the medical records, order laboratory tests or other studies as indicated, and determine which patients need further workup or consultations. The goals are to evaluate patient readiness for anesthesia and surgery, optimize patient health before surgery, enhance the quality of perioperative care, reduce the morbidity of surgery and length of stay, and return the patient to normal functioning.[1,2]

The above goals are generally achieved by directed laboratory testing, managing the patient's medications, stabilizing disorders when possible, and creating plans for postoperative care and pain management. Communication among the surgeon, the anesthesiology team, and the preoperative medical consultant (if there is one) is critical.[1,2]

In contrast, "clearing the patient for surgery" is not a legitimate goal of consultation. The real issues to be taken up in a consult are:

- What is the patient's risk of complications (cardiac and noncardiac)?
- Would further risk stratification alter patient management?
- Can anything be done to reduce the patient's risk?

If indicated, a consult should cover the entire perioperative period, offering opinions on operative risk and suggesting treatments that affect long-term patient outcomes. Rarely is preoperative intervention necessary

just to lower the risk of surgery. Most interventions that are needed should be done regardless of the surgery.

Everyone on the medical team should have the goal of efficient resource utilization, including avoidance of unnecessary visits, laboratory testing, and consultations.

PREOPERATIVE TESTING: WHAT IS NEEDED?

Preoperative testing is extremely expensive: even more than 20 years ago, preoperative medical testing for all types of surgery accounted for approximately $30 billion in US health care costs annually.[3] The likelihood of abnormal test results increases with age, and the more tests performed, the more likely a false positive will occur, further driving up costs.

Preoperative testing should generally be directed by a targeted history and physical examination, and the relevance of any tests should be considered in light of the type of procedure that is planned, particularly the hemodynamic changes and blood loss involved. Before ordering a test, physicians should be sure that there is a good reason for the test, that it is consistent with established guidelines, and that the results will be useful (ie, have the potential to change management).

Case study: Inguinal surgery in a healthy elderly man

A 72-year-old man is being evaluated prior to a right inguinal herniorrhaphy. He has osteoarthritis but is otherwise healthy and jogs 3 to 5 miles several times a week. He takes no medications and has no known drug allergies.

Question: Which of the following tests is necessary prior to surgery?

A. Complete blood cell count (CBC)
B. Prothrombin time and partial thromboplastin time
C. Electrocardiogram (ECG)
D. All of the above
E. None of the above

The correct answer is E (none of the above), for the reasons laid out in the following section.

Unnecessary testing may cause more harm than good

Untargeted testing should be avoided. An unexpected result will probably not be clinically significant for the surgery and will only lead to more needless testing, unnecessary anxiety for the patient, and delays in proceeding to the operating room.[4] The more tests that are ordered, the higher the likelihood of having an abnormal result by chance: for a test with 95% specificity, results for 1 out of 13 ordered tests will likely be abnormal without there being a true underlying physiologic abnormality.

Researchers at Johns Hopkins University assessed the value of routine preoperative medical testing in a randomized study of nearly 20,000 patients undergoing elective cataract surgery whose preoperative history and physical examination was either preceded or not preceded by a standard battery of tests, including ECG, CBC, electrolytes, urea nitrogen, creatinine, and glucose.[5] This was an ideal study population, given the relatively noninvasive nature of the procedure (with minimal hemodynamic changes) and cataract patients' relatively advanced age and resulting likelihood of comorbidities. Notably, there were no differences between the two groups in the overall rate of complications (approximately 3%), which led the researchers to conclude that routine preoperative medical testing does not increase the safety of cataract procedures. These results could be applied to other low-risk cases.

Unnecessary testing is also expensive. Researchers at Stanford University Hospital retrospectively compared preoperative test orders during 6-month periods before and 1 year after development of an anesthesia preoperative evaluation clinic.[6] They found a 55% reduction in the number of preoperative tests ordered from the period before the clinic was established, when tests were ordered by surgeons and primary care physicians, to the period after the clinic was established, when test ordering was transferred to anesthesiologists at the clinic. This reduction in the number of tests ordered resulted in a 59% reduction in the hospital's expenditures for preoperative tests, yielding $112 in cost savings per patient. No operating room cancellations, delays, or adverse patient events were reported as a result of the change.

Similar results were reported more recently by researchers at a Canadian hospital, who found that selective preoperative test ordering by staff anesthesiologists reduced the number and cost of preoperative studies compared with usual practice without a resulting increase in complications.[7]

What are the real legal risks?

Many surgeons express the fear that they will be sued if they do not routinely order preoperative tests. My view is that from a medicolegal standpoint, it is usually better not to order an unnecessary test if the next step to take in the event of an abnormal result would be unclear. The legal risk is greater for not following an abnormal test result than for not ordering a test that was not indicated. One may uncover an abnormal laboratory test finding that is not likely to be clinically significant but that could result in legal action if it were not evaluated further. A complication that may not be related to the abnormal result may develop at some point in the future and be blamed on the lack of follow-up. At our center, we insist that when a physician orders a test, he or she is responsible for the results and for following up on abnormalities.

Should testing be based on age?

Using age as a criterion for preoperative testing is controversial. There is no doubt that the older a patient is, the more likely he or she is to have abnormal test results: patients aged 70 years or older have about a 10%

TABLE 1
Criteria for determining whether a preoperative test is indicated*

Diagnostic efficacy: Does the test correctly identify abnormalities?
Diagnostic effectiveness: Would the test change your diagnosis?
Therapeutic efficacy: Would the test change your management?
Therapeutic effectiveness: Would the test change the patient's outcome?

*Adapted from Silverstein and Boland.[11]

chance of having abnormal levels of serum creatinine, hemoglobin, or glucose[8] and a 75% chance of having at least one abnormality on their ECG (and a 50% chance of having a major ECG abnormality).[9] However, these factors were found not to be predictive of postoperative complications. In contrast, predictive factors for this age group are an American Society of Anesthesiologists (ASA) physical status classification of at least 3 (indicating severe systemic disease), the risk of the surgical procedure, and a history of congestive heart failure.[8,9]

Guidelines for testing—and for not testing

About 10 years ago, the ASA attempted to develop a practice guideline for routine preoperative testing. The available data were so inconsistent, however, that the ASA could not reach a consensus and instead issued a practice advisory.[10]

Even so, there are a number of general principles for avoiding unnecessary preoperative testing:

- Routine laboratory tests are not good screening devices and should not be used to screen for disease
- Repetition should be avoided: there is no need to repeat a recent test
- Healthy patients may not need testing
- Patients undergoing minimally invasive procedures may not need testing
- A test should be ordered only if its results will influence management.

Table 1 lists four criteria for making an educated decision about whether a preoperative test is indicated.[11] In general, a test that meets only one or none of the four criteria is probably not a good test, and if it meets three or four of the criteria, it is a very good test (meeting two criteria would be borderline). These criteria should always be considered when ordering a laboratory test, an ECG, a stress test, or an additional consult.

A CLOSER LOOK AT A FEW SPECIFIC TESTS

Question: Which of the following tests is most likely to provide useful information to aid clinical decision-making during a preoperative evaluation for laparoscopic cholecystectomy?

A. A chest radiograph in a 43-year-old woman with asthma
B. An ECG in a 71-year-old man with hypertension
C. A pregnancy test in an 18-year-old woman with amenorrhea
D. A prothrombin time in a 51-year-old man with anemia
E. A urinalysis in a 67-year-old woman with diabetes

The best answer is C (pregnancy test); an ECG in the 71-year-old man would be less useful (see below). The remaining choices—chest radiograph, prothrombin time, and urinalysis—are even less appropriate. A chest radiograph in an asthmatic patient is not likely to yield more information than what is obtained from the history and physical exam. Patients with anemia are not likely to have abnormal coagulation, and the role of urinalysis in detecting glucose and protein in asymptomatic diabetic patients is limited.

Routine pregnancy testing is justifiable

There are a number of reasons to justify a low threshold for preoperative pregnancy testing[10]:

- Patients, especially adolescents, are often unreliable in suspecting that they might be pregnant (in several studies of routine preoperative pregnancy screening, 0.3% to 2.2% of tests were positive)
- History and physical examination are often insufficient to determine early pregnancy
- Management usually changes if it is discovered that a patient is pregnant.

Using the four criteria from **Table 1**, pregnancy testing rates high as a useful test: it would identify "abnormality," it would determine a diagnosis, and it would likely change management.

Routine ECG has limited utility

In contrast, routine preoperative ECG is not well supported. A recent study from the Netherlands assessed the added value of a preoperative ECG in predicting myocardial infarction and death following noncardiac surgery among 2,422 patients older than age 50 years.[12] It showed that ECG findings were no more predictive of complications than findings from the history and physical examination and the patient's activity level.

From our own data at Brigham and Women's Hospital,[13] we found that the presence of any of the following six risk factors predicted all but 0.44% of ECG abnormalities in patients aged 50 years or older presenting for preoperative evaluation:

- Age greater than 65 years
- Congestive heart failure
- High cholesterol
- Angina
- Myocardial infarction
- Severe valvular disease.

The 2007 guidelines on perioperative risk assessment from the American College of Cardiology and American Heart Association (ACC/AHA) do not consider ECG to be indicated in asymptomatic patients undergoing low-risk noncardiac procedures regardless of patient age,[14] like the 71-year-old man with hypertension in the above case question. These guidelines also state that evidence for routine ECG orders is not well established in patients with at least one clinical risk factor undergoing intermediate-risk procedures.

The aforementioned ASA practice advisory acknowledges that the likelihood of ECG abnormalities rises with increasing patient age, but the ASA was unable to reach consensus on a minimum age for routinely ordering an ECG in surgical candidates.[10] The advisory recommends taking into account other factors, such as cardiac risk factors, the presence of cardiocirculatory or respiratory disease, and the type and invasiveness of the surgical procedure.[10]

In recommendations not specific to the perioperative setting, the US Preventive Services Task Force advises against routine screening for coronary heart disease with ECG or exercise treadmill testing.[15] It gives routine screening a "D" recommendation, indicating that risk is greater than benefit because of the potential for unnecessary invasive procedures, overtreatment, and mislabeling of patients.

Our group at Brigham and Women's Hospital recently surveyed anesthesiology program directors at US teaching hospitals to determine their preoperative test-ordering practices.[16] Among the 75 respondents (58% response rate), 95% said their institutions have no requirements for ordering ECGs unless indicated based on age, history, or surgery type; 71% said their institutions have age-based requirements for ordering ECGs (usually > 50 years). Most respondents reported that their institutions are ordering fewer ECGs since the publication of the 2007 ACC/AHA guidelines on perioperative evaluation.

Whether or not age should be used as a criterion for ECG testing is controversial, and editorials on this subject abound.[17–19] They point out that clinicians must be careful before abandoning routine ECGs in elderly patients, for several reasons:

- An abnormal ECG (or abnormal lab test results) may modify a patient's ASA classification (which is predictive of complications)
- At least one-quarter of myocardial infarctions in elderly persons are "silent" or clinically unrecognized
- A preoperative ECG provides a useful baseline if the patient should develop ECG changes, chest pain, or cardiac complications during the perioperative period.

Most institutions use age as a criterion for ordering tests, especially for ECGs. If such a policy is used, a threshold of 60 years or older is probably most appropriate. However, a patient with good functional capacity who is undergoing a low-risk procedure does not need cardiac testing.[14,20]

An additional consideration is cost. Although the cost of a single ECG is modest, the cumulative cost of preoperative ECGs for all older surgical patients is significant over the course of a year. Because the Centers for Medicare and Medicaid Services (CMS) no longer cover routine preoperative ECGs, routine testing can be very costly to an institution over time.

COST AND REGULATORY BENEFITS OF PREOPERATIVE CENTERS

Preoperative evaluation centers tend to be cost-effective, as they keep consultations and redundant provider interviews to a minimum, encourage more appropriate targeting of tests, and help to avoid last-minute operating room delays and cancellations.[21,22] They also provide an efficient means of compiling the chart for the operating room.

The merits of standardization

Preoperative evaluation centers likewise encourage more standardized preoperative assessment, which can facilitate compliance with surgical quality measures such as those from the National Surgical Quality Improvement Program and the Leapfrog Group. Standardization also fosters more efficient and consistent regulatory documentation, making it easier to follow requirements from CMS (often linked to reimbursement) and the Joint Commission. It also tends to improve reimbursement by encouraging more appropriate coding under CMS' diagnosis-related group (DRG) system to indicate that whatever testing is ordered is related to the surgical diagnosis or to relevant comorbidities.

No excessive dictates from Joint Commission or CMS

Contrary to what many believe, the Joint Commission does not require excessive preoperative testing. The Joint Commission has no mandate for routine diagnostic tests but requires only what is necessary for determining a patient's health care needs.[23]

CMS provides no guidance as to what to do or not do in a preoperative assessment, but it does not reimburse for routine screening tests or for age-based testing.[24] Reimbursement for a preoperative ECG, for example, requires documentation of the patient's signs or symptoms; for an ECG that is indicated, reimbursement includes review and interpretation by the physician.[25]

A new partner for proper preoperative assessment

Appropriate preoperative evaluation and testing is one of the goals promoted by the recently formed Society for Perioperative Assessment and Quality Improvement (SPAQI). The mission of this international nonprofit organization is to optimize surgical outcomes by sharing best practices and promoting research and communication among health professionals across multiple disciplines. More information is available at *www.spaqi.org*.

DISCUSSION

Question from the audience: At my hospital, we teach residents about limiting the preoperative tests they order, but surgeons routinely expect many of these tests, including chest x-rays in patients with pulmonary conditions. Are any surgical societies involved in efforts to reduce preoperative testing? Or are surgical societies' recommendations actually driving some of the unnecessary testing?

Dr. Hepner: I'm not aware of recommendations from surgical societies regarding preoperative testing. Many surgeons believe that the more testing that's done, the likelier they are to uncover an occult disease. They also often want baseline information, which may actually be warranted in some cases.

Question from the audience: If you're already ordering a "type and screen" or "type and hold" for a patient, isn't it worthwhile to just add on a CBC? The patient is already getting the phlebotomy, so isn't there a cost benefit to getting other routine tests done at the same time rather than calling the patient back for more tests if another indication arises?

Dr. Hepner: Charges are generally assessed for each individual test, not for drawing blood, so I would only get the tests that are indicated.

Question from the audience: In institutions without a preoperative clinic, sometimes the surgeons do the workup without discussing the case with the primary doctor, and the surgeons want an ECG so that the case isn't cancelled at the last minute. Can you give straightforward criteria in such cases, such as an age threshold, or would you not order an ECG for anyone?

Dr. Hepner: Based on our most recent data, 60 years seems to be a reasonable cutoff if you are going to use age as a criterion.

Question from the audience: What criteria do you use for preoperative screening with pregnancy tests?

Dr. Hepner: If you have an unreliable patient population, general screening should be done. We don't have such a requirement, but we have a very low threshold. If a patient appears very reliable, knowing the exact date of her last menstrual period, we'll go by that. If a patient is unsure, we'll do a pregnancy test.

Question from the audience: My hospital doesn't have a preoperative clinic, and until recently, the anesthesiology department has helped surgeons with ordering of preoperative tests. We followed a guideline protocol for about 20 years. Now the newer surgeons say they don't want to be responsible for abnormal test results. Yet we anesthesiologists aren't seeing the patients, so we can't use clinical judgment; we can only go by the guidelines. The surgeons are the only physicians on the case who actually do the history and physical exam. So who should sign the test orders and be responsible for abnormal results?

Dr. Hepner: In our preoperative test center, we tell the surgical team that if they are uncertain about which tests to order, we will handle it. And if we order a test, we follow up on the results. You must ensure that orders are signed and not rubber-stamped; that way, the person who orders a test will get called with any abnormal results. If you order it, you own it.

Question from the audience: I agree that no testing is needed for the 72-year-old man you presented who was undergoing surgery for inguinal hernia, but it always worries me not to do an ECG since part of the standard of care for anesthesia is intraoperative ECG monitoring. If we see some sort of unusual arrhythmia when we take the patient in, we might cancel the case if we don't know whether it was present at baseline. Surgeons will ask me, "Why didn't you order a baseline if you're going to monitor the ECG in the operating room? If you're not going to order a baseline, then why monitor the ECG?" These are medicolegal issues that I haven't seen addressed.

Dr. Hepner: A case like you describe will be addressed in the upcoming medicolegal session (see page S119). You make a good point that many times just having a baseline is helpful, but I would argue that it is more helpful for intermediate- or high-risk cases.

DISCLOSURES

Dr. Hepner has indicated that he has no financial relationships with commercial interests that have a direct bearing on the subject matter of this article.

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Perioperative fluid management: Progress despite lingering controversies

ABSTRACT

Perioperative fluid management remains controversial. Nevertheless, its optimization is essential to reducing the risk of postoperative complications, which have been shown to profoundly affect patients' short- and long-term outcomes. Current evidence favors a "flow-guided" approach to perioperative fluid administration, which uses variables such as stroke volume and cardiac output as the basis for guiding fluid requirements. The optimal fluid is controversial, although colloids appear to have some physiologic advantages over crystalloids. Minimally invasive technologies have emerged for intraoperative monitoring of blood flow, which may enable more precise fluid titration.

KEY POINTS

A flow-guided approach to fluid administration is associated with reductions in mortality, postoperative complications, and length of stay compared with fluid management guided by traditional physiologic targets.

Studies to date have shown no consistent difference between colloids and crystalloids in their effects on clinical outcomes.

Intraoperative esophageal Doppler monitoring is a simple technique for titrating boluses of fluid based on continuous estimations of stroke volume.

Administration of sufficient fluids early in the course of surgery may be more important than the total volume of fluid administered in improving patient outcomes.

Intraoperative fluid needs are highly variable, underscoring the need for individual monitoring and assessment.

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Perioperative fluid management remains controversial. Until recently, fluid management was guided by targets such as urine output, static pressures, blood pressure, and other physiologic variables. Such physiologic signs, however, are inadequate for detecting subclinical hypovolemia. This has prompted the emergence of an approach to fluid administration based on stroke volume and cardiac output—a "flow-guided" approach—designed to overcome the inadequacies of conventional physiologic signs and improve outcomes. Recent technological advances are permitting noninvasive guidance of intravenous fluid therapy to optimize intravascular volume status.

This article reviews the rationale for perioperative fluid management, strategies for perioperative fluid therapy and their associated outcomes, the types of volume expanders used, and considerations for improving perioperative fluid administration.

WHY FLUID MANAGEMENT MATTERS

Postoperative complications predict survival

In 2005, Khuri et al published a study of survival after major surgery that starkly illustrated the prognostic importance of postoperative complications.[1] In an effort to identify predictors of long-term survival, they analyzed a National Surgical Quality Improvement Program database of 105,951 patients who underwent eight common operations at Veterans Administration facilities. They found that the most important determinant of reduced postoperative survival over 8 years of follow-up was the occurrence of a complication within 30 days after surgery. The presence of a postoperative complication was a stronger predictor of death than any intraoperative or preoperative risk factor.

Fluid management is key to preventing complications

Optimizing perioperative fluid management is essential to reducing the risk of postoperative complications and mortality. Surgical patients are more likely to have serious complications and die if they have limited physiologic reserve. Adequate fluid administration may reduce the stress response to surgical trauma and support recovery.

Building on early work showing that survivors of major surgery have consistently higher postoperative cardiac output and oxygen delivery (DO_2) than do nonsurvivors,[2,3] a seminal study by Shoemaker et al showed

that these types of blood flow–related parameters are predictive of both survival and complication-free survival.[4] Specifically, Shoemaker and his team showed that a protocol designed to achieve DO_2 of at least 600 mL/min/m^2 was associated with reductions in both postoperative complications and death.[4]

PROBLEMS WITH PERIOPERATIVE FLUID THERAPY—AND EFFORTS TO OVERCOME THEM

Despite the utility of fluid management in reducing postoperative complications, perioperative fluid therapy is fraught with several fundamental problems:

- Blood volume cannot be evaluated accurately.
- Fluid overload cannot be identified accurately, apart from tissue edema as a result of gross fluid overload.
- Hypovolemia cannot be identified accurately. Commonly measured variables (heart rate, blood pressure, base excess, lactate) are late markers, and the patient's status upon admission to the operating room is often unknown.
- Tissue perfusion cannot be evaluated accurately. Although lactate and venous oxygen saturation are surrogate markers, genuinely accurate markers for tissue perfusion are lacking.

For these reasons, fluids are commonly administered without the guidance of direct markers of fluid status.

Assessing flow-guided fluid therapy

These shortcomings prompted me and several other researchers to assess the evidence regarding a flow-guided approach to fluid administration, which aims to achieve maximal cardiac output and stroke volume while avoiding excess fluid administration. We conducted a systematic literature search for randomized controlled trials evaluating the postsurgical effects of perioperative fluid therapy to increase global blood flow to explicitly defined goals, after which we performed a meta-analysis of the 22 qualifying studies.[5] The trials collectively included 4,546 patients undergoing relatively high-risk elective or emergency surgery, consisting of general, vascular, cardiac, orthopedic, and urologic procedures. Overall mortality in these trials was 10.6% (481 deaths). The primary outcome assessed was mortality; secondary outcomes included morbidity and length of stay in the hospital and in the intensive care unit. Outcomes were assessed according to the timing of the intervention, the fluid type, and explicit measured goals. Fluids were given to all patients, usually as a dynamic bolus, using a flow-guided approach above and beyond that of the control group.

Our analysis found that a flow-guided protocol was associated with a significant reduction in mortality compared with control protocols (odds ratio = 0.82 [95% CI, 0.67–0.99]; $P = .04$).[5] However, sensitivity analysis showed that the largest and best-designed studies tended to yield no significant differences in mortality between the groups, which highlights the remaining need for larger studies to more definitively clarify the effect on mortality.

Timing of administration (ie, whether fluid was given pre-, intra-, or postoperatively) influenced the primary outcome: compared with control, flow-guided fluid therapy was associated with a significant reduction in mortality only when administered intraoperatively, but not when given preoperatively or postoperatively.[5]

Length of hospital stay was reduced by approximately 1.6 days with flow-guided therapy compared with control ($P < .00001$), but there was no significant difference between approaches in terms of intensive care unit stay.[5]

Postoperative complication rates are difficult to compare, given the lack of a uniform definition of a complication and the relative importance of different complications. Nevertheless, when grouped as a whole, the rate of complications was 48% lower ($P < .00001$) with flow-guided therapy compared with control. Of all outcomes assessed, the effect on complications was the most consistent among all the studies in the analysis. To provide an example using one easily defined complication, the incidence of renal failure was reduced by 35% with flow-guided therapy compared with control ($P = .002$).[5]

COLLOID OR CRYSTALLOID?

Two pharmacologically distinct classes

Intravenous fluids can be broadly classified into colloid and crystalloid solutions, and the relative merits of these two fluid classes are at the center of an enduring debate that predates the advent of flow-based fluid administration. Despite fundamental differences in their pharmacokinetics and other characteristics, colloids and crystalloids are often not sufficiently distinguished from one another in discussions of perioperative fluid therapy.

The effect of a colloid depends on its molecular weight. Ninety minutes following administration, a significant proportion of a colloid with a high molecular weight (eg, hydroxyethyl starch) will be retained in the circulation. In contrast, crystalloid solutions (eg, 0.9% saline) readily disappear from the circulation, owing to the ease with which they travel across the cell membrane.[6]

No evidence of outcome differences

A systematic literature review by Choi et al reflects the current state of knowledge on the relative effects of colloids and crystalloids for fluid resuscitation.[7] It concluded that there are no apparent differences between these fluid classes in their effects on pulmonary edema, mortality, or length of stay. The authors noted that methodologic limitations of the available comparative studies prevent meaningful conclusions and that larger randomized controlled trials are needed to detect any differences in outcomes between the two classes.

Although using a crystalloid for fluid resuscitation probably results in a greater volume of fluid given, a study known as SAFE (Saline versus Albumin Fluid Evaluation),[8] published after the Choi analysis, showed no differences in 28-day all-cause mortality or other significant outcomes between patients randomized to the colloid (4% albumin) and those assigned to the crystalloid (0.9% saline). Patients receiving the colloid had a higher central venous pressure at all time points, a lower heart rate at the end of the first day, and less overall volume on days 1 and 2 compared with patients receiving the crystalloid. While SAFE was conducted in critically ill patients, these physiologic advantages of the colloid may have implications for results in the perioperative arena, although this remains speculative.

INTRAOPERATIVE MONITORING TO OPTIMIZE FLUID THERAPY

Another important issue is the emergence of minimally invasive technologies for monitoring hemodynamic measures intraoperatively. The aim is to enable more precise tailoring of fluid therapy to meet patient needs on a case-by-case basis.

One of the simplest of these techniques is esophageal Doppler monitoring to measure descending aortic blood flow using Doppler ultrasonography. The technique is used to titrate repeated boluses of fluid based on continuous estimations of stroke volume and surrogate markers of preload indices. Typical protocols for esophageal Doppler monitoring call for administration of colloid to maintain a descending thoracic corrected flow time of no more than 0.35 seconds and stroke volume increments of 10%.

Phan et al recently published a meta-analysis to assess the effect of intraoperative esophageal Doppler monitoring in guiding fluid therapy to optimize intravascular volume status.[9] The analysis, which included nine randomized controlled trials in a total of 920 patients, found statistically significant reductions in the rate of complications and in length of hospital stay with the use of esophageal Doppler monitoring; there was no difference in mortality. Use of Doppler monitoring was associated with an increase (+671 mL) in the volume of colloid administered and a decrease (–156 mL) in the volume of crystalloid.

Timing of fluid administration can be critical

One of the trials in the above meta-analysis illustrated that the timing of fluid administration might be more critical than the volume of fluid given. Noblett et al placed an esophageal Doppler probe in each of a series of 108 patients undergoing colorectal resection;[10] the control group received perioperative fluid at the anesthesiologist's discretion, whereas the intervention group received additional colloid boluses based on Doppler assessment. While the overall volume of colloid given was comparable between the two groups, the intervention group received nearly 100% of the total volume during the first quarter of surgery. The intervention group had significantly fewer postoperative complications than the control group as well as a 2-day reduction in average length of stay. Circulating levels of interleukin-6 and cytokines also were significantly lower in the intervention group, which suggests that the intervention blunted the inflammatory response to surgery.

Fluid management must be individualized

Intraoperative fluid needs are highly variable and patient-specific. Parker et al tested an approach in which they universally administered 500 mL of a gelatin colloid solution prior to hip fracture surgery and compared it with a conventional intravenous saline crystalloid solution; neither approach used invasive intraoperative monitoring.[11] They found no significant difference in length of stay, 30-day mortality, or postoperative complications between the two study arms. They concluded that more invasive investigation of patients before or during surgery may have been able to identify a subgroup in whom the colloid therapy or more precise fluid control would have been beneficial.

THE ROAD AHEAD

Fluid management remains suboptimal

Despite being a fundamental component of surgical and perioperative care, fluid management remains suboptimal in clinical practice. I can speak most directly to the practice of fluid management in the United Kingdom (UK), but the same types of shortcomings apply broadly to the United States as well.

In 1999, the UK's National Confidential Enquiry into Patient Outcome and Death examined perioperative death in the UK, concluding that patients were dying as a result of too much or too little perioperative fluid administration.[12] Their report cited staff inexperience as an important contributor to the problem, as junior physicians order and deliver the majority of postoperative fluid regimens.

This cautionary report from 10 years ago appears not to have produced substantial improvements in practice, at least according to a recent study by Walsh et al.[13] These researchers prospectively audited postoperative fluid management practices in 106 consecutive patients undergoing laparotomy in a UK general surgical unit over a 6-month period in 2003. They found no correlation between available fluid balance data and the quantities of fluids prescribed, suggesting that physicians routinely ignore such data when prescribing. Fifty-four percent of the patients developed at least one fluid-related complication. Patients routinely received significantly greater amounts of fluid and

sodium than were physiologically needed, and multivariate analysis showed that mean daily fluid load predicted development of fluid-related complications.

Guidance from a new British consensus document

Where can clinicians turn for a good synthesis of current evidence to guide better perioperative fluid management? I would recommend the newly released British Consensus Guidelines on Intravenous Fluid Therapy for Adult Surgical Patients,[14] which are available on the Evidence Based Peri-Operative Medicine Web site (*http://www.ebpom.org*). These guidelines were developed by a multidisciplinary team of clinicians to improve perioperative fluid prescribing. They cover principles of preoperative, intraoperative, and postoperative fluid management, as well as fluid therapy in acute kidney injury. They present 28 recommendations in all, at least 12 of which are based on high-level (grade 1a or 1b) evidence.

DISCUSSION

Question from the audience: What is the relationship between perioperative fluid management, gut edema from perioperative fluid use, and postoperative ileus?

Dr. Hamilton: There's no easy answer. Excessive administration of sodium and fluid does predispose to gut and tissue fluid edema. Many of the enhanced surgery recovery programs require no preoperative fasting. There's no bowel prep. The enteral route is used primarily as quickly as possible. In the UK, we no longer use nasogastric tubes for many of those programs. But there's no doubt that tissue edema still occurs with excess fluid therapy.

The premise for individualizing fluid therapy is that less is not more but that more is not the right approach either. The stroke volume approaches or the corrected flow time approaches have been related to return of gastrointestinal function and return of flatus, which is a function of gastrointestinal recovery.

Question from the audience: Can you comment on the perioperative use of the Swan-Ganz catheter for fluid management?

Dr. Hamilton: I don't use it intraoperatively, and not many hospitals in the UK use it apart from liver resection surgery. Having said that, Swan-Ganz catheters were the predominant monitor for 30% to 40% of the original studies of hemodynamic optimization. I cannot give you intraoperative data to support the use of Swan-Ganz catheters for monitoring, but if you lift evidence from the other methods of monitoring hemodynamics, if you're optimizing flow in a bolus and dynamic fashion, then you should see the kinds of improvements in outcomes that are associated with the other modalities.

The drawback with the Swan-Ganz catheter, obviously, is the morbidity associated with its insertion and its interpretation. But if you're confident in doing those things, I think it's a perfectly good monitor.

DISCLOSURES

Dr. Hamilton has indicated that he has no financial relationships with commercial interests that have a direct bearing on the subject matter of this article.

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Giving anesthesiologists what they want: How to write a useful preoperative consult

ABSTRACT

Anesthesiologists are the primary users of preoperative medical consultations (consults), but the information in consults is often of limited usefulness to anesthesiologists and the rest of the surgical and perioperative team. The purpose of a consult is not to "clear" a patient for surgery but rather to optimize a patient's underlying disease states before they are compounded by the insult of surgery. Too often consults provide advice on subjects that are in the realm of expertise of the anesthesiologist—such as the type of anesthesia to administer or what intraoperative monitoring to use—and thus risk being ignored. Consults should instead provide specific data about the patient that are pertinent to the surgery, as well as guidance on preoperative and postoperative disease management.

KEY POINTS

Consults that provide pertinent quantitative data about the patient are helpful—eg, the heart rate at which ischemia was exhibited during stress testing and the degree of ischemia.

Anesthesiologists do not need assistance with managing intravenous drugs (with the exception of unusual agents), but they can use specific guidance on managing oral medications pre- and postoperatively to best achieve optimization and steady-state concentrations.

Pertinent recent information (< 5 years old) from the nonanesthesiology literature should be provided.

Medical consultants should arrange for follow-up care for patients with active conditions not addressed by the surgery.

Absolute recommendations should be avoided in a consult: the surgical team may have good reason not to follow them, and legal repercussions could ensue. The words "consider" or "strongly consider" usually suffice, except where there is an absolute standard of care.

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The ideal preoperative medical consultation (consult) is useful to the whole surgical team, ensures maximal patient readiness for surgery, and promotes optimal perioperative care of the patient. Too often, however, consults are ignored or, even worse, set the stage for legal problems. This article identifies problems frequently seen in preoperative consults, particularly from the perspective of anesthesiologists, and gives guidance to those who write consults—hospitalists, internists, cardiologists, and other medical consultants—on providing the information that is most needed by those who use them.

A WIDE RANGE OF END USERS

Anesthesiologists are most often the primary users of the information in preoperative consults, but many other members of the surgical and perioperative team benefit from a well-developed consult, including surgeons, intensivists, nurses, and pain management specialists. Most important, patients stand to benefit, as a good consult helps to ensure that the full breadth of relevant patient-specific information is brought to bear to anticipate potential difficulties and promote optimal care.

Purpose of a consult is in the eye of the beholder

The literature on medical consults in the perioperative arena is scant. The only fairly recent assessment of physician attitudes toward the role of consults was reported by Katz et al in 1998.[1] These researchers surveyed attitudes about the various perceived purposes of preoperative cardiology consults, and received rather different responses from anesthesiologists, cardiologists, and surgeons.

There was consensus among all three specialties that two particular functions of a consult are important:

- Treating an inadequately managed cardiac condition before surgery
- Providing data to use in anesthetic management.

Additionally, all three specialties deemed the suggestion of intraoperative treatment modalities to be reasonably important when such suggestions were specifically included in the consult request, although anesthesiologists assigned less importance to this function.[1]

In contrast, anesthesiologists considered suggestions about intraoperative treatment generally unimportant when not specifically requested, and they viewed suggestions of intraoperative monitoring and advice on the

safest type of anesthesia as even less important. Anesthesiologists also deemed "clearing the patient for surgery" as an unimportant function of the consult. Cardiologists rated all of these functions as more important than anesthesiologists did and in some cases as considerably more important. To many of the survey questions, surgeons responded that a specific purpose of a consult was "neither important nor unimportant."[1] That may be because the surgeon's purpose in obtaining the consult is often simply to address the concerns of the anesthesiologist, who might otherwise delay or cancel a needed surgery.

Consult deficiencies: Vagueness, illegibility, dictating anesthetic choice

The survey by Katz et al also assessed each specialty's perceptions of the most common deficiencies of preoperative cardiology consults. The deficiencies deemed most common were failure to give specific facts, illegible handwriting, and attempts to dictate the type of anesthesia to be used. Anesthesiologists considered each of the deficiencies assessed as occurring more commonly than their cardiologist or surgeon colleagues did.[1]

The requester–user disconnect

The differing perceptions of preoperative consults by anesthesiologists and surgeons underscore a fundamental problem: the primary requesters of consults (surgeons) are different from the primary users of consults (anesthesiologists).

Ideally, preoperative consults should be requested by anesthesiologists. Unless and until the ordering of consults changes on a wide scale, however, our advice is for consultants to ask the anesthesiologist what he or she needs to know, in addition to any questions directed to the requesting surgeon. Communication between the surgeon and anesthesiologist should be encouraged as much as possible, and consultants should keep both the anesthesiologist and surgeon in mind when writing consult notes.

A final end user: The plaintiff's attorney

It is wise to keep in mind one more potential user of your consult: a plaintiff's attorney. A poorly written consult may benefit plaintiffs' lawyers. Consults should never give absolute instructions; it is better to use such phrases as "Strongly consider…" or "The current literature strongly suggests…" Otherwise, the surgical team is placed in an awkward position if it does not follow your recommendations, even if for good reason. If a certain recommendation absolutely must be followed, then direct oral communication from the consultant to the attending anesthesiologist (or surgeon) is best.

CONSIDER THE PRIMARY USER: WHAT ANESTHESIOLOGISTS ALREADY KNOW

For the purpose of preoperative consults, it is helpful to think of anesthesiologists as experts in acute medical care. Their 4-year training consists of the following:

- 1 year of internship, often in medicine, including 6 months of basic patient care in the ward or clinic (the last time they will manage chronic disease)
- 4 months in the intensive care unit (ICU) and 1 month in the recovery room, which yields solid intensivist training
- 3 months in pain management, covering acute and chronic pain and regional blocks
- ~24 months in the operating room, often devoted to care of complex problems in surgical subspecialties (obstetric, pediatric, neurologic, cardiothoracic, vascular)
- 1 month of preoperative screening and consultations (a recent requirement).

An optional fifth year may be spent in a subspecialty.

Since the large part of anesthesiologists' training is in acute care, they generally do not need advice about the acute treatment of any ailment. Consults should not advise anesthesiologists on subjects in which they have considerable expertise. They already have well-established ideas about addressing hypertension, myocardial ischemia, heart failure, arrhythmias (unless unusual therapies are needed), bronchospasm, glucose levels, and pain in the operating room, so they are apt to ignore advice on such topics.

There are several additional topics in which anesthesiologists have considerable expertise and do not need guidance in consults:

- Choice of anesthetic type and its impact on outcome
- Choice of invasive or noninvasive monitoring for any comorbidity and operation
- Postoperative patient disposition (ie, whether to send a patient home, to the postanesthesia care unit, to the ICU, or to a step-down unit)
- Impact of optimizing organ function on perioperative outcome
- Cardiovascular and respiratory physiology
- Pharmacology of intravenous agents.

WHAT ANESTHESIOLOGISTS MAY NOT KNOW—AND NEED FROM CONSULTANTS

How to manage chronic diseases

Preoperative consults should concentrate on matters in which anesthesiologists are not well trained **(Table 1)**. These largely involve optimizing the *preoperative* treatment of *chronic* diseases—eg, hypertension, diabetes, coronary artery disease, renal failure, malnutrition, hepatic dysfunction, asthma/chronic obstructive pulmonary disease—and managing oral drug regimens. Anesthesiologists generally do not need help, however, in optimizing the function of an organ system once the patient is in the operating room. Advice on preoperative optimization should include guidance on how long the optimization is likely to take.

Follow-up care (eg, for poorly controlled diabetes or hypertension) often can wait until after the operation, and a consultant's opinion about that is appreciated. It is especially

TABLE 1
Useful information to include in preoperative consults*

- How to preoperatively optimize function of an unhealthy organ system
- Guidance on managing *oral* drug regimens
  - –First-line and second-line agents
  - –Initial dosage and titration; recommended combinations
  - –How to manage side effects
- Expected time until patient is optimized for the procedure if above management is followed
- Tests that might be indicated preoperatively to direct therapy to optimize function
- Additional interventions indicated by the patient's disease, and appropriate timing (pre-, intra-, postoperatively)
  - –Include assurance that consultant will follow up with specified nonurgent postoperative care without prompting
- Current pertinent anticoagulation recommendations
- Details on coronary stents—when placed, where placed, and type (drug-eluting or bare metal)
- Focused information on cardiac defibrillators and other implanted devices, specifically:
  - –Whether patient is pacer-dependent
  - –Effect of magnet placement
  - –Has battery recently been checked?
- Recommendations on intra-/perioperative management of:
  - –Rare diseases
  - –Blood disorders, especially coagulation abnormalities
  - –Brittle diabetes (loading doses, optimal make-up of infusions, treatment targets)
  - –Endocrine disorders (eg, perioperative dosing of thyroid drugs)
- *Newer* recommendations/data (< 5 years old) on acute medical management, especially in patients with complex comorbidities
- Explanations/references when recommendations deviate from accepted guidelines
- *Legible* contact information, including an emergency phone number to ensure access prior to early-morning procedures

* In all cases, be as specific as possible and favor quantitative over qualitative information when possible.

helpful to know that the patient will be followed without the surgeon or anesthesiologist having to arrange for it.

New evidence-based guidance from the literature

One case when recommendations on acute medical management should be provided is when they involve new information from the literature—ie, important data or guidelines published within the prior 5 years or so. It can take time for new information and recommendations to reach all clinicians even within a single specialty. Moreover, important information, such as on the perioperative use of beta-blockers and statins, is not necessarily published in the anesthesiology literature. It is critical to relay information such as the recent recommendation not to withdraw statins prior to surgery, as the current editions of most anesthesiology textbooks have incorrect information suggesting discontinuation. Thus, consultants should include pertinent recent data and guideline recommendations, especially if they go against previous dogma.

Rare diseases, blood disorders, other special cases

As outlined in **Table 1**, advice on perioperative management is appreciated for patients with rare diseases, coagulation disorders or other blood disorders, and brittle diabetes and other endocrine disorders, as most anesthesiologists are not intimately familiar with these conditions. Anesthesiologists also need, but often do not get, basic details on coronary stents and other implanted devices (see **Table 1**), as well as guidance on the latest anticoagulation recommendations, with which it is difficult to keep up to date.

A sensitivity to audience and context

It is always appropriate to ask the surgeon requesting a consult—and the anesthesiologist assigned to the case, if known—what he or she wants to know from the consult. If guidance on specific cases is impractical, it is appropriate to ask the chair of the anesthesiology department, or several anesthesiologists collectively, for general guidance on what they look for from preoperative consults.

Anesthesiologists, like consultants, comprise a broad range of people, and it is always important to be sensitive to context. Generalists who work mainly on healthy patients or in a community setting may have forgotten some of their training in acute medicine and are more likely to appreciate advice on intraoperative care. On the other hand, an anesthesiologist who trained in a cardiothoracic subspecialty fellowship, who routinely deals with issues such as left ventricular assist devices and heart transplants, would not benefit from such advice.

WHAT A CONSULT SHOULD—AND SHOULD NOT—BE

The above advice can be distilled into a few principles:

- A consult is an opportunity for the medical consultant to provide helpful management suggestions to the operative team.
- A fundamental objective of a consult is to optimize a patient's underlying disease before it is compounded by the insult of surgery.
- The purpose of a consult is *never* to "clear" a patient for surgery. Whether or not to proceed to surgery is a question for the anesthesiologist, surgeon, and patient to decide after weighing the risks and benefits once the patient's comorbidities are optimally managed. The consult is an important contributing factor to this decision, but it should never be the mechanism of the decision. Though the note from the surgeon requesting a consult may routinely be written as, "Clear the patient for surgery," consultants should recognize this for what it is—the surgeon's attempt to avoid having the anesthesiologist cancel the operation—and refrain from weighing in on "clearance" one way or the other.

CASE STUDY: CARDIAC CONSULT REQUESTED BEFORE FEM-POP BYPASS SURGERY

Cardiovascular problems are the most common reasons for requesting preoperative consults. The following case illustrates a typical scenario for a cardiac consult request and presents examples of good and bad notes requesting consults and good and bad consults written in response.

The case

A 47-year-old man is scheduled for femoral-popliteal bypass surgery. His medical history is significant for diabetes, a myocardial infarction (MI) 3 years ago followed by placement of a stent, and a limited ability to assess exercise tolerance. Evidence of an anteroseptal MI is present on 12-lead electrocardiography. His medications include metoprolol 25 mg twice daily and an oral hypoglycemic agent. His blood pressure is 152/89 mm Hg, heart rate 81 beats per minute, respiratory rate 14 breaths per minute, and arterial oxygen saturation 96% on room air.

The consult request: Bad and good examples

A bad consult request in this case would be, "Clear the patient for surgery." Although this type of request is routinely written, it is routinely useless.

For this complex surgery with significant fluid requirements, a much better consult request would include several specific requests and questions and might read as follows:

—Please evaluate patient's post-MI therapy for his CAD. Is further therapy required to optimize CAD treatment?

—Do his blood pressure or diabetic regimens need modification? If so, can this be done postoperatively?

—Please evaluate patient's myocardial function in light of a lack of info on exercise tolerance. Is an echo indicated?

—Are other tests, therapies, or interventions warranted pre- or postoperatively?

Example of a bad consult

A poorly written consult in a case like this may:

- Include a brief history repeating facts that are already known and noting that "the patient is at his baseline without obvious ischemia."
- State that the patient is cleared for "spinal" anesthesia. "Clearing a patient for anesthesia" is useless to begin with, but clearing for a certain type of anesthesia places the anesthesiologist in a terrible medicolegal position if general anesthesia turns out to be needed. Moreover, there are no proven major outcome differences related to the type of anesthetic chosen.
- Recommend that "a pulmonary artery catheter might be indicated to monitor hemodynamics." Besides the fact that such catheters probably do more harm than good, such a recommendation is unnecessary since the anesthesiologist is already expert in managing perioperative care.
- Recommend that "the anesthesia team should monitor the patient carefully in the perioperative arena for hypoxia and hypotension." Qualitative advice, such as "avoid hypoxia, hypotension, and tachycardia," is not useful, but quantitative information, such as "during ischemic stress testing, the patient exhibited ischemia when his heart rate went to 142," can be very helpful.
- State that the patient be sent to the ICU following surgery. Mandating an ICU stay in advance makes no sense unless the operation itself demands ICU care, which is the call of the surgeon and anesthesiologist anyway.

A consult like this doesn't tell the perioperative team anything that it didn't already know. Such a consult not only is unhelpful but also actually creates more work since much of the advice needs to be "undone" lest a lawyer see the chart and it not be clear why the consultant's recommendations were not followed.

Example of a good consult

In contrast, a good consult for this case would involve:

- A detailed history examining the potential for silent ischemia associated with the diabetes, as well as the relationship of the hypertension and beta-blocker therapy to episodes of ischemia. The level of ischemia should be clearly categorized. If it cannot be determined, this should be noted; if it can be determined only that the ischemia is not New York Heart Association class III or IV, note this as well (the perioperative outcomes literature suggests that no preoperative ischemia testing is needed with class I or II angina).
- Guidance on blood pressure optimization in light of the relative urgency of the procedure. Blood pressure need not be normalized preoperatively in this case, but if the operation were totally elective and the consultant felt it could make a difference, it would be appropriate to suggest that blood pressure be optimized beforehand.
- A recommendation on whether and when to change the beta-blocker dosage. If the dosage needs to be increased, the anesthesiologist will want to know how many doses are needed to reach a new steady state. Joint guidelines from the American College of Cardiology (ACC) and American Heart Association (AHA)[2] recommend 7 to 30 days, but this time frame is unrealistic in this setting, so more practical advice would be appreciated. A good consult notes any deviation from established guidelines, however, and explains the rationale for such deviation.
- Evaluation of the myocardium at risk. This is especially important with left main disease, as it influences the decision whether to test or intervene versus proceeding with careful beta-blocker titration.
- Evaluation of myocardial function and, if appropriate, a therapy suggestion for optimization.
- Notation of the heart rate or blood pressure thresholds at which ischemia develops if a stress test is performed.

GOOD GUIDANCE FROM THE ACC/AHA GUIDELINES

Our advice here is broadly consistent with the aforementioned 2007 ACC/AHA guidelines on perioperative

cardiovascular evaluation for noncardiac surgery.[2] The following observation on cardiac evaluations from these guidelines applies to preoperative consults in general:

> The purpose of preoperative evaluation is not to give medical clearance but rather to perform an evaluation of the patient's current medical status; make recommendations concerning the evaluation, management, and risk of cardiac problems over the entire perioperative period; and provide a clinical risk profile that [can be used] in making treatment decisions that may influence short- and long-term cardiac outcomes.[2]

These guidelines contain a good description of the ideal preoperative evaluation and consult in a short section (Section II, "General Approach to the Patient")[2] that is worthy of wide dissemination.

DISCUSSION

Question from the audience: Many consults are written more for the surgical team than for the anesthesiologists, hence advice such as managing intraoperative diabetes. Isn't that appropriate?

Dr. Lubarsky: There are a variety of users of the information in a consult note. I focused on the anesthesiologist, but certainly the surgical staff and house staff would benefit from suggestions about postoperative management. However, they would not benefit from suggestions on intraoperative management; surgeons simply do not need this information and the anesthesiologist will have his or her own regimen. But if there is a specific type of insulin infusion that's been shown to be best in the specific patient at hand, then detailing that obviously is beneficial.

Question from the audience: We all agree that communication is key, but how does the consultant reach the anesthesiologist to find out what he or she wants to know when the anesthesiologist isn't usually assigned to the case until a day before surgery?

Dr. Lubarsky: If no anesthesiologist is yet assigned to a case, the consultant can discuss the case with the chief of the anesthesiology department. The discussion should be documented in the note. But it's important that the system be changed so that anesthesiologists are assigned to cases well in advance. I instituted such a policy at my previous hospital. Many hospitals schedule surgeries 3 months in advance, and many anesthesiology departments have schedules made at least 1 month and often 2 to 3 months in advance. The department could assign a specific anesthesiologist to a future scheduled case with ease.

Question from the audience: How do anesthesiologists educate all the various people we rely on for consults when we can't get them in one place at one time?

Dr. Lubarsky: It's a challenge. I try many things, such as going to cardiology rounds, but there are always new people coming through. A good monograph or a set of guidelines with examples would help. If each specialty educates the other and speaks at each other's conferences more often, that should help. Anesthesiologists would benefit from hearing about the challenges medical consultants face; we may not be doing all we can to optimize perioperative care. There's room for improvement through communication on both sides. I should also emphasize that we're all trying to do the right thing. Doctors try to be accommodating, but that doesn't always make for good decisions. Recently a consultant in my hospital did a preoperative stress test on a patient who didn't need one. When I asked why, he said, "Because the surgeon asked me to."

Question from the audience: But don't you agree that many anesthesiologists would like to see that negative stress test, even if a stress test is not indicated by the guidelines? Cardiologists know that the anesthesiologists are often looking for that on the morning of surgery.

Dr. Lubarsky: The point is that physicians should be responsible for what they have expertise in. When I am asked to intubate a patient, my response as an expert in intubation might be, "Actually, he doesn't need to be intubated right now." In the case of this unnecessary stress test, the cardiologist probably should have called the surgeon and said, "It's really not indicated because the patient had a negative stress test 2 years ago, there's been no change in symptoms and no angina since then, and he operates well above 4 metabolic equivalents. There's a clear-cut reason not to do it." If the surgeon still wanted the test done just to be reassured, that's simply a poor use of society's resources. We depend on experts to identify the tests that are indicated to evaluate a patient's disease and not just do tests for the sake of doing them.

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Perioperative management of warfarin and antiplatelet therapy

ABSTRACT

Perioperative management of patients on warfarin or antiplatelet therapy involves assessing and balancing individual risks for thromboembolism and bleeding. Discontinuing anticoagulant and antiplatelet therapy is usually necessary for major surgery but increases the risk of thrombotic events. Bridge therapy, the temporary perioperative substitution of low-molecular-weight heparin or unfractionated heparin in place of warfarin, is an effective means of reducing the risk of thromboembolism but may increase the risk of bleeding. The timing of warfarin withdrawal and timing of the preoperative and postoperative components of bridge therapy are critical to balancing these risks. Perioperative management of antiplatelet therapy requires special care in patients with coronary stents; the timing of surgery relative to stent placement dictates management in these patients.

KEY POINTS

Determining when and how to use bridge anticoagulation therapy depends on the patient's risk for thromboembolism, which is in turn based on the indication for warfarin—ie, a mechanical heart valve, atrial fibrillation, or prior venous thromboembolism.

Factor patient preference into whether and how to use bridge therapy: many patients are more concerned about stroke risk than bleeding risk, regardless of the relative frequency of these events.

Anticoagulation with warfarin often does not need to be interrupted for patients undergoing minor surgery, such as some ophthalmic, dental, dermatologic, and gastrointestinal procedures.

Premature discontinuation of antiplatelet therapy in surgical patients with recent coronary stent placement significantly raises the risk of catastrophic perioperative stent thrombosis.

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Perioperative management of surgical patients who require temporary discontinuation of vitamin K antagonists (warfarin) or antiplatelet drugs is complicated. The risk of a thrombotic event during interruption of anticoagulant or antiplatelet therapy must be weighed against the risk of bleeding when such therapy is used in close proximity to a surgical procedure. This balancing of risks is guided by the patient's individual risk for thromboembolism or bleeding and underlying conditions such as the presence of a mechanical heart valve or a coronary stent.

High-profile adverse events have made anticoagulant and antiplatelet management one of the most highly litigated aspects of perioperative medicine. Moreover, there is a paucity of randomized clinical trial data and definitive guidelines to address the perioperative needs of patients on antithrombotic therapy. Treatment protocols vary depending on many underlying factors, such as the presence of mechanical heart valves, comorbidities, stent type and location, patient age and medical history, and type of surgical procedure. While recent attention has focused on genetic variations that result in higher or lower sensitivity to warfarin in some patients, routine genetic testing for warfarin sensitivity is controversial and not part of widespread practice at this time.

The first portion of this article explores key issues and principles in the perioperative management of surgical patients on warfarin therapy, and the second portion does the same for surgical patients on antiplatelet therapy.

ACCP RECOMMENDATIONS FOR PERIOPERATIVE ANTICOAGULANT MANAGEMENT

In 2008 the American College of Chest Physicians (ACCP) published the latest update of its consensus guidelines for the perioperative management of patients receiving antithrombotic therapy.[1] The guidelines' recommendations for anticoagulant management are based on stratification of patients into risk categories **(Table 1)** according to their underlying indication for long-term anticoagulation—ie, presence of a mechanical heart valve, history of atrial fibrillation, or history of venous thromboembolism (VTE).

Patients with mechanical valves who are at high risk for perioperative thromboembolism include those with any mechanical mitral valve, an older valve, or a history of stroke or transient ischemic attack (TIA). Patients

TABLE 1
ACCP's suggested risk stratification for perioperative thromboembolism*

Risk category	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High (>10%/yr risk of ATE or >10%/mo risk of VTE)	Any mechanical mitral valve Older aortic valve Recent (< 6 mo) stroke or TIA	$CHADS_2$ score of 5 or 6 Recent (< 3 mo) stroke or TIA Rheumatic valvular heart disease	Recent (< 3 mo) VTE Severe thrombophilia
Moderate (4%–10%/yr risk of ATE or 4%–10%/mo risk of VTE)	Bileaflet aortic valve and one of the following: atrial fibrillation, prior stroke/TIA, hypertension, diabetes, heart failure, age > 75 yr	$CHADS_2$ score of 3 or 4	VTE within past 3–12 mo Recurrent VTE Nonsevere thrombophilic conditions Active cancer
Low (<4%/yr risk of ATE or <2%/mo risk of VTE)	Bileaflet aortic valve without atrial fibrillation and no other risk factors for stroke	$CHADS_2$ score of 0–2 (and no prior stroke or TIA)	Single VTE within past 12 mo and no other risk factors

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ACCP = American College of Chest Physicians; ATE = arterial thromboembolism; VTE = venous thromboembolism; TIA= transient ischemic attack

with atrial fibrillation who are at high risk include those with a recent stroke or TIA, rheumatic valvular heart disease, or a $CHADS_2$ score of 5 or 6. (The $CHADS_2$ scoring system assigns one point each for a history of congestive heart failure, hypertension, age greater than 75 years, or diabetes, and two points for history of stroke or TIA.) Patients with a history of VTE within the prior 3 months are also considered high risk.

Bridging anticoagulation (bridge therapy)—ie, the temporary use of intravenous unfractionated heparin (IV UFH) or low-molecular-weight heparin (LMWH) prior to surgery—is central to the ACCP's recommendations for perioperative management in patients on long-term anticoagulant therapy. Key ACCP recommendations[1] for these patients, according to their risk for thromboembolism **(Table 1)**, are as follows:

- **High risk**—bridging anticoagulation with therapeutic-dose subcutaneous LMWH or IV UFH
- **Moderate risk**—bridging anticoagulation with therapeutic-dose subcutaneous LMWH, therapeutic-dose IV UFH, or low-dose subcutaneous LMWH
- **Low risk**—bridging anticoagulation with low-dose subcutaneous LMWH or no bridging.

ASSESSING RISKS: DETERMINING WHETHER TO BRIDGE

Considerations in bridge therapy include balancing the risk of thromboembolism against the risk of bleeding, either of which can lead to catastrophic results.[2] Though the objective of bridge therapy is to avoid bleeding complications associated with invasive procedures, the bridge protocol itself can introduce additional serious complications. **Figure 1** presents an algorithm for identifying patient and surgical risk factors for patients on anticoagulation therapy who are undergoing elective surgery.

Patient-specific risk factors

Patient risk factors include the indication for anticoagulation, as detailed above, as well as other individual risks for thromboembolism, as discussed in the article by Michota on preventing VTE on page S45 of this supplement.

If anticoagulation is indicated because the patient has a mechanical heart valve, the valve type and position must be considered because these factors affect thromboembolic risk, as reflected in **Table 1**. For instance, the risk of thromboembolism is greater when the valve is in the mitral position than in the aortic position, and is also greater with an older caged-ball valve than with a newer-generation bileaflet valve.[3]

In patients receiving anticoagulation because of atrial fibrillation, annual stroke risk can be estimated using the validated $CHADS_2$ scoring system, as presented in **Table 2**.[4] Generally, patients with atrial fibrillation who have a $CHADS_2$ score of 3 or higher should receive bridge therapy, while those with a $CHADS_2$ score of 2 or lower probably should not.

Procedure-related risk factors

Surgical risks factors include the type of surgery and its associated risks of bleeding and thromboembolism, as

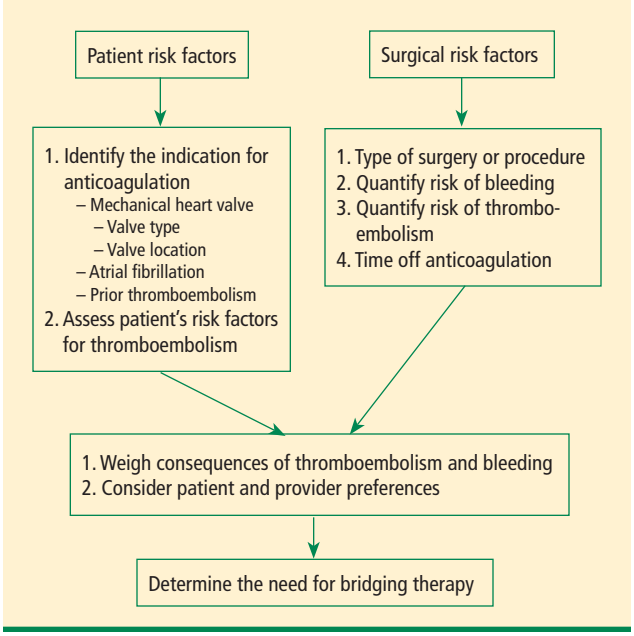

FIGURE 1. Assessment tool for identifying patient-specific and surgical risk factors for patients on anticoagulation therapy who are undergoing elective surgery.

well as the expected time that anticoagulation will be interrupted. Estimating thromboembolic risk is complicated, however, and reliable results are generally not achieved with simplistic calculations or formulas. Such calculations tend not to appropriately account for the hypercoagulable state induced by surgery itself, as the risk of VTE is estimated to be 100 times greater during the perioperative period than in the nonoperative setting, owing to increased levels of plasminogen activator inhibitor-1. Moreover, multiple studies have demonstrated increases in coagulation factors that suggest that a "rebound hypercoagulability" may occur shortly after discontinuation of oral anticoagulant therapy.[5–8]

Net benefit vs risk in trials of bridge therapy

Several prospective studies of bridge therapy have been conducted in more than 2,700 surgical patients with mechanical heart valves, atrial fibrillation, or prior VTE.[9–14] Warfarin was discontinued in these patients and replaced with LMWH as bridge therapy. As shown in **Table 3**, the rate of thromboembolism at follow-up (2 weeks to 90 days) in these studies averaged approximately 1%, while the risk of major bleeding was approximately 3.5%.[9–14]

In an analysis of data from observational studies, Kearon and Hirsh estimated the relative risk reduction for thromboembolism with bridge therapy to be 66% to 80%, depending on the indication for anticoagulation.[8] Thus, if a patient's risk of developing thromboembolism is 1.5%, bridge therapy reduces the risk to 0.5% or less.

TABLE 2
Annual stroke risk in patients with atrial fibrillation, according to $CHADS_2$ score

$CHADS_2$ score*	Adjusted stroke rate† (95% CI)
0	1.9 (1.2–3.0)
1	2.8 (2.0–3.8)
2	4.0 (3.1–5.1)
3	5.9 (4.6–7.3)
4	8.5 (6.3–11.1)
5	12.5 (8.2–17.5)
6	18.2 (10.5–27.4)

* Assessment of the following comorbidities: congestive heart failure, hypertension, age ≥ 75, and diabetes (1 point each), plus history of stroke or transient ischemic attack (2 points).

† Expected rate of stroke per 100 patient-years

Reproduced, with permission, from Snow et al.[4]

Weigh relative consequences of an event with the patient

Determining whether and how to initiate bridge therapy ultimately depends on the consequences of an event. Recurrent VTE is fatal in 5% to 10% of cases,[15] and arterial thromboembolism is fatal in 20% of cases and causes permanent disability in at least 50% of cases.[16] While 9% to 13% of major bleeding events are fatal, bleeding rarely causes permanent disability.[17] Thus, whereas a patient who bleeds can be resuscitated, a patient who develops a thromboembolism may be permanently disabled. These considerations should be shared with the patient, and patient preference should factor into the management strategy. Though the risk of bleeding with anticoagulation may be much higher than the risk of stroke without it, many patients will be more concerned about stroke risk.

CHOICE OF AGENT FOR BRIDGE THERAPY

LMWH appears to offer cost advantage over UFH

For cost reasons, managed care organizations often recommend LMWH, which can be administered subcutaneously in outpatient settings, over IV UFH administered in the hospital. A retrospective analysis of medical costs from the 1990s in a managed care organization found that bridge therapy with LMWH prior to elective surgery cost an average of $13,114 less per patient (in total cost of care) than did bridge therapy with UFH.[18]

LMWH safety issues in valve patients are a myth

Clinical outcomes were not statistically significantly different for patients receiving LMWH or UFH in the above study.[18] Nevertheless, there is a widely held notion that LMWH is not safe to use as bridge therapy for patients with mechanical heart valves. Recent prospective bridge

TABLE 3
Benefits and risks of bridge anticoagulation therapy in prospective clinical trials

Study	Patients (N)	Follow-up (mo)	Reason for anticoagulation	Thromboembolism (%)	Major bleeding (%)
Douketis et al, 2004[9]	650	0.5	AF, MHV	0.6%	1.0%
Kovacs et al, 2004[10]	224	3	AF, MHV	1.3%	6.9%
Dunn et al, 2007[11]	260	1	AF, DVT	2.3%	3.5%
Spyropoulos et al, 2006[12]	901	1	AF, MHV, VTE	1.5%	3.3%
Turpie and Douketis, 2004[13]	220	3	MHV	0.5%	3.5%
Jaffer et al, 2005[14]	493	1	VTE, CVA, AF, MHV	0.8%	3.2%

AF = atrial fibrillation; MHV = mechanical heart valve; DVT = deep vein thrombosis; VTE = venous thromboembolism; CVA = cerebrovascular accident (stroke)

studies do not support that view, demonstrating that LMWH used as bridge therapy is associated with low risks for thromboembolism and major bleeding even in patients with mechanical valves.[9,10,12–14] In contrast, recent data on the use of IV UFH for bridging is minimal, with most bridge studies dating to the 1970s. Accordingly, the latest ACCP guidelines for perioperative management of patients on antithrombotic therapy recommend therapeutic-dose LMWH over IV UFH for bridge therapy, including in patients with mechanical heart valves.[1] Likewise, 2006 guidelines from the American College of Cardiology and American Heart Association on management of patients with valvular heart disease endorse LMWH as an option for bridge therapy.[19]

A PRACTICAL APPROACH TO BRIDGE THERAPY

A bridge therapy protocol for patients receiving warfarin has been successfully used at the Cleveland Clinic, where I previously practiced. Essentials of the protocol[20] are summarized here, followed by commentary that draws on additional sources.

Before surgery

- Discontinue warfarin 5 days before surgery (ie, hold four doses) if the preoperative international normalized ratio (INR) is 2 to 3, and 6 days before surgery (hold five doses) if the INR is 3 to 4.5.
- For bridge therapy, start LMWH (enoxaparin 1 mg/kg or dalteparin 100 IU/kg subcutaneously every 12 hours) beginning 36 hours after the last dose of warfarin.
- Give the last dose of LMWH approximately 24 hours prior to surgery.

After surgery

- For minor surgery, reinitiate LMWH at full dose approximately 24 hours after surgery. For major surgery and for patients at high risk of bleeding, consider using prophylactic doses on the first two postoperative days.
- Discuss the timing of anticoagulant reinitiation with the surgeon.
- Restart warfarin at preoperative dose 1 day after surgery.
- Order daily prothrombin time/INR tests until the patient is discharged and periodically after discharge until the INR is within the therapeutic range.
- Order a complete blood cell count with platelets on days 3 and 7.
- Discontinue LMWH when the INR is between 2 and 3 for 2 consecutive days.

Additionally, the plan should be discussed in advance with the patient, surgeon, and anesthesiologist, along with the risks and benefits associated with LMWH. The patient should receive written instructions for self-administration and information about signs and symptoms of bleeding and thromboembolism.

When to stop warfarin

Warfarin should be discontinued far enough in advance of surgery to achieve a preoperative target INR of less than 1.2.[21] Patients with an initial INR of 2 to 3 tend to achieve that target after discontinuation of warfarin for about 5 days (four doses). A longer wait (6 days, or five doses) is necessary for patients with an initial INR of 3 to 4. Age is associated with a slower rate of decrease in the INR, and there is wide interpatient variation. The INR should always be checked prior to surgery.[21]

Warfarin need not be stopped for all procedures

It is commonly assumed that warfarin should be discontinued for any procedure, including minor surgery. But several procedures, listed in **Table 4**, can be performed safely without discontinuing long-term anticoagulation, as suggested by several literature reviews and comparative studies.[22–25] Additionally, a 2003 systematic review concluded that major bleeding with continuation of therapeutic oral anticoagulation was rare for patients

TABLE 4
Procedures that can be performed without discontinuing warfarin[22–25]

Ophthalmic[22]	Dental[23]	Dermatologic[24]	Gastrointestinal[25]
Cataract surgery	Restorations	Mohs' surgery	Diagnostic esophagogastroduodenoscopy
Trabeculectomy	Uncomplicated extractions	Simple excisions	Colonoscopy without biopsy
	Endodontics		Diagnostic endoscopic retrograde cholangiopancreatography
	Prosthetics		Biliary stent without sphincterotomy
	Periodontal therapy		Endoscopic ultrasonography without biopsy
	Dental hygiene		Push enteroscopy

undergoing dental procedures, arthrocentesis, cataract surgery, upper endoscopy, or colonoscopy.[26]

If warfarin is stopped for minor procedures, bridging may be counterproductive

At the same time, a recent prospective observational study evaluated the effects of brief (≤ 5 days) interruption of warfarin among more than 1,000 patients undergoing minor outpatient procedures and found low rates of both thromboembolism (0.7%) and major bleeding (0.6%).[27] The risk of major bleeding was significantly higher among the small proportion of patients who received bridge therapy with UFH or LMWH. The study concluded that interrupting warfarin for 5 days or less for minor outpatient procedures carries a low risk of thromboembolism and that the risk of clinically significant bleeding should be weighed before bridge therapy is considered in this setting.

When to stop bridge therapy preoperatively

Bridge therapy with LMWH is commonly discontinued 12 hours before surgery, but it is preferable to discontinue 24 hours before surgery. In a study of preoperative anticoagulant activity in 80 patients, LMWH (enoxaparin 1 mg/kg) was administered twice daily and discontinued the night before surgery.[28] Blood anti–factor Xa levels were measured shortly before surgery, at which time 68% of patients still had therapeutic levels of anti–Xa. This suggests that discontinuing LMWH too close to the time of surgery can increase the risk of bleeding.

Consistent with these findings, consensus guidelines from the American Society of Regional Anesthesia and Pain Medicine (ASRA) recommend that needle placement for regional anesthesia take place 12 hours after the last dose of LMWH if prophylactic dosing is used and 24 hours after the last dose of LMWH if therapeutic dosing is used (ie, ≥ 1 mg/kg of enoxaparin every 12 hours).[29]

Dosing and timing of postoperative bridge therapy

Postoperative use of full-dose bridge therapy is associated with increased risks of bleeding, according to a multicenter study of approximately 500 patients who received various doses of UFH or LMWH for bridge therapy.[14] Patients who received full-dose LMWH or UFH after surgery had a fivefold to sixfold increase in the incidence of major bleeding compared with patients who received prophylactic doses. The study centers that frequently used full-dose bridge protocols were four times as likely to report major bleeding events. In light of these findings, waiting a couple of days after surgery to initiate full-dose bridge therapy is recommended, and prophylactic dosing may be considered in the interim.

The ASRA consensus guidelines recommend that indwelling catheters be removed prior to postoperative reinitiation of twice-daily dosing of LMWH. The first dose of LMWH should be given no sooner than 2 hours after catheter removal. Once-daily dosing of LMWH (European dosing) is acceptable under the ASRA guidelines, but the first dose should be given 6 to 8 hours after surgery and the second dose no sooner than 24 hours later. The guidelines state that once-daily (but not twice-daily) LMWH dosing is acceptable in patients with indwelling catheters; neurological status should be monitored in these patients, and the catheter should be removed 12 to 24 hours after the last dose of LMWH.[29]

PERIOPERATIVE MANAGEMENT OF ANTIPLATELET THERAPY: TYPE OF AGENT MATTERS

Unlike the considerations with warfarin, the timing of preoperative discontinuation of antiplatelet therapy in patients undergoing noncardiac surgery depends on the type of agent used and its pharmacokinetic actions. Commonly used antiplatelet drugs include aspirin, the thienopyridine agent clopidogrel, and nonsteroidal anti-inflammatory drugs (NSAIDs).

Aspirin works by irreversibly inhibiting platelet cyclooxygenase. The circulating platelet pool is replaced every 7 to 10 days, so aspirin therapy should be discontinued 7 to 10 days before surgery.[1]

NSAIDs reversibly inhibit platelet cyclooxygenase.

TABLE 5
Preoperative evaluation of patients with stents: A checklist

Determine type of stent(s): Bare metal or drug-eluting? If drug-eluting, sirolimus or paclitaxel?
Determine how long ago each stent was implanted
Determine location of each stent in the coronary circulation
How complicated was the revascularization? Were there any complications (eg, malapposition)?
Is there a prior history of stent thrombosis?
What antiplatelet regimen is being used?
Determine patient's comorbidities to further ascertain risk level (ejection fraction, diabetes, renal insufficiency)
What is the recommended duration of dual antiplatelet therapy for the specific patient at hand?
Consult with patient's cardiologist to review current antiplatelet management and discuss optimal management strategy

Knowing whether a patient is using short- or long-acting NSAIDs is important for determining when to discontinue therapy. For a short-acting NSAID such as ibuprofen, discontinuation 24 hours before surgery may be adequate to normalize platelet function.[1,30]

Thienopyridines inhibit adenosine diphosphate receptor–mediated platelet activation and aggregation. Short-acting thienopyridines may be discontinued 24 hours before surgery, but long-acting agents such as clopidogrel should be stopped 7 days prior to surgery (including when used with aspirin as dual antiplatelet therapy),[1] although some outcomes data suggest that 5 days may be sufficient.[31]

All of these agents should be resumed as soon as adequate hemostasis is achieved after surgery. The ACCP guidelines on perioperative management of antithrombotic therapy recommend resumption of aspirin at the usual maintenance dose the day after surgery, but they make no specific recommendations on when to resume other antiplatelet drugs.[1]

ANTIPLATELET THERAPY: SPECIAL CONSIDERATIONS IN PATIENTS WITH STENTS

Patients who are on antiplatelet therapy because they have a coronary stent merit special consideration due to the high risk of thrombosis if therapy is interrupted. The risk of stent thrombosis is especially elevated in the postoperative period, particularly if surgery follows soon after stent placement.

Optimal preoperative management of patients with coronary artery stents depends on many factors, as outlined in **Table 5**. Some patients carry a wallet card that provides some of this crucial information, such as the type of stent and the date and location of its placement, but speaking with the patient's cardiologist is always recommended. This information, determined in conjunction with the cardiologist, should be used to inform the key perioperative considerations in this setting:

- Relative risks and benefits of stopping versus continuing antiplatelet therapy
- Identification of patients at high risk for a perioperative event after cessation of antiplatelet therapy
- Identification of patients at high risk of bleeding.

Bleeding vs stent thrombosis: Consider relative consequences

The risk of bleeding varies by individual patient. No laboratory tests are available to determine individual bleeding risk, but the risk of perioperative bleeding increases when two or more antiplatelet agents are used, as in dual antiplatelet therapy with aspirin and clopidogrel.[31]

When balancing risks of bleeding versus thrombotic events, the relative consequences of each event again must be considered. Bleeding is rarely life-threatening in comparison with the potential consequences of stent thrombosis. In a prospective observational study of 2,229 patients who received drug-eluting stents, 29 (1.3%) developed stent thrombosis during 9-month follow-up.[32] Among these patients, 20 (69%) had a nonfatal myocardial infarction and 13 (45%) died. The most significant independent risk factor for stent thrombosis was premature discontinuation of antiplatelet therapy (hazard ratio = 89.78 [95% CI, 29.90–260.60]; $P < .001$). Other independent risk factors included renal failure, bifurcation lesions, diabetes, and low ejection fraction.

Premature interruption of antiplatelet therapy: Why it matters

Abrupt discontinuation of antiplatelet therapy can lead to a rebound effect marked by an inflammatory prothrombotic state, increased platelet adhesion and aggregation, and excessive thromboxane A_2 activity. Surgery further increases the prothrombotic and inflammatory state, which, combined with incompletely endothelialized drug-eluting stents, can lead to stent thrombosis and, consequently, myocardial infarction and/or death.[33]

Timing of surgery after stenting: Getting it right

The US Food and Drug Administration recommends that dual antiplatelet therapy be continued for at least 3 months after placement of a sirolimus-eluting stent and at least 6 months after placement of a paclitaxel-eluting stent. Recent data suggest, however, that this duration of antiplatelet therapy may not be sufficient and that at least 1 year of therapy may be needed.[34]

A recent joint science advisory from the American

College of Cardiology (ACC) and the American Heart Association (AHA) emphasizes the importance of educating providers about the "potentially catastrophic" risks of premature stopping of thienopyridine therapy in patients with coronary stents.[34] In addition to recommendations in this joint advisory, the ACC and AHA issued updated guidelines in 2007 on perioperative cardiovascular evaluation and care for noncardiac surgery.[35] Below is a summary of recommendations on the timing of surgery following stenting in light of these and other sources:

- Following placement of a bare metal stent, elective and nonurgent procedures should be delayed for at least 1 month, according to the ACC/AHA joint advisory,[34] or at least 6 weeks, according to the ACC/AHA guidelines.[35] Newer data suggest that the optimal interval for delay is likely to be 3 months.[36,37]
- For patients with recent (< 6 weeks) bare metal stent placement who require urgent surgery, dual antiplatelet therapy should be continued during the perioperative period.[1]
- Following placement of a drug-eluting stent, elective and nonurgent procedures should be delayed for at least 12 months.[34,35]
- For patients with recent drug-eluting stent placement in whom surgery cannot be delayed, dual antiplatelet therapy should be continued without interruption if the stent was placed within the prior 6 months.[1,35] If the stent was placed more than 6 months before urgent surgery, aspirin should be continued without interruption (at ≥ 81 mg/day) and clopidogrel should be continued until 5 days before surgery and resumed as soon as possible after surgery (at a loading dose of 300 mg followed by 75 mg/day). If the surgeon is comfortable continuing dual antiplatelet therapy in a patient whose stent was placed 6 to 12 months earlier, that course should be considered.[1]

It is important to note that the ACC/AHA joint advisory[34] and other documents have medicolegal implications, so delaying nonurgent surgery for the periods recommended is the most prudent approach.

CONCLUSIONS

Perioperative management of anticoagulant and antiplatelet therapy is complicated by the paucity of randomized clinical trial data and the risk for serious adverse events. The underlying indications for anticoagulant and antiplatelet therapy vary widely, so the best approach to perioperative management is to involve all members of the health care team—hospitalist, surgeon, cardiologist, and anesthesiologist, together with the patient—to ensure that care is individualized and all relevant considerations are accounted for. Patient and surgical risks can be identified and quantified to some extent, but patients often have greater concerns about the risk of stroke than the risk of bleeding. Ideally, nonemergency surgeries should be scheduled to allow enough time to thoroughly plan the management protocol, reducing risks for bleeding and thrombotic events as much as possible.

DISCUSSION

Question from the audience: If a patient's INR is 1.3 or 1.4, rather than the recommended 1.2, is it necessary to cancel a planned epidural?

Dr. Jaffer: It depends on how comfortable the surgeon or anesthesiologist is with the INR level. Generally, an INR less than 1.5 is probably acceptable, but it depends on the procedure. For a craniotomy, for example, 1.2 is recommended.

Question from the audience: Is it necessary to use anti–Xa levels to guide bridge therapy when administering LMWH or UFH in a patient with a mechanical heart valve?

Dr. Jaffer: It's not generally necessary, except for pregnant women. For most patients, doses are calculated as milligrams of LMWH per kilogram body weight or as International Units of LMWH per kilogram.

Question from the audience: You mentioned medicolegal disputes arising from adverse events associated with bridge therapy, drug discontinuation, or related issues. Who has final responsibility for making decisions about discontinuation of antiplatelet therapy, for example?

Dr. Jaffer: I don't know if it ultimately comes down to just one person. Several physicians should be involved in the decision, and communication protocols within an institution should be very clear. It's important to make certain everyone involved in the decision is reviewing the same literature. The final decision has to be something everyone involved can accept and support.

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Prevention of venous thromboembolism after surgery

ABSTRACT

Most surgical patients who require hospitalization are at high risk for venous thromboembolism (VTE) and should receive VTE prophylaxis, usually including pharmacologic prophylaxis. Nevertheless, rates of appropriate perioperative thromboprophylaxis remain stubbornly low, though an expansion in quality-improvement efforts has led to widespread hospital implementation of prophylaxis strategies in recent years. This article reviews important principles and recent developments in perioperative VTE prophylaxis, with a focus on key recommendations and changes in the 2008 update of the American College Chest Physicians' (ACCP) evidence-based guidelines on antithrombotic therapy.

KEY POINTS

Effective October 1, 2009, the Centers for Medicare and Medicaid Services is refusing to reimburse for hospital treatment of a primary diagnosis of deep vein thrombosis or pulmonary embolism following recent (within 30 days) hip or knee replacement surgery.

Mechanical methods of thromboprophylaxis are not effective unless used for at least 18 to 20 hours a day.

The latest ACCP guidelines recommend extended pharmacologic VTE prophylaxis for up to 28 days in select high-risk patients undergoing general or gynecologic surgery. Extended prophylaxis of varying duration is recommended for patients undergoing major orthopedic procedures.

Aspirin alone is not recommended for perioperative VTE prophylaxis in any patient group by the ACCP or the International Union of Angiology.

Patients with renal impairment have fewer anticoagulant options and may require dose adjustment. Weight-based dosing appears to be safe and effective for obese surgical patients.

New selective and orally administered direct thrombin inhibitors and oral direct factor Xa inhibitors may soon be available for perioperative VTE prophylaxis.

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Most surgical patients who require hospitalization should be considered at high risk for venous thromboembolism (VTE) and be given appropriate prophylaxis. For lower-risk procedures such as knee arthroscopy, prophylaxis is needed for those with individual risk factors such as morbid obesity, limited mobility after surgery, or a history of deep vein thrombosis (DVT) or malignancy. Too often, however, prophylaxis is not provided appropriately or not given at all.

This review surveys the essentials of perioperative VTE prophylaxis and important new developments in the field, which include the 2008 release of new evidence-based clinical practice guidelines on antithrombotic and thrombolytic therapy from the American College of Chest Physicians (ACCP). This 8th edition of the guidelines updates the previous edition, published in 2004, and includes a section by Geerts et al devoted to VTE prevention.[1] Other major guidelines are also discussed, as are developments in VTE-related quality measurement, management of special patient populations (those with renal impairment or morbid obesity), and emerging therapies for VTE prophylaxis.

IMPETUS FOR QUALITY IMPROVEMENT IN VTE

A new seriousness about VTE quality measures

The 8th edition of the ACCP guidelines recommends that every hospital develop a formal, active strategy to consistently identify medical and surgical patients at risk for VTE and to prevent VTE occurrence.[1] Although prior editions of the ACCP guidelines have made this recommendation for more than 2 decades, fewer than 1 in 10 acute care hospitals had any such strategy in place as recently as 5 years ago. Now, however, most US hospitals have implemented such a strategy, thanks to the growing national emphasis on health care quality measurement in recent years.

The Surgical Care Improvement Project (SCIP) has been at the forefront of this recent quality measures movement. SCIP, a joint project of the American Medical Association and federal government agencies, set a goal to reduce surgical complications in the United States by 25% from 2005 to 2010.[2] Two SCIP process measures relate to improving VTE prophylaxis[2,3]:

- The proportion of surgical patients for whom recommended VTE prophylaxis is ordered

TABLE 1
Recommended prophylaxis in surgical patients by level of procedural thromboembolic risk*

Level of risk	Recommended prophylaxis options
Low risk (minor same-day surgery)	Early and aggressive mobilization
Moderate risk (most general, open gynecologic or urologic procedures)	LMWH, low-dose UFH (twice or three times daily), or fondaparinux
High risk (orthopedic surgery, trauma, spinal cord injury, cancer surgery)	LMWH, warfarin, or fondaparinux

*Adapted from the 8th edition of the American College of Chest Physicians guidelines.[1]

UFH = unfractionated heparin; LMWH = low-molecular-weight heparin

- The proportion of surgical patients who actually receive appropriate VTE prophylaxis within 24 hours before or after surgery.

The Joint Commission and the National Quality Forum recently endorsed these two SCIP performance measures for perioperative VTE prophylaxis along with several others relating to VTE treatment.

CMS raises the stakes with reimbursement restrictions

More significantly, the federal government's Centers for Medicare and Medicaid Services (CMS) will soon refuse to reimburse for hospital treatment of a primary diagnosis of DVT or pulmonary embolism (PE) following recent (within 30 days) total hip or knee arthroplasty. Effective October 1, 2009, a primary VTE diagnosis following these joint replacement procedures will be added to CMS' current list of "never events," or hospital-acquired conditions for which CMS will not provide reimbursement because they are considered the result of preventable medical errors. (Notably, treatment of DVT or PE as a *secondary* diagnosis will still be reimbursed—for example, if a joint replacement patient develops nosocomial pneumonia, is transferred to the intensive care unit, and then develops VTE.) This addition of DVT and PE to the list is highly controversial since these events sometimes develop even if prophylactic therapy is appropriate and aggressive.

Strategies to promote best practices

In the update for the new 8th edition of its guidelines, the ACCP added recommendations on specific ways for hospitals to identify patients at high risk for VTE and ensure that they receive appropriate prophylaxis. These include the use of computer decision-support systems, preprinted orders, and periodic audit and feedback.[1]

Researchers at Brigham and Women's Hospital evaluated the effectiveness of a computer alert system for notifying physicians of newly hospitalized patients at risk for DVT who were not receiving prevention therapy within the first 24 hours of hospital admission.[4] These patients presumably "fell through the cracks" and warranted prophylaxis but were otherwise not recognized by the health care team. Risk was determined by a scoring system based on multiple variables, including malignancy, previous DVT or PE, hypercoagulability, major surgery, advanced age, obesity, ordered bed rest, and treatment with hormone replacement therapy or oral contraceptives. Study physicians had to acknowledge having received the alert but could choose whether or not to order VTE prophylaxis. Prophylaxis was used in considerably more patients from the intervention group than from a control group of high-risk patients whose physicians did not receive alerts (34% vs 14%, respectively); accordingly, the risk of a symptomatic DVT or PE event at 90 days was reduced by 41% in the intervention group.

Despite this evidence of improved practice under the alert system, the study begs the question of why the percentage of patients at risk for VTE who were given prophylaxis was still so low (34%), demonstrating how much progress in improving practice remains to be achieved.

PROPHYLAXIS STRATEGIES: MATCHING THERAPY TO RISK

A fundamental consideration in determining the degree of VTE prophylaxis that a surgical patient may need is the thromboembolic risk of the procedure itself. **Table 1** presents a procedure-based ranking of risk based on recommendations in the 8th edition of the ACCP guidelines.[1] As risk increases, so does the intensity of prophylaxis, with increasing reliance on pharmacologic strategies. The vast majority of patients who are hospitalized for surgery will fall into the moderate- or high-risk categories in **Table 1**.

A patient's risk of thrombosis is also influenced by individual risk factors **(Table 2)**,[1,5] many of which are nonmodifiable. A thorough preoperative evaluation is important to reveal "hidden" risk factors such as thrombophilia and a family or personal history of VTE.

NONPHARMACOLOGIC PROPHYLAXIS STRATEGIES

Does ambulation prevent DVT?

Although it is commonly accepted that walking prevents DVT, this has never been directly tested. Walking may simply be a marker of health, and healthy people are less prone to develop thromboses. We have almost no evidence to show that forcing an unhealthy person to walk helps prevent DVT. Early ambulation offers many benefits and should be encouraged, but it should not be considered DVT prophylaxis; it is simply good hospital care.

Mechanical devices: Adherence is key

Amaragiri and Lees conducted a systematic literature review of randomized controlled trials evaluating the effectiveness of graduated compression stockings (elastic stockings) for preventing DVT in various groups of hospitalized patients.[6] The analysis demonstrated a statistically significant reduction in DVT incidence with graduated compression stockings compared with control both among the nine trials in which stockings were used alone (odds ratio = 0.34) and among the seven trials in which stockings were used in addition to another method of thromboprophylaxis (odds ratio = 0.24). Although benefit was demonstrated, many of the trials in this review involved patients undergoing gynecologic surgery and date from the 1970s and 1980s (when obesity was less prevalent), so the applicability of their results today may be limited.

The 8th edition of the ACCP guidelines recommends that mechanical methods of VTE prophylaxis be used primarily in patients who are at high risk of bleeding and that careful attention be directed to ensuring their proper use and optimal adherence.[1] The latter point about adherence cannot be emphasized enough, as graduated compression stockings and other mechanical devices have been shown not to be effective unless they are worn at least 18 to 20 hours a day. This degree of adherence is difficult to achieve, as it can severely limit patient mobility and leave patients susceptible to development of pressure ulcers.

Mechanical compression should be initiated prior to induction of anesthesia and continue intraoperatively and then into the postanesthesia care unit. Orders for use of mechanical devices should include instructions in the patient's medical chart specifying how—and for how many hours per day—they are to be worn. Not doing so leaves the physician vulnerable to litigation, especially as the ACCP guidelines include language on optimal adherence to these devices ("they should be removed for only a short time each day when the patient is actually walking or for bathing"[1]).

Continuous external compression therapy

Newer mechanical device options include a continuous external compression therapy system that allows patients to be mobile while wearing it and provides rhythmic compression that results in good peak venous flows. Ideally such a device could be put on the patient preoperatively and worn during surgery, throughout the hospital stay, and even at home during recovery. Anecdotally, however, I see patients turn these new devices off at the side of the bed just as often as they do with traditional devices.

Vena caval interruption

Vena caval interruption involves placement of a retrievable vena cava filter before surgery and removal some time later; it offers the potential for VTE prophylaxis in patients who could not tolerate even minor amounts of bleeding, such as certain trauma patients. The Eastern Association for the Surgery of Trauma has put forth a consensus recommendation to consider vena caval interruption in high-risk trauma patients who cannot receive pharmacologic prophylaxis.[7] A randomized trial evaluating the usefulness of vena caval interruption for patients undergoing surgery is needed. For now, this intervention should be regarded as experimental and considered only on a highly individualized basis.

TABLE 2
Patient risk factors associated with venous thromboembolism (VTE)[1,5]

Age > 60 years	Thrombophilia
Prolonged surgery	Cancer
Congestive heart failure	High-estrogen states*
Severe chronic obstructive pulmonary disease	Inflammatory bowel disease
Central venous access	Nephrotic syndrome
Trauma	Sepsis
Prior history of VTE	Blood transfusions
Family history of VTE	

* Obesity, use of hormone replacement therapy, use of oral contraceptives, pregnancy, postpartum status

PHARMACOLOGIC PROPHYLAXIS

The ACCP guidelines' recommendations for pharmacologic VTE prophylaxis in surgical patients are lengthy, and many remain unchanged from prior editions, so this discussion will focus on broad principles and new recommendations adopted in the recent 8th edition.[1] **Table 3** lists notable new recommendations for patients undergoing specific surgical procedures.

Timing of initiation

Pharmacologic VTE prophylaxis generally should begin 8 to 24 hours postoperatively. Of course, adequate hemostasis is required before initiation, and the net risk/benefit tradeoff with regard to timing of anticoagulant initiation has still not been well studied in many surgical patient populations.

Extended prophylaxis

In the update for the 8th edition of its guidelines, the ACCP added an explicit recommendation for extended outpatient prophylaxis with low-molecular-weight heparin (LMWH) for up to 28 days postoperatively in selected high-risk patients undergoing general or gyne-

TABLE 3
New procedure-specific recommendations for thromboprophylaxis in the latest ACCP guidelines[1]

Surgery type	Recommended options (grade*)
Major vascular surgery in patient with risk factors	LMWH, low-dose UFH, fondaparinux (1C for all)
Major gynecologic surgery or laparoscopy in patient with risk factors	LMWH (1A), low-dose UFH (1A), intermittent pneumatic compression (1A), or fondaparinux (1C), ± graduated compression stockings (1C)
Major open urologic surgery	Low-dose UFH (1B), intermittent pneumatic compression/graduated compression stockings (1B), LMWH (1C), fondaparinux (1C)
Bariatric surgery	Higher-dose LMWH, low-dose UFH three times daily, fondaparinux (1C for all)
Thoracic surgery	LMWH, low-dose UFH, intermittent pneumatic compression (1C for all)
CABG	LMWH over low-dose UFH (2B)

*Guide to recommendation grades in the ACCP guidelines:
1A = strong recommendation; high-quality evidence
1B = strong recommendation; moderate-quality evidence
1C = strong recommendation; low-quality or very-low-quality evidence
2B = weak recommendation; moderate-quality evidence

ACCP = American College of Chest Physicians; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; CABG = coronary artery bypass grafting

cologic surgery, including those with cancer or a history of VTE.[1] This recommendation was based largely on studies of extended prophylaxis in patients with cancer undergoing colorectal surgery.[8]

Increased appreciation of the value of extended VTE prophylaxis after discharge is linked to a growing recognition that DVT and PE episodes in the community setting are often related to a recent hospital stay for either medical illness or surgery. A population-based study found that 59% of all community cases of a first lifetime VTE event in residents of Olmsted County, Minn., over a 15-year period could be linked to current or recent (< 30 days) hospitalization or nursing home residence.[9] A similar population-based study in the Worcester, Mass., area found that three-fourths of all VTE events in a 3-year period occurred in the outpatient setting.[10] Among patients with these outpatient VTE events, a large proportion had undergone surgery (23%) or hospitalization (37%) in the prior 3 months; among those, 67% experienced their VTE within 1 month of their time in the hospital.

These findings are no surprise, since surgery induces a hypercoagulable state that, when combined with individual risk factors such as obesity, old age, or poor heart function, cannot be assumed to return to baseline on postoperative day 4 or 5 just because the patient is being discharged.

Orthopedic surgery

For patients undergoing major orthopedic procedures, the ACCP guidelines recommend against routine screening for VTE with Doppler ultrasonography before discharge if the patient is asymptomatic.[1] Such screening is not considered cost-effective because asymptomatic clots often are found, for which treatment is uncertain, and proximal clots may be missed, giving a false sense of security.

ACCP recommendations for prophylaxis in patients undergoing orthopedic surgery are summarized in **Table 4**.[1] As shown, the recommended options for hip and knee replacement and hip fracture surgery are almost exclusively medication-based. The vast majority of patients undergoing these major orthopedic procedures need prophylaxis beyond their typical hospital stay of 3 or 4 days. About 90% of DVTs following knee replacement occur within 2 weeks of surgery, so 10 to 14 days of therapy is probably the best practice in this setting, although a longer period may be justified depending on the patient's risk profile. For hip replacement, in contrast, 28 to 30 days of prophylaxis is often preferable, since about half of all DVTs in that setting occur more than 2 weeks after surgery.

New to the ACCP guidelines in the 8th edition is the recommendation that patients undergoing knee arthroscopy who have risk factors for VTE (or whose procedure is complicated) should receive 1 week of prophylaxis with LMWH.[1] Also new are recommendations for patients with risk factors undergoing single- or multilevel laminectomy **(Table 4)**.

Recommendations unchanged in neurosurgery, spinal injury, trauma, burns

Recommendations for neurosurgery remain unchanged from the prior (2004) edition of the ACCP guidelines and are still based on the 2000 meta-analysis by Iorio and Agnelli of LMWH prophylaxis in neurosurgery cases.[11] In the United States, the standard is overwhelmingly to use mechanical devices for thromboprophylaxis in neurosurgery, even for patients with cancer.

For prophylaxis in surgical patients with spinal cord injury, multisystem trauma, or burns, LMWH is predominantly used, and the ACCP recommendations are unchanged from 2004.

Drug-specific considerations

LMWH vs vitamin K antagonist. Although vitamin K antagonists (warfarin) still appear in the latest ACCP recommendations,[1] LMWH is preferable. A 2004 meta-analysis of studies comparing vitamin K antagonists with LMWH for prophylaxis in patients undergoing orthopedic surgery found that vitamin K antagonists were associated with more episodes of total DVT (relative risk [RR]

= 1.51; 95% CI, 1.27–1.79) and proximal DVT (RR = 1.51; 95% CI, 1.04–2.17) compared with LMWH.[12] No difference was found in rates of wound hematoma or major bleeding. This finding of inferiority for vitamin K antagonists came despite the likelihood that warfarin was more often administered correctly (ie, with dose adjustment to achieve an international normalized ratio [INR] of 2.0 to 3.0 within 72 hours after surgery) in the studies in this analysis than it is in real-world practice.

Fondaparinux. The indirect factor Xa–specific inhibitor fondaparinux has had a surprisingly limited clinical adoption despite having been widely studied and found to be safe and effective. This is likely attributable in part to its 17-hour half-life, which raises concerns that it may take 3 days for its effects to stop if a patient begins to bleed. Large phase 3 studies have found fondaparinux to be equivalent to LMWH in VTE prevention after hip replacement, marginally superior to LMWH after knee replacement, and superior to LMWH following hip fracture repair.[13] Fondaparinux was associated with an increase in bleeding events and instances of transfusion requirement, but only in one of the studies, which was in the setting of knee replacement surgery.[14]

Aspirin not recommended by ACCP. Although aspirin reduces the risk of VTE, practice guidelines from both the ACCP[1] and the International Union of Angiology[15] contain no recommendation for its use as prophylaxis because it is considered less effective and more risky than other therapies. In contrast, clinical practice guidelines from the American Academy of Orthopaedic Surgeons suggest that aspirin is reasonable for VTE prophylaxis.[16] The varying recommendations reflect differences in perspective among these different specialties.

Aspirin has the advantages of ease of use and low cost, but it is clearly not the best evidence-based approach for VTE prophylaxis. The only recent randomized trial evidence in support of aspirin comes from the Pulmonary Embolism Prevention trial, a study with a flawed design involving more than 13,000 patients undergoing surgery for hip fracture or elective arthroplasty in five countries.[17] Patients were randomized to receive aspirin 160 mg daily or placebo for 35 days along with any other prophylaxis deemed necessary (an important potential confounder). Aspirin was associated with an absolute reduction in symptomatic events of less than 1% relative to placebo, and no benefit was observed within the first week. The best results with aspirin were among patients with hip fracture. No benefit was shown among patients undergoing hip arthroplasty or knee arthroplasty; in those groups, both the aspirin and placebo recipients were also treated with LMWH. An absolute increase in rates of wound bleeding (0.6% increase) and gastrointestinal bleeding (1.0% increase) was observed in the aspirin group. The absolute increase in complications was greater than the absolute reduction in episodes of symptomatic DVT: for every episode of symptomatic DVT averted, one wound bleed and 10 gastrointestinal bleeds occurred.

TABLE 4
Recommendations for thromboprophylaxis in orthopedic surgery from the latest ACCP guidelines[1]

Procedure	Recommended options (grade*)	Duration of prophylaxis (grade*)
Total hip replacement	LMWH, VKA†, or fondaparinux (1A for all)	10–35 days (1A) (typical patient, 28–30 days)
Hip fracture surgery	Fondaparinux (1A), LMWH (1B), VKA† (1B), or low-dose UFH (1B)	10–35 days (1A)
Total knee replacement	LMWH (1A), VKA† (1A), fondaparinux (1A), or intermittent pneumatic compression (1B)	10–35 days (2B) (typical patient, 10–14 days)
Arthroscopic knee surgery	In patients without risk factors, routine prophylaxis not recommended (2B) In patients with risk factors or a complicated procedure, LMWH (1B)	
Spine surgery	In patients without risk factors, routine prophylaxis not recommended (2C) In patients with risk factors, postoperative low-dose UFH (1B), postoperative LMWH (1B), intermittent pneumatic compression (1B), or graduated compression stockings (2B)	

*Guide to recommendation grades in the ACCP guidelines:
1A = strong recommendation; high-quality evidence
1B = strong recommendation; moderate-quality evidence
1C = strong recommendation; low-quality or very-low-quality evidence
2B = weak recommendation; moderate-quality evidence
2C = weak recommendation; low-quality or very-low-quality evidence
†Dosed to an international normalized ratio of 2.0–3.0
ACCP = American College of Chest Physicians; LMWH = low-molecular-weight heparin; VKA = vitamin K antagonist (warfarin); UFH = unfractionated heparin

SPECIAL PATIENT POPULATIONS

Renal impairment

The 8th edition of the ACCP guidelines recommends that renal function be kept in mind when considering LMWH, fondaparinux, and other antithrombotic drugs that are cleared by the kidneys. Fondaparinux and LMWH can bioaccumulate in patients with renal insufficiency, who have a higher risk of bleeding to begin with, thereby compounding the risk. Options for patients with renal compromise include avoiding drugs that bioaccumulate, using a lower dosage, and monitoring the drug level or anticoagulant effect.[1]

Fondaparinux is explicitly contraindicated in patients with low body weight (< 50 kg) or renal impairment (creatinine clearance < 30 mL/min). Renal function should be

assessed periodically in any patients receiving the drug.[18]

I also would not use fondaparinux or LMWH in patients with rapidly changing renal function. For patients with chronic, stable renal impairment, one can reduce the dose of LMWH empirically; one LMWH, enoxaparin, has specific dosing guidelines in its package insert (one-third reduction in dose), but this option does not hold for patients with rapidly changing renal function.[19]

Obesity

The 8th edition of the ACCP guidelines recommends weight-based dosing of thromboprophylactic agents in obese patients. The guidelines particularly recommend that patients undergoing inpatient bariatric surgery be given higher doses of LMWH or unfractionated heparin.[1,20]

Frederiksen et al measured the anticoagulant effect of a single fixed dose of a LMWH (using anti-factor Xa heparin activity levels) and found that it was dependent on body weight.[21] This suggests that fixed doses that are effective in normal-weight patients may have no detectable anticoagulant effect in patients with very high body weight.

Weight-based dosing: mounting nonprospective evidence. Weight-based dosage adjustment for the morbidly obese has not been directly studied in a prospective, randomized fashion. A nonrandomized study by Scholten et al compared two regimens of enoxaparin (30 mg twice daily vs 40 mg twice daily) among 481 obese patients undergoing bariatric surgery; each regimen was used along with mechanical thromboprophylaxis.[22] They found that the higher-dose regimen was associated with significantly fewer postoperative DVT complications (0.6% vs 5.4%; $P < .01$) without an increase in bleeding complications.

Separately, Shepherd et al used weight-adjusted doses of unfractionated heparin (started on the evening of surgery) to achieve subtherapeutic peak anti–factor Xa heparin activity levels of 0.11 to 0.25 IU/mL in a series of 700 patients undergoing laparoscopic gastric bypass surgery.[23] The resulting doses were greater than those in traditional fixed-rate protocols, but rates of bleeding and VTE events were low and comparable to those reported in patients receiving standard doses.

Don't rule out multimodal approaches. Multimodal prophylaxis can also be used in obese patients and need not be abandoned as a result of size considerations. For instance, two intermittent compression therapy devices can be pieced together with a Velcro binder if a single device is too small to be worn.

EMERGING ANTICOAGULANT OPTIONS

For many years, unfractionated heparin was the only available parenteral anticoagulant. While heparin has broad anticoagulant properties, it also has well-established limitations, including the need for parenteral delivery, recent problems related to contamination (it is derived from pig intestines), and of course heparin-induced thrombocytopenia (HIT). HIT is an immune-mediated form of platelet activation that can lead to widespread thrombosis throughout the body. It is more commonly associated with venous thrombosis, but arterial events with limb-threatening ischemia may also occur. LMWH is associated with a reduced risk of HIT, but LMWH does not avoid the risk entirely.

Beyond the issue of avoiding HIT, newer anticoagulant therapies are being developed with the aim of oral administration and more targeted inhibition of coagulation factors IIa (thrombin) and Xa.[24]

Oral direct thrombin inhibitors

One of the two most promising classes of emerging anticoagulants is the direct thrombin inhibitors, most of which are being developed for oral administration. There were high hopes for the initial compound in this class, ximelagatran, but it was abandoned about 5 years ago because of hepatotoxicity.

Dabigatran is the direct thrombin inhibitor furthest along in development today. Currently approved in Europe for prevention of VTE in patients undergoing total hip or knee replacement surgery, dabigatran is likely to be available soon in the United States. It is administered orally, has a rapid onset of action (< 1 hour), and has a predictable anticoagulant response that requires no monitoring.[24] Because dabigatran is excreted essentially unchanged by the kidneys and may bioaccumulate, it should not be used in patients with renal impairment or rapidly changing renal function.

In phase 3 clinical trials for VTE prevention in knee replacement surgery, dabigatran was at least as effective as enoxaparin 40 mg once daily and had a comparable safety profile,[25] but it was slightly less effective than enoxaparin 30 mg twice daily.[26] In a phase 3 trial in patients undergoing hip replacement surgery, dabigatran was equivalent in efficacy and safety to enoxaparin 40 mg once daily.[27]

Oral direct factor Xa inhibitors

A key rationale for direct inhibition of factor Xa is that it results in inhibition of thrombin production on the activated platelet. Whereas fondaparinux is an *indirect* inhibitor of factor Xa, *direct* factor Xa inhibitors offer an advantage in that they inhibit factor Xa within the prothrombinase complex, which occurs on the surface of a platelet and is the main site for thrombin development (very little thrombin is actually produced on endothelial cells). Recall the adage that "thrombin begets more thrombin": it activates not only platelets but the intrinsic and extrinsic pathways.[28]

Factor Xa may be a better target than thrombin for a number of other reasons:

- Factor Xa is believed to have few functions (compared with thrombin) outside of coagulation
- In vitro studies show that factor Xa has a wider therapeutic window than thrombin, which translates to greater separation between drug levels that will confer efficacy and bleeding

- Thrombin inhibitors are associated with rebound thrombin generation (there is no evidence of this with factor Xa inhibitors)
- The efficacy of heparin-based anticoagulants improves as selectivity for factor Xa increases (unfractionated heparin is less effective than LMWH, which is less effective than fondaparinux).

Two direct factor Xa inhibitors—both administered orally—are far along in development, as detailed below.

Apixaban has shown promise, but the phase 3 ADVANCE-1 study of apixaban for VTE prevention in patients undergoing knee surgery did not meet statistical criteria for noninferiority compared with enoxaparin 30 mg twice daily.[29] This prompted a delay in regulatory filings for apixaban in the United States, and the drug's prospects for approval for VTE prevention may be unclear until release of results from two other comparative phase 3 trials with enoxaparin in 2009 and 2010.

Rivaroxaban is more likely to become clinically available soon, in light of recent results from the phase 3 RECORD4 trial demonstrating that it was significantly superior to enoxaparin 30 mg twice daily in preventing VTE following knee replacement surgery with comparable rates of major bleeding.[30]

DISCUSSION

Question from the audience: Some surgeons in my hospital prescribe warfarin immediately after surgery without a bridge of LMWH. Is that appropriate?

Dr. Michota: Warfarin is an option for prophylaxis in orthopedic surgery, beginning on the day of surgery. It could even be started the day before surgery, but the dose should be monitored to achieve an INR between 2.0 and 3.0 within 72 hours of the procedure. If the INR is not in this optimum range, prophylactic doses of LMWH can be given until it is therapeutic.

Follow-up question: In practice, do you actually encourage INR monitoring? Usually we just put patients on a certain dose without monitoring. When we do check the INR, it's usually 1.4 or 1.5.

Dr. Michota: Warfarin was shown to be effective in reducing VTE risk in orthopedic surgery with dose adjustment based on INR monitoring. On that basis, warfarin remains in the guideline recommendations. Unmonitored, warfarin has not been shown to reduce risk, so to give it that way would not be evidence-based.

Question from the audience: I work with several plastic surgeons who use compression stockings intraoperatively because they've heard of several patients who developed a PE during surgery. Is there any benefit to using compression stockings for 2 to 3 hours and then sending the patient home?

Dr. Michota: I don't know. Theoretically, a device that is on and working before induction may reduce stasis.

The plastic surgery societies do have guidelines. Risk depends on the type of plastic surgery procedure; for example, risk probably increases due to inflammation in procedures that involve scraping the fat pads.

This is an area where we don't have much data. These patients may be at risk, but we don't know the best way to mitigate it. It is important that risks be discussed with patients in the informed-consent process and be documented. If the surgeon thinks it is reasonable to give pharmacologic prophylaxis after surgery, I wouldn't hesitate to do that, but any form of bleeding in the setting of plastic surgery is catastrophic because it defeats the reason for which the surgery was done in the first place.

Question from the audience: How do the guidelines address being aggressive with pharmacologic thromboprophylaxis when a patient is already taking dual antiplatelet therapy?

Dr. Michota: For patients with an indication for VTE prophylaxis in a setting for which there is a specific strategy, the ACCP guidelines recommend that they be put on that regimen whether they are on antiplatelet agents or not. For example, consider a high-risk patient having colorectal surgery who should get unfractionated heparin or LMWH postoperatively and who is currently taking clopidogrel and aspirin. There is no evidence that the dual aspirin–clopidogrel therapy alone is effective in decreasing the risk of DVT. However, we do know that if we add on additional agents, the risk of bleeding is increased. The guidelines consider risk and benefit, and they recommend adding the agents that we know work to prevent DVT.

Question from the audience: You briefly mentioned prophylaxis for knee arthroscopy, which is the most frequently performed orthopedic procedure. Do these recommendations apply to all patients undergoing knee arthroscopy?

Dr. Michota: No. Prophylaxis is indicated only for patients with what the ACCP considers to be additional risk factors for thrombosis. They didn't specify which risk factors, but good indications for prophylaxis would include morbid obesity, limited mobility after the procedure, a personal history of DVT, features of stasis noted on physical examination, stasis dermatitis (or other features that could indicate prior thrombosis), advanced age, and malignancy. If a patient undergoing knee arthroscopy has other nonmodifiable risk factors, you should also think about prophylaxis. But the vast majority of patients do not need it.

Question from the audience: I'm an academic hospitalist who works closely with orthopedic surgeons. Certain surgeons will only use aspirin for prophylaxis, and it is nonnegotiable. Where does that leave me from a medicolegal standpoint? Our model is to follow ACCP recommendations, but these orthopedic surgeons still use only aspirin.

Dr. Michota: You must do everything you can to come to a consensus with your surgeon colleagues. If you are uncomfortable, as a group you must say to the surgeons, "We are uncomfortable. This is how we view the data. How do you view the data?" If they answer, "We're doing it because it's easy, and the American Academy of Orthopaedic Surgeons says we can do it," I don't have a good response. But it is more likely that their use of aspirin is based on their own observations; they may not see many clots. Of course, the problem with observational data is that the numbers are not large and they are not generated in a randomized and prospective fashion. Perhaps you can come to some middle ground, but you could always make the difficult choice and say, "I'm just not going to follow your patients."

DISCLOSURES

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Perioperative management of diabetes: Translating evidence into practice

ABSTRACT

Glycemic control before, during, and after surgery reduces the risk of infectious complications; in critically ill surgical patients, intensive glycemic control may reduce mortality as well. The preoperative assessment is important in determining risk status and determining optimal management to avoid clinically significant hyper- or hypoglycemia. While patients with type 1 diabetes should receive insulin replacement at all times, regardless of nutritional status, those with type 2 diabetes may need to stop oral medications prior to surgery and might require insulin therapy to maintain blood glucose control. The glycemic target in the perioperative period needs to be clearly communicated so that proper insulin replacement, consisting of basal (long-acting), prandial (rapid-acting), and supplemental (rapid-acting) insulin can be implemented for optimal glycemic control. The postoperative transition to subcutaneous insulin, if needed, can begin 12 to 24 hours before discontinuing intravenous insulin, by reinitiation of basal insulin replacement. Basal/bolus insulin regimens are safer and more effective in hospitalized patients than supplemental-scale regular insulin.

KEY POINTS

Surgery and anesthesia can induce hormonal and inflammatory stressors that increase the risk of complications in patients with diabetes.

Elevated blood glucose levels are associated with worse outcomes in surgical patients, even among those not diagnosed with diabetes.

The perioperative glycemic target in critically ill patients is 140 to 180 mg/dL. Evidence for a target in patients who are not critically ill is less robust, though fasting levels less than 140 mg/dL and random levels less than 180 mg/dL are appropriate.

Postoperative nutrition-related insulin needs vary by nutrition type (parenteral or enteral), but ideally all regimens should incorporate a basal/bolus approach to insulin replacement.

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Diabetes confers an increased risk of perioperative morbidity and mortality, mostly from infection and cardiovascular events. It is not unusual for surgical patients with diabetes to have a number of comorbidities or underlying chronic vascular complications that put them at risk for cardiovascular events or an infectious complication. Silent ischemia, coronary artery disease, and autonomic neuropathy are common among patients with diabetes, and each can contribute to perioperative morbidity and mortality. These are important considerations since nearly one-fifth of surgical patients have diabetes and since a person with diabetes has a 50% risk of undergoing surgery at some point in his or her lifetime.[1]

This article reviews the preoperative evaluation of patients with diabetes, discusses the relation between glycemic control and perioperative outcomes, and examines targets and strategies for glycemic control in patients with type 1 and type 2 diabetes throughout the perioperative period.

PREOPERATIVE EVALUATION

The preoperative evaluation must consider first and foremost the status of the patient's diabetes and his or her surgical risk factors. Also important are the characteristics of the procedure to be performed, the method of anesthesia to be used, and select laboratory values.

Diabetes status

The type of diabetes and its treatment must be considered. Type 1 diabetes requires continuous insulin therapy to prevent ketoacidosis; patients with type 2 diabetes are usually treated with oral medications with or without insulin. Baseline control of blood glucose is a predictor of morbidity following surgery. Hypoglycemia is associated with increased morbidity in the inpatient setting, so a history of severe hypoglycemic events or of difficulty recognizing hypoglycemia (hypoglycemia unawareness) should be elicited in the preoperative evaluation. Complications of diabetes and other comorbidities also must be evaluated, along with their treatments.

Surgical risk factors

Patients with diabetes have surgical risk factors specific to their health—namely, cardiovascular risk factors that may or may not have been previously diagnosed. Patients with diabetes may have silent ischemia, atypical manifestations

of coronary ischemia, or underlying cardiomyopathy. Many patients with type 2 diabetes have hypertension, which may complicate perioperative management. Other common surgical risk factors in this population include obesity, chronic kidney disease, and undiagnosed autonomic dysfunction, which may compromise hemodynamic stability in the perioperative period. Additionally, patients with long-standing diabetes experience reductions in pulmonary function (eg, forced expiratory volume, peak expiratory flow, and diffusion capacity for carbon monoxide) related to disease duration and vascular injury,[2] which may complicate weaning from ventilatory support.

Characteristics of the procedure and anesthetic

Both surgery and anesthesia may induce an increase in levels of stress hormones (epinephrine, cortisol, growth hormone) and inflammatory cytokines (interleukin-6 and tumor necrosis factor–alpha), resulting in insulin resistance and impaired insulin secretion (even among patients who present with adequate insulin secretion). These in turn contribute to lipolysis and protein catabolism, leading to hyperglycemia and, if a patient is severely insulin deficient, ketoacidosis. Other factors that particularly affect insulin resistance and secretion include cardiovascular bypass surgery, sepsis, the need for total parenteral nutrition, and steroid therapy.

The characteristics of the surgical procedure, including the type of surgery as well as its urgency, duration, and timing (morning vs later in the day), are important in planning for perioperative glycemic management. For example, a short, minor procedure may require only observation, whereas more extensive procedures warrant periodic monitoring and active glycemic management with insulin infusions.

The type of anesthesia should also be considered. Compared with epidural anesthesia, general anesthesia is associated with greater stimulation of the sympathetic nervous system and increased catecholamine levels, resulting in more pronounced hyperglycemia.[3]

Preoperative tests

Preoperative testing and laboratory evaluation should include, at minimum, an electrocardiogram, a basic metabolic panel to assess renal function, electrolyte levels, and hemoglobin A_{1c} measurement. For low-risk procedures in patients with adequate exercise tolerance, no diagnostic tests might be needed. In any case, knowledge of the hemoglobin A_{1c} level may help not only to classify perioperative risk but also to determine postoperative care, including the choice of antiglycemic medications at discharge.

IMPORTANCE OF GLYCEMIC CONTROL

Preoperative glycemic control has a significant impact on the risk of infectious complications—including pneumonia, wound infection, urinary tract infection, and sepsis—in patients with diabetes across a variety of surgical procedures.[4] Similarly, postoperative glycemic control—to a mean blood glucose level less than 200 mg/dL in the immediate postoperative period—significantly reduces the incidence of deep sternal wound infection after open heart surgery.[5]

Among patients undergoing cardiothoracic surgery, both cardiac-related and overall mortality are greater with increasing postoperative blood glucose levels, although a cause-and-effect relationship has not been established.[6]

Glycemic control matters regardless of diabetes status

Hyperglycemia affects mortality regardless of diabetes status. In a study of 779 consecutive patients admitted for acute myocardial infarction, mortality at 180 days was highly associated with hyperglycemia on admission independent of a history of diabetes; the highest mortality was among hyperglycemic patients without previously known diabetes.[7] Similarly, a large study of glycemic control in intensive care unit (ICU) patients receiving insulin found that mortality in nondiabetic patients increased with median glucose level and was higher than mortality in diabetic patients.[8] These findings suggest a need for vigilance in the perioperative and critical care management of all patients with hyperglycemia, regardless of preadmission diabetes diagnosis, as they carry significant morbidity and mortality risk.

GLYCEMIC CONTROL IN THE CRITICALLY ILL: SOME SUPPORT FOR A MODIFIED TARGET, BUT VIGILANCE FOR HYPOGLYCEMIA NEEDED

The landmark study by Van den Berghe et al of intensive insulin therapy in surgical ICU patients demonstrated significant reductions in morbidity and mortality when glucose levels were controlled aggressively (80 to 110 mg/dL; average, 103 mg/dL) compared with conventional control (180 to 200 mg/dL).[9] The benefit of intensive glycemic control was evident on outcomes such as the occurrence of sepsis, need for dialysis, need for blood transfusion, and development of acute polyneuropathy. Intensive insulin therapy was also associated with cost savings compared with conventional insulin therapy in mechanically ventilated patients.[10]

However, a number of subsequent studies have clearly shown that as blood glucose levels approach normoglycemia, the risks of hypoglycemia, especially severe hypoglycemia, can offset the benefits of tight blood glucose control.

A follow-up study by Ven den Berghe et al in a medical ICU failed to show a mortality benefit from tight glycemic control, though patients in the intensive control arm experienced less renal injury, faster weaning from ventilation, and earlier discharge from the ICU and hospital.[11]

The recent NICE-SUGAR study of aggressive glucose control in the ICU randomized patients to a target blood glucose of 81 to 108 mg/dL (intensive group) or 180 mg/dL or less (control group).[12] At study's end, the groups' mean blood glucose levels were 115 mg/dL and 144 mg/

dL, respectively, while rates of severe hypoglycemia (blood glucose < 40 mg/dL) were 6.8% and 0.5%, respectively. Mortality rates were higher in the intensive therapy group (27.5%) than in the control group (24.9%), driven by severe hypoglycemic events. Notably, blood glucose monitoring in this and other studies was conducted at a frequency of anywhere between 1 and 4 hours.

The conclusions of the available data would support, for the time being, a modified glycemic target in critically ill patients, with strict avoidance of severe hypoglycemia. The recent consensus statement from the American Association of Clinical Endocrinologists and the American Diabetes Association recommends using insulin therapy if blood glucose levels exceed 180 mg/dL, with target glucose levels less than 180 mg/dL in critically ill patients and less than 140 mg/dL in non–critically ill patients.[13] Development and implementation of safer insulin infusion algorithms and more frequent and accurate blood glucose monitoring in this setting should enable us to achieve better glycemic targets with lower risk.

ELEMENTS OF PHYSIOLOGIC INSULIN REPLACEMENT

In hospitalized patients with hyperglycemia, three different components of insulin replacement require management[1]:

Basal insulin replacement consists of a long-acting insulin preparation administered regardless of the patient's oral intake status, with the premise of matching hepatic (endogenous) glucose production

Prandial insulin replacement requires a rapid-acting insulin preparation given to cover nutritional needs

Supplemental (or correction) insulin replacement requires a rapid-acting preparation (usually the same insulin type as for prandial coverage) to correct blood glucose values that exceed predetermined glycemic targets.

For most patients, basal insulin replacement might be appropriate preoperatively to control fasting glucose, whereas during surgery, especially if prolonged or high risk, an intravenous (IV) insulin drip is the most effective means of glucose control. The postoperative transition from the IV insulin drip usually involves basal insulin replacement plus supplemental rapid-acting insulin. Prandial or nutritional insulin should be started once the patient begins to receive nutrition (oral, enteral, or hyperalimentation).

GOALS OF PERIOPERATIVE GLYCEMIC CONTROL

Perioperative glycemic management has several key objectives:

- Avoidance of clinically significant hyper- or hypoglycemia
- Maintenance of electrolyte and fluid balance
- Prevention of ketoacidosis, which is imperative in patients with type 1 diabetes, who require insulin at all times
- Achievement of specific glycemic targets, as discussed above—ie, less than 180 mg/dL in critically ill patients and less than 140 mg/dL in stable patients.[13]

Strategies differ across the perioperative timeline

Strategies for perioperative glycemic control differ before, during, and after surgery, as summarized immediately below and detailed in the following sections.

Preoperatively, glycemia should be stabilized, typically with subcutaneous insulin, if there is enough time to do so. For patients who have not previously been on insulin, placing them on an insulin supplemental scale to correct glycemia to desired targets might be a first step. In the setting of hyperglycemia, these patients may also be started on a low dose of basal insulin, with preference given to basal insulin analogs, given their consistent and relatively peakless action profile and lower risk of hypoglycemia. A starting dose of 0.2 to 0.4 U/kg is appropriate and carries a low risk of hypoglycemia. For patients already using insulin on an outpatient basis, continuing their basal insulin dose, possibly at a reduced dosage (25% less), together with supplemental-scale insulin coverage, should stabilize blood glucose levels. For patients on combination insulin or premixed insulin types, the basal insulin dose for preoperative management can be estimated by taking the patient's usual total daily dose and delivering 40% to 50% of that dose as a basal insulin analog injection. Clearly, a supplemental scale should be implemented along with basal insulin replacement.

Intraoperatively, switching to IV insulin may be appropriate for stabilizing glycemia, depending on the type of surgery. A number of IV insulin protocols have been proposed, although no consistent comparisons of efficacy or safety among these protocols have been published.

Postoperatively, patients eventually should be transitioned from IV to subcutaneous insulin when glycemic control stabilizes. This transition may be complicated for many reasons. Oral intake may be inconsistent. The surgery and surrounding environment can induce stressors, promote susceptibility to infection, and increase insulin resistance. Additionally, some patients may be on hyperalimentation. Specific instructions for the transition from IV to subcutaneous insulin are covered later in this article.

PREOPERATIVE GLYCEMIC MANAGEMENT

In patients with type 2 diabetes, oral agents pose certain safety risks and should be discontinued prior to surgery.

Sulfonylureas may induce hypoglycemia in patients who are placed on NPO ("nothing by mouth") orders and should be held in patients who are fasting.

Metformin can induce lactic acidosis if kidney function declines and should be withheld 1 to 2 days before planned surgery if a need for IV contrast is anticipated or the procedure could potentially lead to hemodynamic instability and reduced renal perfusion.

Thiazolidinediones may cause fluid retention that can complicate the postoperative period; they can be discontinued several days prior to a planned surgery.

GLP-1 agonists, such as exenatide, can slow gastric

motility and potentially delay gastrointestinal recovery after major surgery; they should be held the day of surgery.

DPP-4 inhibitors (incretin enhancers), such as sitagliptin, do not have significant side effects and, if need be, can be continued. Because incretin therapies act via a glucose-dependent mechanism, they are unlikely to cause hypoglycemia, even in a patient whose oral intake is held or delayed. On the other hand, since their effect is mostly in reducing postprandial glycemia, there may be little need to use them in a patient who is NPO.

Patients with type 1 diabetes must continue basal insulin replacement preoperatively (0.2 to 0.3 U/kg/day of a long-acting insulin). Patients with type 2 diabetes may benefit from basal insulin replacement, as previously noted.

Supplemental insulin scales are used to correct hyperglycemia regardless of a patient's oral intake status. They can be individualized based on the estimated total daily insulin dose and require glycemic targets to be established. Fingerstick glucose monitoring should be done every 4 to 6 hours in a patient who is NPO, and supplemental-scale insulin should be used to correct glucose values that exceed target. For supplemental-scale coverage, rapid-acting insulin analogs have a shorter duration of action than human regular insulin and may be given subcutaneously every 4 to 6 hours, whereas regular insulin should not be given more often than every 6 hours to correct hyperglycemia. These differences in action duration should be kept in mind to minimize the potential for insulin stacking.

INTRAOPERATIVE GLYCEMIC MANAGEMENT

Procedure length is an important determinant

Strategies for intraoperative glucose management vary according to the length of the procedure.

For minor, short procedures, the preoperative glucose management orders may be continued.

For longer, more complex procedures, a switch to an IV insulin drip is safe and allows rapid adjustments in dosing and plasma glucose levels. Ideally, IV insulin is started prior to the procedure so that the glucose level is stable once the patient arrives in the operating room. Given the logistics of IV insulin management, including the need for frequent monitoring (hourly) and dose adjustments, this type of treatment should be reserved for environments with adequate numbers of trained staff.

IV regular insulin is therapy of choice

Regular insulin delivered IV has a serum half-life of 7 minutes with a duration of effect of approximately 1 hour. These properties make IV regular insulin an effective tool for adjusting insulin therapy and addressing rapid changes in blood glucose values in critically ill patients. For this reason, IV regular insulin has become the preferred insulin for perioperative and critical care management. Although rapid-acting analogs can also be used IV, they confer no benefit over IV regular insulin and are more expensive.

Several different algorithms for IV regular insulin therapy are in use. Some are static, such as those of Markovitz et al[14] and Stockton et al,[15] while others are dynamic (ie, doses are self-adjusted based on changes in blood glucose level), such as the "Yale protocol" of Goldberg et al **(Figure 1)**.[16]

POSTOPERATIVE GLYCEMIC MANAGEMENT

Start subcutaneous transition before stopping IV drip

Transitioning from IV to subcutaneous insulin is often complicated. Nonoral nutrition options (ie, parenteral nutrition or enteral supplementation) must be considered. As noted, insulin must be replaced according to physiologic needs, which requires that a long-acting basal insulin be used regardless of oral intake status, a rapid-acting insulin be given to cover prandial or nutritional needs, and supplemental rapid-acting insulin be used to correct hyperglycemia.

In the transition from IV insulin, basal insulin replacement can begin at any time. I recommend starting the transition from IV to subcutaneous insulin about 12 to 24 hours before discontinuing the insulin drip. In type 1 diabetes, this transition ensures basal insulin coverage and minimizes the risk of developing ketones and ketoacidosis. In type 2 diabetes, it can ensure a more stable transition and better glycemic control.

Determining the basal insulin dose

The starting dose of basal insulin should be 50% to 80% of the prior IV insulin total daily dose, if stable glycemic control had been achieved with IV insulin. Alternatively, a calculation called the "Miami 4/12 rule" can be used, whereby the basal insulin replacement dose is equal to the patient's weight in kilograms divided by 4 **(Figure 2)**. I recommend that basal insulin replacement be given either once daily or divided twice daily as a long-acting insulin analog (eg, insulin glargine or insulin detemir).

Switching to subcutaneous supplemental insulin

Instructions must be given for switching to subcutaneous supplemental doses of insulin. Glycemic targets, generally from less than 130 to 150 mg/dL, must be established, as must the frequency of fingerstick testing:

- If the patient is being fed enterally or parenterally, fingerstick testing is recommended every 4 to 6 hours if a rapid-acting insulin analog is used and every 6 hours if regular insulin is used.
- If the patient is eating, fingerstick testing should be performed before meals and at bedtime.

The increment in supplemental insulin to correct hyperglycemia can be individualized based on a patient's perceived sensitivity to insulin, as detailed in **Table 1**.[17] Adjustments to supplemental doses are needed to maintain glycemic targets.

Covering nutritional requirements

Nutrition-related insulin needs depend on the type of caloric intake prescribed:

In patients receiving total parenteral nutrition (TPN),

Initiating an insulin infusion

1) **Insulin infusion:** Mix 1 U regular human insulin per 1 mL 0.9% NaCl. Administer via infusion pump (in increments of 0.5 U/hr)
2) **Priming:** Flush 50 mL of infusion through all IV tubing before infusion begins (to saturate the insulin binding sites in the tubing)
3) **Target blood glucose (BG) levels: 100–139 mg/dL**
4) **Bolus and initial insulin infusion rate:** Divide initial BG level by 100, then round to nearest 0.5 U for bolus *and* initial infusion rate
   Examples: (a) Initial BG = 325 mg/dL: 325 ÷ 100 = 3.25, round up to 3.5: IV bolus 3.5 U + start infusion at 3.5 U/hr
   (b) Initial BG = 174 mg/dL: 174 ÷ 100 = 1.74, round down to 1.5: IV bolus 1.5 U + start infusion at 1.5 U/hr

Blood glucose (BG) monitoring

1) Check BG hourly until stable (3 consecutive values within target range). In hypotensive patients, capillary blood glucose (ie, fingersticks) may be inaccurate and obtaining the blood sample from an indwelling vascular catheter is acceptable.
2) Then check BG every 2 hours. Once stable for 12–24 hours, BG checks can then be spaced to every 4 hours ***if***:
   (a) No significant change in clinical condition *and* (b) no significant change in nutritional intake
3) If any of the following occurs, consider temporary resumption of hourly BG monitoring until BG is again stable (2–3 consecutive BG values in target range):
   (a) Any change in insulin infusion rate (ie, BG out of target range)
   (b) Significant changes in clinical condition
   (c) Initiation or cessation of pressor or steroid therapy
   (d) Initiation or cessation of renal replacement therapy (hemodialysis, CVVH, etc)
   (e) Initiation, cessation, or rate change of nutritional support

Changing the insulin infusion rate

If BG < 50 mg/dL:
DISCONTINUE INSULIN INFUSION—Give 1 amp (25 g) D50 IV; recheck BG every 15 minutes
➢ When BG ⩾ 100 mg/dL, wait 1 hour, then restart insulin infusion at 50% of original rate

If BG 50–74 mg/dL:
DISCONTINUE INSULIN INFUSION—If ***symptomatic*** (or unable to assess), give 1 amp (25 g) D50 IV; recheck BG every 15 minutes
If ***asymptomatic***, give ½ amp (12.5 g) D50 IV or 8 ounces juice; recheck BG every 15–30 minutes
➢ When BG ⩾ 100 mg/dL, wait 1 hour, then restart infusion at 75% of original rate

If BG ⩾ 75 mg/dL:
STEP 1: Determine the **current BG level**—identifies a **column** in the table below

STEP 2: Determine the **rate of change** from the prior BG level (identifies a **cell** in the table below), then move right for INSTRUCTIONS (in green)
*(Note: If the last BG was measured 2–4 hours before the current BG, calculate the **hourly** rate of change. Example: If the BG at 2:00 PM was 150 mg/dL and the BG at 4:00 PM is 120 mg/dL, the total change over 2 hours is −30 mg/dL; however, the hourly change is −30 mg/dL ÷ 2 hours = −15 mg/dL/hr.)*

BG 75–99 mg/dL	BG 100–139 mg/dL	BG 140–199 mg/dL	BG ⩾ 200 mg/dL	INSTRUCTIONS*
		BG ↑ by > 50 mg/dL/hr	BG ↑	↑ INFUSION by "2Δ"
	BG ↑ by > 25 mg/dL/hr	BG ↑ by 1–50 mg/dL/hr *OR* BG UNCHANGED	BG UNCHANGED *OR* BG ↓ by 1–25 mg/dL/hr	↑ INFUSION by "Δ"
BG ↑	BG ↑ by 1–25 mg/dL/hr, BG UNCHANGED, *OR* BG ↓ by 1–25 mg/dL/hr	BG ↓ by 1–50 mg/dL/hr	BG ↓ by 26–75 mg/dL/hr	NO INFUSION CHANGE
BG UNCHANGED *OR* BG ↓ by 1–25 mg/dL/hr	BG ↓ by 26–50 mg/dL/hr	BG ↓ by 51–75 mg/dL/hr	BG ↓ by 76–100 mg/dL/hr	↓ INFUSION by "Δ"
BG ↓ by > 25 mg/dL/hr *see below*†	BG ↓ by > 50 mg/dL/hr	BG ↓ by > 75 mg/dL/hr	BG ↓ by > 100 mg/dL/hr	HOLD for 30 min, then ↓ INFUSION by "2Δ"

† Discontinue insulin infusion. Check BG every 30 min; when BG ⩾ 100 mg/dL, restart infusion at 75% of the most recent rate.

*** Changes in infusion rate** ("Δ") are determined by the current rate:

Current rate (U/hr)	Δ = Rate change (U/hr)	2Δ = 2× rate change (U/hr)
< 3.0	0.5	1
3.0–6.0	1	2
6.5–9.5	1.5	3
10–14.5	2	4
15–19.5	3	6
20–24.5	4	8
⩾ 25	⩾ 5	10 *(consult MD)*

FIGURE 1. Yale insulin infusion protocol (for use in hyperglycemic adults in intensive care settings, but not specifically for diabetic emergencies).
Adapted, with permission, from *Diabetes Care* (Goldberg PA, et al. Diabetes Care 2004; 27:461–467), Copyright © 2004 by the American Diabetes Association.

start 1 U of regular insulin (placed in the bag) for every 10 to 15 g of dextrose in the TPN mixture.

In patients receiving enteral nutrition, use regular insulin every 6 hours or a rapid-acting insulin analog every 4 hours. Start 1 U of insulin subcutaneously for every 10 to 15 g of delivered carbohydrates. For example, if a patient is receiving 10 g of carbohydrates per hour, a rapid-acting analog given at a dose of 4 U every 4 hours (1 U per 10 g of carbohydrates) should adequately cover enteral feedings. For any bolus feedings, give the injection as a full bolus 15 to 20 minutes in advance, based on the carbohydrate content of the feeding.

In patients who are eating, use regular insulin or a rapid-acting insulin analog before meals. Again, start 1 U of insulin subcutaneously for every 10 to 15 g of carbohydrates, or use the prandial portion of the Miami 4/12 rule **(Figure 2)**.

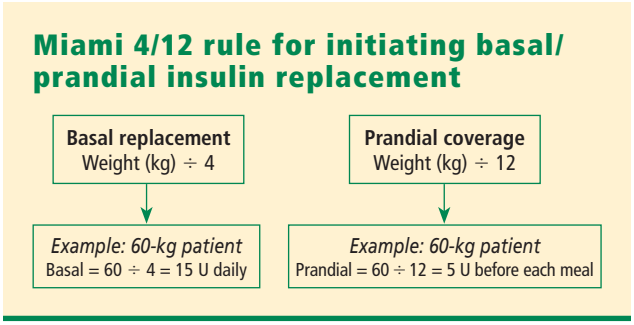

FIGURE 2. The Miami 4/12 rule determines insulin dosing by dividing the patient's weight in kilograms by 4 to calculate initial basal insulin replacement (in units per day) and by 12 to calculate prandial coverage (in units before each meal).

For example, in a 60-kg patient one would start with 5 U (60 ÷ 12) of a rapid-acting insulin before each meal.

Basal/bolus replacement outperforms supplemental-scale regular insulin

Use of a basal/bolus insulin regimen appears to be more beneficial than supplemental-scale regular insulin in hospitalized patients with type 2 diabetes, according to a recent randomized trial comparing the two approaches in 130 such patients with blood glucose levels greater than 140 mg/dL.[17] In the group randomized to basal/bolus insulin, the starting total daily dose was 0.4 to 0.5 U/kg/day, with half the dose given as basal insulin (insulin glargine) once daily and half given as a rapid-acting insulin analog (glulisine) in fixed doses before every meal. A rapid-acting analog was used for supplemental insulin in the basal/bolus regimen. By study's end, patients in the basal/bolus group were receiving a higher total daily insulin dose than those in the supplemental-scale group (mean of 42 U/day vs 13 U/day).

Mean daily blood glucose levels were 27 mg/dL lower, on average, in patients who received basal/bolus therapy compared with the supplemental-scale group, yet there was no difference between groups in the risk of hypoglycemia. More patients randomized to basal/bolus therapy achieved the glycemic goal of less than 140 mg/dL (66% vs 38%). Fourteen percent of patients assigned to supplemental-scale insulin had values persistently greater than 240 mg/dL and had to be switched to the basal/bolus regimen.[17]

SUMMARY

Perioperative glycemic control can reduce morbidity, particularly the incidence of infectious complications, in surgical patients, even in those without diagnosed diabetes. Optimal management of glycemia in the perioperative period involves applying principles of physiologic insulin replacement. Postoperatively, the transition from IV to subcutaneous insulin can be achieved through the use of basal insulin for coverage of fasting insulin needs, regardless of the patient's feeding status, and the use of rapid-acting insulin to cover hyperglycemia and nutritional needs. Management of hospitalized patients exclusively with supplemental-scale regular insulin should be abandoned.

TABLE 1
Protocol for supplemental insulin to correct hyperglycemia

Blood glucose (mg/dL)	Insulin sensitive*	Usual*	Insulin resistant*
141–180	2	4	6
181–220	4	6	8
221–260	6	8	10
261–300	8	10	12
301–350	10	12	14
351–400	12	14	16
> 400	14	16	18

* Numbers indicate the number of supplemental units of glulisine or regular insulin per dose. Supplemental dose is to be added to the scheduled dose.

Adapted, with permission, from *Diabetes Care* (Umpierrez GE, et al. Diabetes Care 2007; 30:2181–2186), Copyright © 2007 by the American Diabetes Association.

DISCUSSION

Question from the audience: As an attending physician in a preoperative clinic I'm never sure what to do with NPH insulin the morning of surgery. What guidance can you give?

Dr. Meneghini: NPH is a peaking basal insulin, and the peak can induce hypoglycemia in a patient who is NPO. If we have the opportunity, we try to switch patients previously receiving insulin therapy to a long-acting basal insulin analog, which has a much flatter action profile and is safer in the fasting state. If there is no opportunity for switching, we instruct the patient to take two-thirds of his or her usual morning dose of insulin and we initiate a D5 drip when the patient arrives at the hospital.

Question from the audience: How do you handle perioperative insulin in patients on insulin pumps?

Dr. Meneghini: The pumps provide a subcutaneous basal insulin infusion, which should, if set correctly, maintain stable blood glucose levels when the patient is NPO. Supplemental doses of insulin to correct hyperglycemia can be delivered via the usual subcutaneous practice with a syringe or insulin pen. If you are uncomfortable with pump function, or if the pump insertion site interferes with the surgery site, simply replace the 24-hour basal amount delivered via pump with an injection of glargine or detemir divided into twice-daily injections. Correct hyperglycemia with supplemental-scale insulin as per usual protocol.

Question from the audience: The manufacturer of insulin glargine makes no recommendations for its use the night before or morning of surgery. What do you recommend?

Dr. Meneghini: It depends on whether the glargine is dosed appropriately. Most patients with type 2 diabetes require 0.4 to 0.6 U/kg/day of a long-acting insulin. If they're on much more, they may be overdosed, and I would cut the basal dose by about half. Otherwise, 75% to 100% of the usual basal amount is appropriate. In type 1 diabetes, the usual replacement dose of basal insulin is 0.2 to 0.3 U/kg/day. If a patient is in this range, the basal insulin can be continued. Patients who experience hypoglycemia, or a substantial fall in blood glucose if meals are skipped or delayed, may be getting too much basal insulin and might benefit from a dose reduction when placed on NPO status.

Question from the audience: Metformin has a black-box warning advising that it be stopped at least 48 hours before surgery, but patients often come to surgery having taken metformin within the prior 12 to 24 hours. How should we manage such patients coming for elective surgery?

Dr. Meneghini: Metformin is cleared exclusively by the kidneys; its accumulation as a result of impaired kidney function (eg, due to hemodynamic instability or radiology studies using IV iodine) can result in increased lactic acid production by the liver and lactic acidosis. A patient who has taken metformin within the prior 48 hours but doesn't have a risk of hemodynamic dysfunction is at low risk of lactic acidosis if hydrated appropriately. There's not much choice if a patient needs urgent surgery and has recently taken metformin; in that case, just ensure maintenance of adequate glomerular filtration via fluid repletion to clear the drug.

Question from the audience: What's the evidence for tight glycemic control or any type of glycemic control in patients undergoing outpatient surgery or "same-day" patients who will be admitted to a regular surgical floor? Also, what would you consider maximal glucose values for a patient going into elective surgery?

Dr. Meneghini: I haven't seen any guidelines for glycemic control in patients undergoing outpatient surgery. If a patient has poor glycemic control coming into surgery, even for a minor procedure, the risk of an infectious complication may be increased. Keeping blood glucose below 180 mg/dL and avoiding electrolyte imbalances is likely sufficient in such patients. On the second question, if it's an elective procedure and can be delayed a few hours, you can certainly institute IV insulin therapy to correct hyperglycemia rapidly—just ensure adequate replacement of fluids since the patient may have had volume depletion or dehydration as a result of the preceding osmotic diuresis. Once glycemic control is improved (blood glucose < 180–200 mg/dL), the patient can proceed to surgery.

Question from the audience: What are your recommendations for resuming oral diabetes medications after surgery?

Dr. Meneghini: Once patients are tolerating their meals and being considered for discharge, you may want to resume their oral medications, assuming their admission hemoglobin A_{1c} levels were near goal. If glycemic control was inadequate preoperatively, this may be a good opportunity to adjust their prior regimen to more appropriate therapy. In some cases, this might include some form of insulin, either basal therapy or basal and supplemental insulin.

DISCLOSURES

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Postoperative pulmonary complications: An update on risk assessment and reduction

ABSTRACT

Postoperative pulmonary complications are common, serious, and expensive. Important predictors of risk are advanced age, poor health as assessed by American Society of Anesthesiologists class, and surgery near the diaphragm. Effective strategies to reduce risk include postoperative lung expansion techniques, preoperative intensive inspiratory muscle training, postoperative thoracic epidural analgesia, selective rather than routine use of nasogastric tubes, and laparoscopic rather than open bariatric surgery.

KEY POINTS

Pulmonary complications are as common as cardiac complications following noncardiac surgery.

Surgical site is the most important predictor of risk for postoperative pulmonary complications: aortic, thoracic, and upper abdominal surgeries are high-risk procedures, even in healthy patients.

Obstructive sleep apnea and pulmonary hypertension have recently been identified as risk factors, but the limited available evidence does not support preoperative screening for these conditions in patients without symptoms.

Postoperative continuous positive airway pressure therapy is effective for reducing pulmonary complications in patients who are unable to perform deep breathing or incentive spirometry exercises.

The jury is out on whether smoking cessation shortly before surgery lowers risk for postoperative pulmonary complications.

Although pulmonary complications are not as well studied as cardiac complications in the postoperative setting, they are just as common following noncardiac surgery and are even more costly. It is worthwhile to identify surgical patients most at risk of postoperative pulmonary complications and take measures known to mitigate risk. This paper discusses important risk factors to identify during a preoperative pulmonary evaluation and then focuses on recent advances in strategies for reducing postoperative pulmonary complications. Teaching questions are included throughout, along with the rationale behind their answers.

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POSTOPERATIVE PULMONARY COMPLICATIONS: WHAT ARE WE TRYING TO PREVENT AND WHY?

The definition of postoperative pulmonary complications is more variable and less intuitive than that of cardiac complications. Cardiac complications—postoperative myocardial infarction, cardiac death, and pulmonary edema—are more consistently defined and measured in clinical trials. Studies of postoperative pulmonary complications often group together pneumonia, respiratory failure, atelectasis, bronchospasm, and exacerbation of chronic obstructive pulmonary disease (COPD), making it more difficult to individually evaluate risk factors for different outcomes.

There are several reasons why it is important to consider pulmonary risk when evaluating patients preoperatively:

Pulmonary complications are as common as cardiac complications following noncardiac surgery. For example, in a secondary analysis of the cohort of noncardiac surgical patients used to validate the Revised Cardiac Risk Index,[1] Fleischmann et al found that the incidence of pulmonary complications (2.7%) was highly comparable to that of cardiac complications (2.5%).[2]

Respiratory failure is a marker of ill health and predicts further complications. Postoperative respiratory failure (often defined as the need for ventilation for more than 48 hours after surgery) is an extremely morbid event. Johnson et al compared the outcomes of patients with and without respiratory failure as a complication of surgery.[3] Among patients with respiratory failure, 26% died within 30 days, 6% had a myocardial infarction, 35% developed pneumonia, 10% developed acute renal failure, and 3% developed a deep vein thrombosis or pulmonary embolism; in contrast, rates of each of these events were lower than 2% among patients without respiratory failure.

Pulmonary complications are expensive and require lengthy hospitalization. The National Surgical Quality Improvement Program (NSQIP) compared hospitalization costs and length of stay among patients with various postoperative complications.[4] Among infectious, cardiovascular, venous thromboembolic, and pulmonary complications, pulmonary complications were by far the

most costly and, along with venous thromboembolic complications, required the longest mean hospital stay.

For these reasons, identifying patients at risk for pulmonary complications and developing a strategy to reduce the risk is clearly worthwhile.

IDENTIFYING RISK FOR PULMONARY COMPLICATIONS

Question: Which of the following is the most important risk factor for postoperative pulmonary complications?

A. High-risk surgical site
B. General anesthesia
C. COPD
D. Obesity

The correct answer is A. Pulmonary complications differ from cardiac complications in an important way: procedure-related factors are more predictive of pulmonary complications than are patient-related factors. Even healthy patients undergoing high-risk surgery are at risk for pulmonary complications. As for the other answer choices, general anesthesia and COPD are risk factors but are not as important as surgical site, and obesity has not been shown to be a risk factor at all.

Take-home points from the 2006 ACP guideline

Along with my colleagues Valerie Lawrence and John Cornell, I co-authored the systematic reviews that supported the 2006 American College of Physicians (ACP) guideline on risk assessment for and strategies to reduce perioperative pulmonary complications in patients undergoing noncardiothoracic surgery.[5–7] We reviewed the literature since 1980 that used multivariate analysis to adjust for potential confounders, and we performed a meta-analysis to estimate odds ratios for various risk factors. We then assigned letter grades to the risk factors based on the strength of evidence, as summarized in **Table 1**.[6]

Patient-related risk factors. As noted in **Table 1**, the most important patient-related risk factors identified in the ACP guideline are increasing age and increasing American Society of Anesthesiologists (ASA) classification of comorbidity.

The effect of advanced age becomes particularly notable around age 60 years and escalates from there. This effect of age differs from that for cardiac complications, for which age drops out as a risk factor after adjustment for other diseases and risk factors. For pulmonary complications, in contrast, even older patients who are healthy are at increased risk.

The ASA classification is a general index of overall morbidity that ranges from class 1 (normal healthy patient) to class 5 (moribund patient who is not expected to survive without the operation).

Notably, COPD and smoking were only minor risk factors in the ACP analysis.

Procedure-related risk factors. Surgical site was found to be the most important of any of the patient- or procedure-related risk factors. The closer the incision is to the diaphragm, the greater the risk for pulmonary complications. Aortic, thoracic, and abdominal procedures carry the highest risk **(Table 1)**, and among abdominal procedures, upper abdominal surgery (eg, cholecystectomy) is riskier than lower abdominal surgery (eg, gynecologic).

Other procedure-related risk factors identified were emergency surgery, surgery lasting more than 3 hours, use of general anesthesia, and multiple transfusions **(Table 1)**.

TABLE 1
Risk factors for postoperative pulmonary complications*

Patient-related factors†	Procedure-related factors†
Supported by good evidence	
Advanced age	Aortic aneurysm repair
ASA class ⩾ 2	Thoracic surgery
Congestive heart failure	Abdominal surgery
Functional dependency	Upper abdominal surgery
Chronic obstructive pulmonary disease	Neurosurgery
	Prolonged surgery
	Head and neck surgery
	Emergency surgery
	Vascular surgery
	Use of general anesthesia
Supported by fair evidence	
Weight loss	Perioperative transfusion
Impaired sensorium	
Cigarette use	
Alcohol use	
Abnormal chest exam	
Good evidence *against* being a risk factor	
Well-controlled asthma	Hip surgery
Obesity	Genitourinary/gynecologic surgery
Insufficient data	
Obstructive sleep apnea‡	Esophageal surgery
Poor exercise capacity	

*Adapted from the systematic review by Smetana et al[6] for the 2006 American College of Physicians guideline.
†Within each evidence category, risk factors are listed according to strength of evidence, with the first factor listed having the strongest evidence.
‡ Subsequent evidence indicates that this is a probable risk factor.
ASA = American Society of Anesthesiologists

Newly identified risk factors

Question: Which of the following has recently been identified as a risk factor for postoperative pulmonary complications?

A. Epidural anesthesia
B. Insulin-treated diabetes
C. Obstructive sleep apnea
D. Immobility

The correct answer is C. There is no evidence that epidural anesthesia or insulin-treated diabetes are risk factors. Immobility seems intuitively correct but has not emerged as

TABLE 2
Select independent predictors of respiratory failure from the updated respiratory failure index*

Risk factor	Odds ratio
ASA class 3 (severe systemic disease)	2.9
ASA class 4 or 5 (severe disease that is a constant threat to life, or moribund status in which survival is not expected without operation)	4.9
Orofacial surgery	6.6
Work RVU > 17 (proxy for high-complexity procedures)	4.4
Albumin ⩽ 3.5 g/dL	1.5
Aneurysm surgery	1.6
Age > 65 years	2.1
Smoker	1.1

*Adapted from Johnson et al.[3]
ASA = American Society of Anesthesiologists; RVU = relative value unit (based on Medicare definitions)

a risk factor among high-quality studies in the literature.

Obstructive sleep apnea. The role of obstructive sleep apnea was unclear prior to publication of new data in the last couple of years. Hwang et al enrolled 172 patients who were soon to have elective surgery and had at least two of four clinical features of obstructive sleep apnea (snoring, daytime somnolence, witnessed apnea event, or crowded oropharynx).[8] Patients underwent nocturnal oximetry before surgery and were divided into two groups based on number of desaturation episodes per hour. Patients with five or more desaturations had markedly higher rates of postoperative respiratory complications (8 complications among 98 patients) than did patients with fewer than five desaturations (1 complication among 74 patients). The presence of five or more desaturations was also associated with higher rates of cardiac, gastrointestinal, and bleeding complications. Though this was a small study, its results suggest a significant association between obstructive sleep apnea and pulmonary complications.

The issue of whether to screen patients for obstructive sleep apnea before major noncardiac surgery is still unresolved.

Pulmonary hypertension has also been identified as a risk factor in recent years with the publication of two studies that estimated its impact on morbidity and mortality after major noncardiac surgery.[9,10] One of the studies, a retrospective database review, found a 28% incidence of respiratory failure among 145 surgical patients with pulmonary hypertension.[9] In the other study, a prospective case-control trial, respiratory failure occurred in 21% of patients with pulmonary hypertension compared with only 3% of matched controls.[10] In the case-control study, pulmonary hypertension was also associated with significantly elevated rates of heart failure and in-hospital death.

The results of these studies do not support preoperative screening for undiagnosed pulmonary hypertension, but they do underscore the need to recognize established pulmonary hypertension as an important risk factor for postoperative complications.

AN UPDATED INDEX FOR RESPIRATORY FAILURE

Several years ago, investigators from the Veterans Affairs Medical Centers developed a respiratory failure index using a design similar to those of well-established indices for cardiac risk.[11] The same group also developed a separate risk index for pneumonia.[12]

This respiratory failure index was recently updated[3] to reflect experience from private and academic hospitals, making the results more generally applicable. The researchers evaluated data from 180,000 patients undergoing major general or vascular surgery (defined according to the NSQIP) over a 3-year period. Respiratory failure was defined as requiring at least 48 hours of ventilation or unplanned reintubation.

Of the 45 potential risk factors evaluated, 28 were identified as independent risk factors for respiratory failure on the basis of a multivariate analysis. Each factor was weighted according to risk and combined into a point-based index, which performed very well in predicting postoperative respiratory failure: the highest of the three broad point-based risk groups had a 6.8% risk of respiratory failure, while the lowest-risk group had a 0.1% risk. Important observations are listed in **Table 2**.[3]

Comparison and contrast with the ACP guideline

Question: How does the updated respiratory failure index differ most significantly from the 2006 ACP guideline?

A. New index places greater emphasis on ASA class
B. New index offers a simplified weighted point scheme
C. New index ranks low albumin as a less important risk factor
D. New index attributes low risk to cigarette use

The correct answer is C: low albumin is a minor risk factor in the respiratory failure index, whereas it was one of the single most important predictors in the ACP guideline. As for the other answer choices, the new index places about the same emphasis on ASA class and cigarette use as does the ACP guideline, and it does *not* offer a simplified approach, as it incorporates 28 different factors.

Overall, most risk factors were similar in the updated respiratory failure index and the ACP guideline, but the index differs in several important ways:

- The index assigns less risk to low albumin, functional dependence, and congestive heart failure
- The index assigns greater risk to orofacial surgery
- The index identifies several new risk factors—high-complexity surgery, preoperative sepsis, ascites, and hypernatremia (serum sodium > 145 mmol/L).

STRATEGIES FOR RISK REDUCTION

The 2006 ACP guideline assigned evidence grades to various strategies to reduce risk for postoperative pulmonary complications based on a systematic review of the literature (**Table 3**).[7] The only strategy that was supported by good evidence was postoperative lung expansion modalities, which comprise incentive spirometry, deep breathing exercises, intermittent positive-pressure breathing, and continuous positive airway pressure. Fair evidence supported selective postoperative use of nasogastric tubes and use of short-acting neuromuscular blockade.

TABLE 3
Strength of evidence for strategies to reduce risk of postoperative pulmonary complications*

Supported by good evidence	Postoperative lung expansion modalities
Supported by fair evidence	Selective postoperative nasogastric tube use Short-acting neuromuscular blockade
Balance of benefit and harm too close to justify recommendation	Laparoscopic (vs open) operation†
At least fair evidence that strategy does *not* reduce risk or harm outweighs benefit	Routine total parenteral or enteral nutrition Right heart catheterization
Insufficient or conflicting data	Intraoperative neuraxial blockade Postoperative epidural analgesia‡ Smoking cessation

*Adapted from the systematic review by Lawrence et al[7] for the 2006 American College of Physicians guideline.
†More recent data provide fair evidence to support this risk factor
‡More recent data provide good evidence to support this risk factor

Postoperative CPAP: Good option when exercise ability is limited

Among the postoperative lung expansion modalities, continuous positive airway pressure (CPAP) is particularly useful for patients who are unable to perform deep breathing or incentive spirometry exercises. A recent systematic literature review identified nine randomized controlled trials of CPAP vs standard therapy in a total of 654 patients undergoing abdominal surgery.[13] Meta-analysis of these studies showed that CPAP was associated with significant reductions in the risk of overall postoperative pulmonary complications (odds ratio [OR] = 0.66; 95% CI, 0.52–0.85), atelectasis (OR = 0.75; 95% CI, 0.58–0.97), and pneumonia (OR = 0.33; 95% CI, 0.14–0.75) relative to standard therapy.

Use nasogastric tubes selectively

Nasogastric tubes can be used either routinely following abdominal surgery or only in select patients—eg, those who have symptomatic abdominal distention or nausea. The difference is important since nasogastric tubes may potentially increase the risk of aspiration and thus lead to a pulmonary complication. Nelson et al conducted a meta-analysis of 24 studies that compared routine nasogastric tube use in abdominal surgery with selective use based on symptoms or abdominal distention.[14] They found that routine use was associated with a significant increase in postoperative pulmonary complications (OR = 1.45; 95% CI, 1.08–1.93) relative to selective use, without achieving any of its intended goals.

Laparoscopic vs open surgery: Evidence begins to follow intuition

Intuitively, it seems that laparoscopic procedures should reduce risk for postoperative pulmonary complications compared with open surgical procedures, as they are associated with less postoperative pain, which should facilitate deep breathing and improve postoperative lung volumes. Nevertheless, evidence for whether laparoscopic surgery reduces the risk of pulmonary complications has been mixed until recently.

In 2008, however, Weller and Rosati published an analysis of a nationally representative database of 19,156 patients who underwent bariatric surgery in 2005.[15] After adjusting for comorbidities, they found that the rate of postoperative pulmonary complications was nearly double if patients underwent open surgery as opposed to laparoscopic surgery (OR = 1.92; 95% CI, 1.54–2.38). Open surgery was also associated with significantly higher rates of sepsis, cardiovascular events, and reoperation compared with laparoscopic procedures. This study suggests that choosing laparoscopic procedures is another strategy that may reduce pulmonary complication rates, at least in the setting of bariatric surgery.

Postoperative thoracic epidural analgesia

Question: Thoracic epidural analgesia reduces rates of which of the following?

A. Pneumonia following abdominal aortic aneurysm repair
B. Pulmonary complications following coronary bypass surgery
C. Respiratory failure following abdominal surgery
D. All of the above

The correct answer is D. Thoracic epidural analgesia is another important strategy for reducing postoperative pulmonary complications, as demonstrated by a 2007 systematic literature review by Liu and Wu.[16] Their analysis showed that rates of pneumonia, respiratory failure, and pulmonary complications overall were reduced by approximately one-third to more than one-half with the use of postoperative thoracic epidural analgesia in patients undergoing aortic aneurysm repair, coronary bypass surgery, and abdominal surgery.

Smoking cessation: The jury is still out

Whether preoperative cigarette cessation reduces pulmonary complication rates has been controversial over the past decade. Early reports showed that among patients who smoke, those who quit shortly before surgery actually had higher complication rates than patients who continued to smoke. The most reasonable explanation seems to be that many patients who stop smoking report increased coughing and sputum production for the first month or two. Selection bias also may have played a role in these findings.

More recently, two randomized trials studied the impact of perioperative smoking intervention programs involving counseling and nicotine replacement.[17,18] Unfortunately, both studies primarily studied patients undergoing low-risk procedures and were insufficiently powered to show a difference in pulmonary complication rates. The question of whether smoking cessation is an effective strategy to reduce postoperative pulmonary risk remains unanswered.

Preoperative intensive lung expansion: A promising new intervention

While the effectiveness of postoperative lung expansion techniques is undisputed,[7] *preoperative* lung expansion—also known as inspiratory muscle training—has only recently been investigated. Hulzebos et al randomized 279 patients undergoing coronary artery bypass graft surgery who were at high risk for developing pulmonary complications to either usual care or inspiratory muscle training.[19] The latter intervention involved 20 minutes per day of incentive spirometry, active breathing, and forced expiration techniques for at least 2 weeks prior to surgery. Rates of high-grade postoperative pulmonary complications were cut in half (OR = 0.52; 95% CI, 0.30–0.92) and rates of pneumonia were reduced by 60% (OR = 0.40; 95% CI, 0.19–0.84) in patients who received inspiratory muscle training relative to the usual-care group.

In clinical practice, preoperative inspiratory muscle training can be done in a chest physical therapy outpatient setting or a pulmonary rehabilitation clinic in the hospital.

SUMMARY

There have been a number of significant recent developments in the perioperative management of pulmonary complications:

- Obstructive sleep apnea has been confirmed as a risk factor, and pulmonary hypertension has emerged as a novel risk factor.
- An updated respiratory failure index has emerged as a useful research tool to identify high-risk patients and to ensure uniform risk stratification in future research.
- Evidence has mounted for the effectiveness of several risk-reduction strategies, including the use of laparoscopic procedures for bariatric surgery; selective use of nasogastric tubes; postoperative thoracic epidural analgesia; and intensive preoperative inspiratory muscle training.

DISCUSSION

Question from the audience: I do preoperative evaluations in an orthopedic ambulatory surgery center. Our surgeons often tell me, "Just order preoperative pulmonary function tests," or, "Get a blood gas." How should I respond?

Dr. Smetana: This is an area of some controversy, but in general, spirometry does not add much to a preoperative risk assessment that is based on a history and physical exam. Usually if the spirometry is abnormal, it will not be a surprise after careful clinical assessment. Arterial blood gases have no role in routine preoperative assessment.

Question from the audience: A chest x-ray is often requested preoperatively, but is it a necessary study?

Dr. Smetana: The data for preoperative chest x-rays are fairly poor and don't allow us to assess whether they accurately predict complication rates. Most studies on chest x-rays have looked at how they affect preoperative management—eg, whether they change the anesthesia or even the surgery—and have shown that preoperative management changes in only about 1% to 2% of cases. So the chest x-ray is a fairly low-yield test in this setting.

One could argue that a preoperative chest x-ray might provide a baseline for postoperative comparison, but actually it is not usually helpful in this regard. Having a baseline does not make it easier to correctly diagnose pneumonia postoperatively, for example. Abnormal chest x-rays correlate with higher risk, but most patients with abnormal films would be suspected of being at higher risk anyway based on findings from the clinical assessment.

Question from the audience: Many primary care doctors in my hospital screen patients for pulmonary hypertension, but this raises the question of what to do with any information gained. What do you tell patients? Anesthesiologists?

Dr. Smetana: I don't recommend preoperative screening for pulmonary hypertension unless there is some specific clinical reason to look for it. We don't know if the perioperative risks that I described for patients with diagnosed or symptomatic pulmonary hypertension would also apply to patients with unrecognized, asymptomatic pulmonary hypertension that happened to be identified by screening.

Patients with pulmonary hypertension are at very high risk, especially for respiratory failure. But we don't have any risk-reduction strategies specific to these patients, although I would recommend applying the general risk-reduction strategies that I discussed.

Question from the audience: I saw a man at my high-risk preoperative clinic who scored normally on a 6-minute walk test but then was found sound asleep when I was ready to see him a little while later. I suspected he had undiagnosed sleep apnea, and therefore had an increased risk of postoperative pulmonary complications, but what evidence would I have to delay his surgery to diagnose

the sleep apnea and stabilize him on CPAP?

Dr. Smetana: For a patient with clinically suspected but undiagnosed sleep apnea, we have some evidence that the diagnosis should be pursued before surgery is performed.[8] If the surgery were elective, it would be appropriate to have the patient evaluated and, if obstructive sleep apnea were diagnosed, treated in the customary way with CPAP. For patients who are hospitalized after surgery, CPAP can be continued as soon as possible in the hospital.

I would not have made this recommendation a few years ago, but now the evidence is more compelling. However, at this point I would not recommend routine preoperative screening of all patients for sleep apnea. Ongoing research is looking at this question.

Follow-up question: How long should surgery be delayed to optimize the patient on CPAP?

Dr. Smetana: Risk for postoperative respiratory failure is reduced very quickly after initiating CPAP therapy. A week would probably be sufficient, but there are no good data to specifically address that question.

Question from the audience: What about patients with asthma who are undergoing surgery—which ones benefit from stress-level steroids and preoperative nebulizer therapy?

Dr. Smetana: Surprisingly, asthma—if well controlled—is not a risk factor for postoperative pulmonary complications. Patients within 80% of their predicted or personal best peak flow appear to have a risk similar to that of patients without asthma. For patients with uncontrolled or poorly controlled asthma, the general rule is the same as for patients with COPD: treat them the same as if they weren't having surgery. If a patient with asthma has a clinical indication for corticosteroids based on his or her condition, give corticosteroids whether or not surgery is planned. Corticosteroids are safe and do not raise the risk of postoperative wound complications. But we have no evidence to support routine use of steroids for all patients with asthma simply because elective surgery is planned.

Follow-up question: Do you optimize poorly controlled patients with oral prednisone for several days preoperatively, or do you use a stress protocol?

Dr. Smetana: For a patient whom you would normally treat with an outpatient course of prednisone, you should do just that. For a patient with an exacerbation severe enough to require admission for intravenous steroids and inhaled nebulizer therapy, then you should use that strategy. If the surgery is elective, it should be delayed until the patient is at his or her personal best.

DISCLOSURES

Dr. Smetana has indicated that he has served on an advisory board for SafeMed. All conflicts of interest have been resolved.

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Postoperative gastrointestinal tract dysfunction: An overview of causes and management strategies

ABSTRACT

Postoperative gastrointestinal (GI) tract dysfunction is common and has a complex, multifactorial pathogenesis. Perioperative administration of targeted amounts of fluid to optimize ventricular filling and end-organ perfusion has consistently been shown to improve mortality and other outcomes, particularly GI tract perfusion and function. The choice of fluid loading affects postoperative recovery, with colloid showing superiority over crystalloid, and lactated Ringer's solution proving better than normal saline. Other methods of reducing postoperative GI tract dysfunction with some proven degree of success include simple, low-cost interventions such as early initiation of oral feeding, early use of laxatives, and gum chewing. There is no evidence that prophylactic nasogastric decompression accelerates return of bowel function.

KEY POINTS

GI tract dysfunction is the most common type of postoperative morbidity and frequently delays hospital discharge.

Low-grade hypovolemia leading to gut ischemia is a common but neglected mechanism of postoperative GI tract dysfunction.

Administration of colloid to achieve target levels of cardiac output improves gut perfusion and lowers the incidence of GI tract dysfunction.

Doppler-guided fluid management reduces GI morbidity and length of hospital stay in surgical patients.

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Tolerance of an enteral diet is one of the fundamental components of postoperative wellness, along with the ability to mobilize freely without supplemental oxygen and a readiness to be discharged home as soon as possible. Accordingly, postoperative gastrointestinal (GI) tract dysfunction is best defined as intolerance of an enteral diet after having been tolerant of one preoperatively. I prefer the term *postoperative GI tract dysfunction* over *postoperative ileus*, as ileus is ill defined, covering a wide spectrum of clinical signs and having a range of published incidences so broad (5%–100%) that it defies useful discussion.

Table 1 presents a schema for classifying postoperative GI tract dysfunction.[1] This review focuses on the causes and management of early-onset GI dysfunction—ie, developing within 6 to 48 hours of surgery—which can develop into persistent dysfunction (> 72 hours) and thereby prolong the hospital stay and potentially manifest systemically. This review will not address immediate and transient postoperative nausea and vomiting, which is distinct from intolerance of an enteral diet and has been reviewed extensively elsewhere.[2]

GI DYSFUNCTION: A COMMON POSTOPERATIVE MORBIDITY

Postoperative GI tract dysfunction is common, as illustrated by a large prospective cohort study at Duke University Medical Center[3] that used the Postoperative Morbidity Survey (which has since been validated[4]) to document complications following major noncardiac surgery (ie, anticipated duration > 2 hours and anticipated blood loss > 500 mL). Hospital discharge was delayed in 27% of the study's 438 patients as a result of a postoperative complication, and GI dysfunction was the most common type of complication overall and on postoperative days 5, 8, and 15. Episodes of GI dysfunction ranged from intolerance of an enteral diet to ischemic gut resulting in multiple organ failure.[3]

A similar prospective cohort study conducted in the United Kingdom yielded comparable findings, with GI dysfunction being the most common type of postoperative complication reported.[4] This study served to validate the Postoperative Morbidity Survey, which is now used worldwide to describe morbidity after major surgery.

Figure 1 presents rates of postoperative GI dysfunction relative to other common types of postoperative complications in both the Duke study and the UK study.[3,4]

A MULTIFACTORIAL PATHOGENESIS

The pathophysiology of postoperative GI tract dysfunction can be ischemic, metabolic, toxic, neurogenic, myogenic, pharmacologic, or mechanical.

It is important to recognize that in many cases no single factor explains the whole story behind postsurgical GI tract dysfunction, and none of these factors is an ipso facto cause of such dysfunction. For instance, a "mechanical" pathogenesis refers to any manipulation of the gut that causes an inflammatory response in the gut's various layers, resulting in injury.[5,6] However, GI tract dysfunction commonly occurs after operations (including laparoscopic procedures) in which the gut was not handled at all. Similarly, in terms of a pharmacologic pathophysiology, while opioids can affect GI propulsion and cause constipation,[7,8] avoidance of opioid use does not ensure prevention of GI tract dysfunction. Moreover, opioid abusers do not generally exhibit intolerance of enteral nutrition.

A common mechanism that is often ignored is perioperative gut ischemia resulting in low-grade injury. Low-grade hypovolemia can cause loss of perfusion to the tip of the microvillus, triggering apoptosis and potentially necrosis, which typically requires about 3 days for recovery. An experiment among 6 healthy volunteers who underwent elective hemorrhage (25% of blood volume removed) over 1 hour demonstrated that gastric tonometry was an earlier indicator of hypovolemia than were commonly measured hemodynamic variables such as invasive blood pressure, stroke volume, heart rate, and lactate and arterial blood gas measurements.[9]

FLUID LOADING AIDS GI RECOVERY

A targeted increase of intravascular volume and global blood flow perioperatively has been shown repeatedly to improve surgical outcome.[10–24] In clinical trials, the most common intervention to achieve the predetermined hemodynamic goal has been fluid loading. Overall, targeted increases in perioperative global blood flow have been associated with reduced mortality,[25] with the presumed mechanism being maintenance of end-organ perfusion.

The role of end-organ perfusion maintenance was confirmed in a controlled study of 60 patients undergoing cardiac surgery in which perioperative fluid loading (with colloid) maintained gut perfusion as measured by gastric tonometry, whereas a control group had a reproducible reduction in gut perfusion.[15] Fluid loading was associated with a significant reduction in the incidence of gut mucosal hypoperfusion—from 56% to 7%—and significant reductions in the incidence of minor and major complications, mean days in the hospital, and mean days in the intensive care unit.

TABLE 1
Schema for classifying postoperative gastrointestinal tract dysfunction

Onset
- Immediate (< 6 hours)
- Early (6–48 hours)
- Delayed (2–7 days)

Duration
- Transient (< 72 hours)
- Persistent (> 72 hours)

Severity
- Minor—Tolerant of adequate enteral diet
- Moderate—Intolerant of adequate enteral diet
- Severe—Systemic manifestation/prolongation of hospital stay/life-threatening

Reprinted, with permission, from *Anesthesia and Analgesia* (Mythen MG. Postoperative gastrointestinal tract dysfunction. Anesth Analg 2005; 100:196–204).[1]

Fluid type matters

The type of intraoperative fluid loading is a factor in postoperative recovery.

Colloid vs crystalloid. Moretti et al found that colloid (6% hetastarch in saline or 6% hetastarch in balanced salt) was superior to crystalloid (lactated Ringer's solution) in preventing nausea, severe pain, vomiting, periorbital edema, and double vision postoperatively ($P < .05$ for all) despite comparable hemodynamic profiles.[26]

Ringer's vs normal saline. Williams et al compared intravenous lactated Ringer's solution with normal saline (0.9% sodium chloride) in a randomized study of healthy volunteers.[27] The group that received normal saline demonstrated central nervous system changes and a much higher incidence of abdominal discomfort, a finding consistent with the toxic properties of chlorine to the gut.

Balanced electrolyte solutions vs saline-based fluids. Wilkes et al compared crystalloid and colloid solutions with physiologically balanced electrolyte formulations (Hextend) against saline-based fluids (Hespan) in elderly surgical patients.[28] They found that balanced electrolyte solutions were superior in improving gastric mucosal perfusion and preventing hyperchloremic metabolic acidosis. As a result of a reduction in GI tract perfusion, postoperative vomiting was more frequent in the group receiving saline-based fluids.

Evidence for Doppler-guided fluid management

Use of esophageal Doppler ultrasonography to guide fluid administration intraoperatively is fairly common

GI complications dominate in two large studies of postoperative morbidity

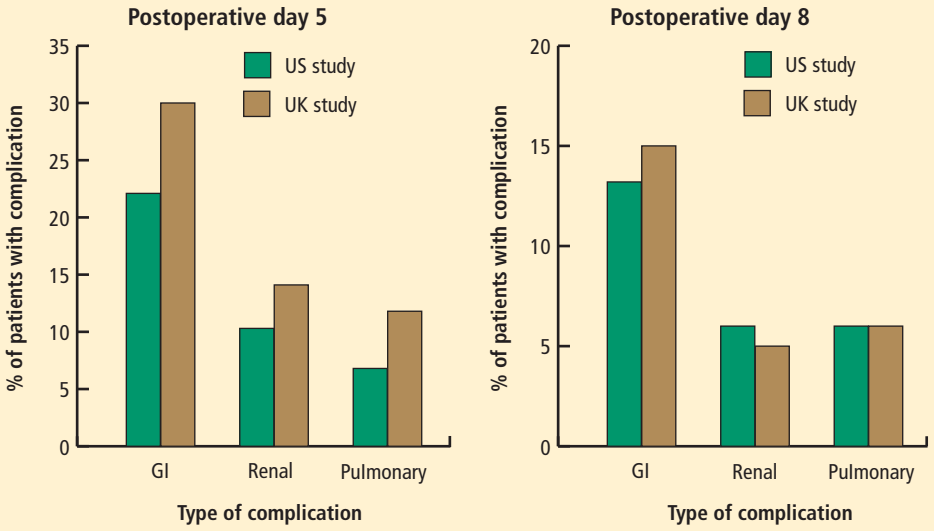

FIGURE 1. Gastrointestinal (GI) tract dysfunction was the most common postoperative complication at both 5 days and 8 days in two large prospective cohort studies of patients undergoing major noncardiac surgery in the United States[3] and the United Kingdom,[4] with rates more than double those of renal or pulmonary complications.

Adapted from a PowerPoint slide developed by Dr. M.P.W. Grocott.

in the United Kingdom and is based on randomized controlled trials showing that Doppler-guided colloid administration to maximize stroke volume reduces morbidity and length of hospital stay in surgical patients. In one government-supported study of 128 colorectal resection patients, Doppler-guided small boluses of colloid increased stroke volume, cardiac output, and oxygen delivery compared with conventional (central venous pressure–based) fluid management.[29] Gut function improved significantly faster with Doppler-guided fluid management as evidenced by a more rapid return of flatus, opening of bowels, and achievement of a full diet, and by faster discharge from the hospital. The incidence of GI complications was reduced from 45.3% in the conventional management group to 14.1% in the Doppler group. The relative risk of GI tract dysfunction was 5.3 times higher with conventional management.

OTHER STRATEGIES TO REDUCE POSTOPERATIVE GI DYSFUNCTION

In addition to fluid loading, a number of other methods have been studied in an attempt to reduce the incidence of postoperative GI tract dysfunction.

Epidural neostigmine: Improvement in some measures

Epidural neostigmine was compared with saline control in a randomized study of 45 patients scheduled for abdominal aortic surgery.[30] Time to first bowel sounds and time to first flatus were significantly shorter in the neostigmine group, but time to first defecation and the incidence of postoperative complications were similar between the groups.

Laxatives speed return of GI function

In a study of 53 women undergoing fast-track hysterectomy, recovery of GI tract function was faster in those randomized to receive laxatives (magnesium oxide and disodium phosphate) starting 6 hours postoperatively compared with those receiving placebo.[31] Median time to first defecation was reduced from 69 hours in the placebo group to 45 hours in the laxative group ($P < .0001$), and postoperative hospitalization was shortened by a median of 1 day in the laxative group. There were no significant between-group differences in pain scores, postoperative nausea and vomiting, or the use of morphine or antiemetics.

Fentanyl reduces gastric myoelectrical activity

Intravenous administration of the opioid fentanyl significantly reduced gastric myoelectrical activity in an uncontrolled study of 20 patients undergoing elective surgery, but wide variation in effect was observed among patients.[32] There was no correlation between the myoelectrical outcome and the presence of polymorphisms of the mu-opioid receptor gene.

Systemic lidocaine accelerates return of bowel function

Perioperative administration of systemic lidocaine, given as a 1.5-mg/kg bolus followed by continuous infusion at 2 mg/min, accelerated the return of bowel function and shortened the length of hospital stay compared with placebo in a randomized study of 60 colorectal surgery patients.[33]

Early oral feeding cuts length of stay

A recent meta-analysis of randomized trials found that early oral intake of fluids and food after major abdomi-

nal gynecologic surgery was associated with an increased risk of nausea but a reduced length of hospital stay.[34] The authors recommended an individualized approach to early feeding, and called for cost-effectiveness and patient satisfaction studies.

Mosapride improves gastric emptying

Mosapride is a 5-HT_4 agonist that has been shown to improve gastric emptying in a randomized controlled study of 40 patients undergoing laparoscopic colectomy.[35] Time to first postoperative bowel movement, time to maximal gastric emptying rate, and postoperative hospital stay were all significantly shorter in patients receiving mosapride versus control. Mosapride is not currently approved for marketing in the United States.

Mu-opioid antagonists: Some show promise, others don't

Mu-opioid receptor antagonists have been developed primarily to reverse opioid-induced bowel dysfunction. Commercially available drugs in this class include alvimopan, methylnaltrexone, nalbuphine, and naloxone. A recent meta-analysis of 23 randomized controlled studies of these agents for opioid-induced bowel dysfunction concluded that alvimopan and methylnaltrexone were superior to placebo but that evidence was insufficient for the safety or efficacy of naloxone and nalbuphine.[36]

Nasogastric decompression: Usually more harm than benefit

Prophylactic nasogastric decompression is an intervention devoid of evidence. A meta-analysis of 33 studies encompassing 5,240 patients randomized to routine nasogastric tube placement, selective nasogastric tube use, or no nasogastric tube placement after abdominal surgery found no advantage to routine nasogastric tube use.[37] In fact, patients not receiving routine tube placement had a significantly earlier return of bowel function and a significant decrease in pulmonary complications. The incidence of anastomotic leak was not different among the groups. Routine tube use was associated with a lower incidence of vomiting but more patient discomfort. The clear conclusion is that, in most situations, elective placement of a nasogastric tube only causes harm.

Chewing gum: A simple intervention that works

In a recent meta-analysis of five randomized controlled trials, the simple intervention of gum chewing after colorectal surgery significantly accelerated the time to flatus and time to defecation, and was associated with a nonsignificant trend toward a shorter postoperative hospital stay.[38]

CONCLUSIONS ON MANAGEMENT

Traditional measures intended to reduce the incidence of postoperative GI tract dysfunction—administration of prokinetic drugs, placement of nasogastric tubes, avoidance of food and fluids—are not beneficial and are often harmful. Administration of targeted amounts of fluid to optimize ventricular filling and end-organ perfusion has repeatedly been demonstrated to improve outcomes, particularly those related to GI tract perfusion and function. Administration of larger volumes of colloid, to achieve predetermined increases in stroke volume, improves gut perfusion and reduces the incidence of GI tract dysfunction.

Many simple, inexpensive, and readily available strategies for preventing or reversing postoperative GI tract dysfunction have some degree of evidence-based support and should be considered. I would recommend a multimodal approach that includes a limited surgical incision, regional local anesthesia without use of opioids, immediate postoperative mobilization, early enteral feeding, and postoperative gum chewing.[1] Such an approach promises to reduce GI tract dysfunction and other postoperative complications as well as to shorten hospital stay.

DISCUSSION

Question from the audience: You mentioned the selective use of nasogastric tubes. In which patients would you use them?

Dr. Mythen: For upper GI surgeries—esophagectomy, for example—a nasogastric tube is inevitable. Beyond that, the specific indications for tube placement are very limited. At our institution, we no longer place nasogastric tubes following the vast majority of GI tract operations, with esophagectomy being the exception.

Question from the audience: Would you comment on the selective contribution of thoracic epidural analgesia with respect to early feeding after abdominal or colon surgery?

Dr. Mythen: If you're an enthusiast for thoracic epidurals, you can present the literature in a way that definitively demonstrates a huge advantage to thoracic epidurals. When they work well for the individual, they are fantastic, but you must have a very effective team and system to deliver success to the whole patient population. At our institution the failure rate 20 to 24 hours postoperatively is about 50%.

Question from the audience: I'm an internist and I've never heard of the esophageal Doppler-directed fluid bolus protocol—or of anyone using colloids at all. Is that something that is generally practiced in the United States?

Dr. Mythen: Some institutions are practicing goal-directed fluid management now. If you measure stroke volume and give small boluses of colloid, you need a lot less fluid to achieve a higher intravascular volume and goal. At

our institution, we've repackaged it as "goal-directed fluid restriction" to gain acceptance among surgeons. Uptake has been slower in the United States, though studies here have reinforced the message and been supported by editorials. Guessing about fluids, which we've done historically, is not very smart. One thing that differentiates an anesthesiologist from an anesthetic technician is the ability to give goal-directed fluid therapy. The ability to act in a targeted fashion makes it possible to achieve an appropriate physiological goal, but it is more difficult.

Question from the audience: In terms of maintenance fluids and chloride toxicity, is there an alternative to D5 half-normal saline for maintenance fluid?

Dr. Mythen: We don't have a very good postoperative maintenance fluid; D5 half-normal with some potassium is probably as good as it gets at present. I emphasize getting patients to drink as quickly as possible. If they're not drinking (not using the GI tract), they need a very high level of physician input because fluid balance *is* rocket science. The GI tract is very clever. Once patients are drinking and eating, they're fine, but if they still have an intravenous line in, close attention is required.

Question from the audience: Would you use lactated Ringer's solution in a patient who is just not eating or drinking?

Dr. Mythen: I do, actually. I tend to mix it in with some D5 half-normal saline because lactated Ringer's is a great solution. The body can use the lactate to make sugar if necessary. The brain is one of the few organs that will metabolize lactate.

Follow-up question: Would you use it at a lower rate to prevent volume overload?

Dr. Mythen: Yes, at 60 mL/hr. The important thing is that if intravenous fluids are still required, the patient needs to be in a fairly supervised, high-dependency environment. You must address the real issue: Why aren't they drinking? If the patient is not drinking postoperatively, someone's done a bad job or there is something that needs fixing.

Question from audience: In the operating room, do you have a preference between albumin and a high-molecular-weight hetastarch like Hextend?

Dr. Mythen: Europe is slightly different in its choice of colloids. We've pretty much abandoned the high-molecular-weight starches. We do not use albumin at our institution for cost reasons, and we can't find any evidence to support its use. We would have to close one intensive care unit bed to be able to afford using albumin. We use low-molecular-weight hydroxyethyl starches, which I believe are now coming into the United States. They have no major coagulation effect.

DISCLOSURES

Dr. Mythen has indicated that he has received grants/research support from Deltex Medical and speaking honoraria and travel expenses from Fresenius-Kabi and B. Braun. All conflicts of interest have been resolved.

This article was developed from an audio transcript of Dr. Mythen's lecture at the 4th Annual Perioperative Medicine Summit. The transcript was edited by the *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness, and was then reviewed, revised, and approved by Dr. Mythen.

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Case studies in perioperative management: Challenges, controversies, and common ground

ABSTRACT

This collection of case studies is designed to illustrate challenging and controversial aspects of perioperative medicine. The authors guide readers through four case narratives punctuated by practical multiple-choice questions followed by the authors' commentary on the evidence supporting various answer choices and related considerations. The objective is to examine issues and key evidence that should inform the decision-making process in important aspects of perioperative management.

CASE 1: RADICAL PROSTATECTOMY IN A MAN WITH ACUTE DEEP VEIN THROMBOSIS

A 69-year-old man is seen in the preoperative clinic 1 week before a scheduled radical prostatectomy. He has been diagnosed with femoral deep vein thrombosis (DVT) following a complaint of calf soreness.

Question 1.1: *How would you treat him for his DVT?*

A. Intravenous (IV) unfractionated heparin (UFH)
B. Low-molecular-weight heparin (LMWH)
C. Inferior vena cava (IVC) filter
D. Combination of pharmacologic therapy and then an IVC filter

Dr. Steven L. Cohn: The latest edition of the American College of Chest Physicians (ACCP) evidence-based guidelines on antithrombotic therapy recommends the use of therapeutic-dose subcutaneous LMWH over IV UFH for initial treatment of acute DVT in the outpatient or inpatient setting.[1] Additionally, indications for an IVC filter include the prevention of pulmonary embolism (PE) in a patient with DVT who requires full-dose anticoagulation but cannot receive it, as would be the case here if the patient proceeds with surgery as scheduled. So if surgery will be postponed, the best option is LMWH; if surgery will not be postponed, the best answer is a combination of pharmacologic therapy with low-dose LMWH and an IVC filter, preferably a retrievable one.[2]

Question 1.2: *You recommend postponing surgery, but the patient is worried about metastatic disease. For how long should surgery be postponed?*

A. 2 weeks
B. 1 month
C. 2 months
D. 3 months
E. 6 months

Dr. Cohn: In the absence of anticoagulation therapy, the risk of venous thromboembolism (VTE) is approximately 40% (~1% per day) during the first month following an acute VTE and then declines markedly, to approximately 10%, during the second and third months following the acute event.[3] Therefore, I would suggest that the patient wait at least 1 month after an acute DVT before undergoing surgery.

Dr. BobbieJean Sweitzer: This patient is in a hypercoagulable state, and the surgery itself will induce excess hypercoagulability. With a femoral DVT already present, his risk of VTE or PE is likely to be greater than 1% per day during the first month. If he does develop a PE, it may potentially be fatal.

Question 1.3: *According to the patient, the surgeon and the internist discussed options, but the surgeon "doesn't believe in filters" and the patient doesn't want to postpone the procedure, despite your recommendation. Two weeks later he shows up for surgery having stopped his LMWH 3 days before. What would you do?*

A. Cancel the surgery and restart full-dose LMWH
B. Proceed with prophylactic-dose LMWH
C. Proceed after giving a full therapeutic dose
D. Insert a filter and give DVT prophylaxis

Dr. Cohn: A bridging protocol should have been discussed with the surgeon and anesthesiologist before the procedure. Therapeutic levels of LMWH persist as long as 18 hours after discontinuation; therefore, the ACCP recommends interrupting LMWH 24 hours before surgery.[4]

Dr. Sweitzer: The lack of a bridging protocol in this case created a problem. The patient was afraid to continue anticoagulation after hearing the internist and surgeon disagree about the plan, and thus stopped it entirely, and he did not want to delay surgery because he was fearful of metastasis. The surgeon was adamant that IVC filters don't work. The internist was concerned that

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the patient was at high risk for a PE. Even though the documented risk of postponing radical prostatectomy for a short time is inconsequential, I was convinced that the patient would not believe this if metastasis were to develop in the future.

Question 1.4: *How would you have managed his anticoagulation perioperatively?*

A. Stop LMWH 12 hours before surgery and restart at full dose 12 to 24 hours after surgery
B. Stop LMWH 24 hours before surgery and restart at full dose 24 hours after surgery
C. Stop LMWH 24 hours before surgery and restart prophylactic dosing 12 to 24 hours after surgery, and then full-dose LMWH in 48 to 72 hours
D. Stop LMWH 24 hours before surgery and restart at full dose 72 hours after surgery

Dr. Cohn: The correct timing for stopping LMWH is 24 hours before surgery. As for how to resume anticoagulation in patients at high risk for VTE or those undergoing major surgery, the latest ACCP guidelines recommend the following[4]:

- Reinitiation of anticoagulation 12 to 24 hours postoperatively, assuming adequate hemostasis in patients not at high risk for bleeding
- Use of a prophylactic dose or no anticoagulation for up to 72 hours if the patient is at high risk for bleeding.

These recommendations are a departure from previous practice, in which we routinely restarted anticoagulation 6 to 12 hours postoperatively.

Dr. Sweitzer: According to guidelines from the American Society of Regional Anesthesia and Pain Medicine (ASRA),[5] if twice-daily LMWH is stopped 24 hours ahead of time (as long as patients have normal renal function), it is safe to perform epidural or spinal anesthesia, if either is an option. If full-dose UFH is used, the partial thromboplastin time (PTT) is monitored and central neuraxial blockade may be done if the PTT is in the normal range, which typically is 2 to 6 hours after UFH is stopped.

Additionally, the platelet count should be checked every 3 days postoperatively while the patient is on UFH or LMWH. It may be just as important to monitor the platelet count preoperatively if the patient has been on UFH or LMWH for an extended duration, especially if a central neuraxial anesthetic technique is planned.

Dr. Cohn: The reason for monitoring the platelet count is the potential for heparin-induced thrombocytopenia in patients on UFH. I recently encountered a patient who developed postoperative heparin-induced thrombocytopenia with thrombosis while on LMWH, which is relatively uncommon compared with UFH.

Case resolution

After much discussion of the risk of a significant PE with the patient, family, urologist, and vascular surgeon, it is decided that a temporary IVC filter will be placed in the operating room immediately after induction of general anesthesia and before the prostatectomy. The operation is delayed about 1 hour to allow this option. The patient is successfully treated and has the IVC filter removed 1 month postoperatively.

CASE 2: RADICAL CYSTECTOMY IN ELDERLY MAN WITH CARDIAC RISK FACTORS

A 78-year-old obese Russian-speaking man is seen in the preoperative clinic prior to a scheduled radical cystectomy for highly invasive bladder cancer. He is a poor historian and argues with the several family members accompanying him, but it is determined that his medical history includes hypertension, diabetes mellitus, a myocardial infarction (MI) 5 years previously (in Russia), and stable angina that is determined to be class II.

He had no previous work-up and no electrocardiogram (ECG). His medications are aspirin, metoprolol, and metformin. His blood pressure is 190/100 mm Hg, heart rate 90 beats per minute, and body mass index 32. On examination, there is no murmur, S3 gallop, or rales. His blood glucose is 220 mg/dL, and his creatinine is slightly elevated (1.4 mg/dL). ECG verifies a prior MI.

Question 2.1: *Which of the following additional tests should be ordered preoperatively?*

A. Hemoglobin (Hb) A_{1c}
B. Lipid profile
C. Both
D. Neither

Dr. Sweitzer: Because the surgery is not elective, no immediate benefit would be achieved by ordering either an HbA_{1c} or a lipid profile. However, if you view the preoperative evaluation as an opportunity to manage risk factors over the long term, then it may be a good idea to order the lipid profile because this patient has rarely engaged the health care system. Likewise, the HbA_{1c} can be ordered to set in place his long-term management. Sometimes we focus on the preoperative visit only in the context of the surgery, but if a test or intervention is appropriate and needed for long-term management, then it is appropriate to do now.

Dr. Cohn: There is no evidence to support using the preoperative HbA_{1c} to alter management decisions. I would not postpone surgery based on the HbA_{1c} value, as I would if his glucose level were 600 mg/dL. Most of the studies that have assessed postoperative complications based on preoperative HbA_{1c} did not control for postoperative glucose levels. The incidence of complications varies based on the type of complication and the type of surgery.

Similarly, I would not use lipid values to guide management of this patient. Studies suggest that perioperative statin therapy may reduce postoperative morbidity and mortality in patients undergoing vascular surgery (see article by Poldermans on page S79 of this supplement), but our patient already has indications for a statin—a remote MI and diabetes—independent of what his lipid values are.

Question 2.2: *How would you manage his elevated blood pressure (190/100 mm Hg)?*

A. Discontinue metoprolol and start a different antihypertensive drug
B. Increase the metoprolol dose
C. Continue metoprolol and add a second drug
D. Observe him on his current regimen

Dr. Cohn: I would increase the dose of metoprolol and consider adding another drug, in view of his heart rate (90 beats per minute) and his cardiac status. Beta-blocker therapy should not be discontinued because doing so in the perioperative period is associated with an increased risk of adverse events such as cardiac death and MI.

Dr. Sweitzer: I would push up the metoprolol a bit to reduce the heart rate, knowing that beta-blockers are probably not the most efficacious antihypertensive agents. I would caution against starting an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB) because he is scheduled to undergo a fairly significant procedure with expected blood loss and fluid shifts, and either of those agents in combination with a beta-blocker would be challenging to manage on the day of surgery.

Question 2.3: *How would you manage his metformin perioperatively?*

A. Discontinue it 48 hours preoperatively
B. Discontinue it 24 hours preoperatively
C. Withhold it on the morning of surgery
D. Continue it on the morning of surgery

Dr. Sweitzer: We routinely advise patients to hold all their oral diabetes medications the morning of surgery, primarily because many anesthesiologists are uncertain about the differing risks of hypoglycemia associated with the various oral agents.

Most of us will never see a patient who has lactic acidosis from metformin use. A systematic literature review and analysis found no increase in the risk of lactic acidosis with metformin compared with other oral hypoglycemics,[6] so fear of lactic acidosis is not a valid reason to discontinue metformin. In fact, I think it is inappropriate to ever postpone or cancel surgery simply because the patient inadvertently took metformin on the morning of surgery. Some may argue that patients with renal insufficiency are at higher risk of lactic acidosis from metformin use on the morning of surgery, but keep in mind that renal insufficiency is a relative contraindication to metformin use in the first place. Unless the patient is scheduled for a bilateral nephrectomy, his or her renal function is not going to be acutely reduced enough to enable a morning dose of metformin to cause lactic acidosis.

Dr. Cohn: Additionally, in a recent study of patients undergoing coronary artery bypass graft surgery (CABG), there was no increased risk of in-hospital morbidity or mortality in patients who received metformin on the morning of surgery,[7] although I typically stop it 24 hours before major surgery.

Question 2.4: *With respect to statin therapy, which course would you choose preoperatively?*

A. Start a statin at a low dose
B. Start a statin at an intermediate dose
C. Start a statin at a high dose
D. Do not start a statin

Dr. Cohn: The answer to this question is not clear cut. The reason not to start a prophylactic statin would be the lack of evidence of benefit in patients undergoing noncardiac, nonvascular surgery, although there is evidence of potential benefit in patients undergoing vascular surgery.* The arguments in favor of starting a statin are that this patient has independent indications for a statin and the planned surgery is a high-risk procedure.

In cohort studies, perioperative death rates have been lower in statin recipients than in those not taking a statin.[8] In the Dutch Echographic Cardiac Risk Evaluation Applying Stress Echo III (DECREASE III), which randomized noncardiac vascular surgery patients to perioperative fluvastatin or placebo, rates of MI and the composite end point of nonfatal MI or cardiovascular death were significantly lower in the statin group than in the placebo group.[9]

Question 2.5: *Which of the following cardiac tests would you order preoperatively?*

A. Exercise ECG
B. Dobutamine stress echocardiogram
C. Dipyridamole nuclear imaging
D. Coronary angiography
E. No further cardiac testing

Dr. Cohn: I wouldn't do any cardiac testing since this patient needs surgery for his malignancy and the results of

* *Editor's note:* In the time since this summit, results of the DECREASE-IV trial were published (Dunkelgrun et al, *Ann Surg* 2009; 249:921–926), showing a statisically nonsignificant trend toward improved outcomes at 30 days with fluvastatin in intermediate-risk patients undergoing noncardiovascular surgery.

any testing would be highly unlikely to change management, in terms of canceling the surgery. This approach is consistent with the 2007 guidelines on perioperative cardiovascular evaluation for noncardiac surgery issued by the American College of Cardiology (ACC) and the American Heart Association (AHA).[10]

Dr. Sweitzer: I would differ on this question. This patient has not been evaluated adequately for his coronary artery disease. He has poor functional capacity that complicates assessment of his symptoms. He also has diabetes, so he is more likely to have silent myocardial ischemia. At age 78, he is understandably concerned about his survival: radical cystectomy is a major operation associated with significant blood loss, fluid shifts, and a long-term recuperative state. In this case, a cardiac evaluation may change management, not in terms of considering coronary revascularization before the surgery, but in terms of affecting the assessment of his chance of surviving this major operation, his life span following the operation, and his quality of life. For example, a highly positive dobutamine stress echocardiogram or certain wall motion abnormalities would suggest that he might not be protected even by optimal perioperative medical management.

Question 2.6: *Which of the following would you do preoperatively to assess pulmonary risk?*

A. Obtain pulmonary function tests
B. Order a sleep study
C. Both
D. Neither

Dr. Sweitzer: There is no evidence supporting routine pulmonary function tests for patients undergoing procedures other than lung resection. If obstructive sleep apnea were suspected, I would order a sleep study only if I had access to one quickly to avoid delaying the surgery. Cancer surgery should never be delayed to get a sleep study. However, if this patient were seen in the primary care clinic, I would order a sleep study and, if indicated, put him on continuous positive airway pressure (CPAP). Whether or not preoperative CPAP makes a difference hasn't been shown. No randomized controlled trials have been conducted, but there are some suggestions that the risks of ischemia and atrial arrhythmias in patients with known coronary artery disease can be reduced with CPAP. It is not always easy to initiate CPAP postoperatively because the number of CPAP machines is limited and titration by a respiratory technician is required, which is typically done in a sleep lab.

How the case was actually managed

Neither an HbA_{1c} measurement nor a lipid profile was ordered preoperatively, for lack of supportive evidence. The patient was continued on his beta-blocker and the dosage was increased sufficiently to control his blood pressure and heart rate. Metformin was continued, and statin therapy was begun preoperatively in light of the patient's independent indications for it and the high-risk nature of the procedure. Stress testing was not ordered, in light of the lack of indication, given the patient's stable angina. The patient refused a sleep study. The operation was lengthy and involved significant blood loss. The patient had a complicated postoperative course and ultimately died from multiorgan failure.

CASE 3: OPERATIONS OF VARIABLE RISK IN ELDERLY MAN WITH ACTIVE CARDIAC CONDITION

Scenario A: *A 75-year-old man with diabetes, class III angina, and Q waves in inferior leads on his ECG is scheduled for elective femoropopliteal bypass surgery. His medications include isosorbide mononitrate (120 mg), amlodipine (10 mg), metoprolol controlled release (100 mg), atorvastatin (80 mg), insulin, and aspirin (81 mg). His heart rate is 64 beats per minute, blood pressure is controlled at 120/80 mm Hg, low-density lipoprotein cholesterol is 80 mg/dL, and creatinine is 1.5 µmol/L.*

Scenario B: *Consider the same patient undergoing elective cholecystectomy instead of a femoropopliteal bypass.*

Scenario C: *Consider the same patient scheduled for a cystoscopy instead of the other procedures. He had one episode of gross hematuria 1 week ago that resolved. Work-up by his urologist included a urinalysis and culture that were normal, cytology that was negative for malignancy, and a sonogram and computed tomography scan that were both negative. He has had no further bleeding and is not anemic. The urologist wants to do the cystoscopy for the sake of completeness.*

Question 3.1: *What would be your preoperative course of action in the above scenarios?*

A. Order a dobutamine stress echocardiogram
B. Order nuclear imaging with dipyridamole or adenosine
C. Order coronary angiography
D. Order a resting two-dimensional echocardiogram
E. Continue his current medications and send to surgery with no further testing

Dr. Cohn: This is a man with an active cardiac condition and class III angina, which is considered severe angina in the ACC/AHA 2007 guidelines on perioperative cardiac evaluation and care.[10] The guidelines' recommendation is to delay surgery for further evaluation and treatment. He is already on maximal medical therapy, which has failed to control his symptoms. He has poor exercise capacity. The only difference among the case scenarios is a variation in surgical risk.

This patient has independent indications for coronary angiography *regardless of whether or not he's undergoing surgery*. He deserves evaluation for possible revascularization to improve his quality of life and symptoms.

I would send the patient to the catheterization lab in every one of these instances, with the possible exception of the cystoscopy scenario, where one could argue that revascularization with stenting would require antiplatelet therapy that might increase the bleeding risk, and also that the antiplatelet therapy would have to be interrupted for the cystoscopy, potentially increasing thrombotic risk.

Dr. Sweitzer: I disagree. The ACC/AHA 2007 guidelines do not recommend going directly to catheterization but rather recommend delaying surgery for further evaluation and treatment.[10] We must ask whether this patient is truly receiving optimal medical management. After all, he is not on an ACE inhibitor or an ARB.

We must also consider whether the surgery is truly elective. In the first scenario, if he has peripheral vascular disease, he is likely to develop gangrene and have a further decrease in exercise capacity, which reduces his functional ability and increases his risk of comorbid conditions. He is at significant risk of developing worsening renal insufficiency or renal failure if he undergoes angiography. Coronary revascularization will delay treatment of his peripheral vascular disease. The Coronary Artery Revascularization Prophylaxis (CARP) trial showed no benefit of coronary revascularization relative to medical management in patients undergoing vascular surgery,[11] as is planned for this patient. I believe one must balance two competing risks and have an in-depth discussion with the patient.

In the second scenario, not treating gallstones or preventing cholelithiasis poses more risk to the health of this diabetic patient than does elective surgery if he needs a cholecystectomy. Emergency surgery, especially for acute cholecystitis, also significantly increases the risk of a cardiac event.

In the third scenario, the cystoscopy may uncover bladder cancer, which may be adversely affected by a delay of surgery. Regardless, the patient had gross hematuria and would be at risk for further bleeding should he undergo stenting with the requisite antiplatelet therapy.

Catheterization is not normally recommended unless CABG or stenting is being considered, yet I have seen no data that either of these procedures prolongs life except in very limited circumstances such as left main disease treated with bypass grafting. Though it is true that CABG reduces the incidence and severity of angina, it does not modify the physiologic cause of angina but rather may result in symptom improvement by damaging somatic nerve fibers to the heart. Putting a stent in this patient would be like applying a bandage: his symptoms will likely recur if he does not receive optimal medical management.

In a 2007 science advisory, several major medical societies cautioned against percutaneous coronary intervention (PCI) with drug-eluting stent placement in patients expected to undergo noncardiac surgery that would require interruption of antiplatelet therapy in the following 12 months (and against PCI with bare metal stent placement in patients undergoing such surgery in the following 4 to 6 weeks).[12] Therefore, I would not recommend catheterization for a patient whose noncardiac disease is likely to require surgery in the very near future, as is the case in each of the surgical scenarios above. One could consider noninvasive stress testing, which would be a safer approach and would almost certainly identify either significant stenosis of the left main coronary artery or three-vessel disease, which would be the only possible reasons to recommend CABG. I don't believe there is any role for PCI for this patient.

Dr. Cohn: I argue for symptom relief even if it doesn't prolong life. This patient cannot walk across the room without having symptoms despite taking multiple medications. I think he deserves a chance at revascularization if the angiogram shows he has a stenosis amenable to it, but I agree that a drug-eluting stent should not be placed if we know that he will undergo surgery within a few months.

CASE 4: VENTRAL HERNIA REPAIR IN A MIDDLE-AGED WOMAN

A 60-year-old woman is scheduled for ventral hernia repair. Her medical history is unremarkable, with the exception of hypertension. She denies any bleeding problems and had no complications after a laparoscopic cholecystectomy 10 years ago. She has no family history of bleeding disorders.

Question 4.1: *Would you order a prothrombin time (PT)/partial thromboplastin time (PTT)?*

A. Yes
B. No

Dr. Cohn: I would not.

Dr. Sweitzer: I agree.

Question 4.2: *Although not requested, a PT/PTT was ordered anyway. The PT is normal (12.2 sec/12 sec) and the PTT is abnormal (40 sec/25 sec). What is the most likely cause of the PTT abnormality?*

A. Laboratory error
B. Factor VII deficiency
C. Factor IX deficiency
D. Factor XI deficiency
E. Factor XII deficiency

Dr. Cohn: The most likely cause is a sample with insufficient blood in the tube. The test wasn't indicated in the first place, but now it must be done again.

Question 4.3: *The PTT is repeated and remains abnormal:*

42 sec/25 sec. Mixing studies correct the abnormality to 29 sec/25 sec. Based on this information, what is the most likely cause of the PTT abnormality?

A. Laboratory error
B. Lupus anticoagulant
C. Prekallikrein factor deficiency
D. Factor XII deficiency

Dr. Cohn: This is not a case of lupus anticoagulant because the abnormal PTT was corrected by the mixing study. Causes of a prolonged PTT include deficiencies of factors XII, XI, and IX, so factor XII deficiency is the most likely explanation, though a deficiency higher up the coagulation cascade (ie, prekallikrein factor deficiency) is possible. In the absence of any personal or family bleeding history, it is unlikely to be a deficiency of factors VII or IX (the hemophiliac) or of factor XI, so a deficiency of factor XII or one of the prekallikrein factors is more likely.

Dr. Sweitzer: A mixing study is indeed the appropriate first step. It is ordered from the lab and involves mixing the patient's blood with normal plasma and incubating the mixture. If the mixture corrects the PTT result, as was the case with this patient, it indicates a coagulation factor deficiency in the patient's blood; if it doesn't correct, that should prompt evaluation for lupus anticoagulant or the presence of some other protein or hormone that's prolonging the PTT.

Question 4.4: *How would you manage this patient perioperatively?*

A. Fresh frozen plasma
B. Platelet transfusion
C. Cryoprecipitate
D. Factor VII
E. No treatment necessary

Dr. Cohn: No treatment is necessary. Factor XII deficiency does not cause bleeding, regardless of the PTT. Factor XI deficiency is associated with bleeding, but usually there is a family history or a personal history of bleeding with surgery.

Screening coagulation studies are not usually indicated in a patient without a personal or family history of bleeding, liver disease, alcohol or drug use, or current anticoagulant therapy. Such studies are usually normal in such patients, and when they are not, it's usually because of a lab error or a disease (hypercoagulable state) or factor deficiency that does not cause bleeding

Dr. Sweitzer: However, if the PTT is prolonged, the cause should be identified, because if the patient is sent to the operating room without an explanation for the prolongation, the perioperative team might think the patient has a bleeding problem and use fresh frozen plasma too readily. Fresh frozen plasma is not appropriate for everyone and may actually make a potentially hypercoagulable state worse.

DISCUSSION

Question from the audience: It was said that use of ACE inhibitors and ARBs should be avoided around the time of surgery. I've done an extensive literature search and found minimal to no evidence to support this practice. To the contrary, I found fairly good evidence to indicate that heart failure can be exacerbated significantly and acutely, as early as within 24 hours, when patients are taken off their ACE inhibitor or ARB. I would like your viewpoint on this basic pathology in perioperative medicine.

Dr. Cohn: The literature on the use of ACE inhibitors or ARBs prior to noncardiac surgery consists of five studies with fewer than 500 patients in total, as recently reviewed by Rosenman et al.[13] Although there was no excess of death or MI associated with taking these medications on the morning of surgery, they did increase the need for fluid and pressors.

Dr. Sweitzer: Patients with hypertension have bigger variations of blood pressure, both hypo- and hypertension, in the perioperative period. For this reason, it was standard of care 30 years ago to stop all antihypertensive drugs, including beta-blockers, preoperatively. We soon found that although this practice prevented many episodes of hypotension, it increased the occurrence of perioperative hypertension and the likelihood of cardiac events. It then became standard of care to always continue antihypertensive drugs on the morning of surgery. In the late 1980s and early 1990s, several studies showed that ACE inhibitors and ARBs were associated with a more profound drop in blood pressure upon induction of general anesthesia compared with other antihypertensives.

The usual ways we treat drops in blood pressure—with phenylephrine and ephedrine—are not very effective in treating hypotension associated with general anesthesia in patients taking ACE inhibitors or ARBs. Vasopressin is effective in treating refractory hypotension during surgery, but anesthesiologists don't use it often. Reducing the doses of induction agents is another means of attenuating the hypotension induced by ACE inhibitors and ARBs.

We should not routinely stop ACE inhibitors and ARBs on the day of surgery, particularly in patients being treated for heart failure, angina, or a prior MI. My bias is to selectively hold ACE inhibitors and ARBs on the morning of surgery in patients who are undergoing a significant operation with a high likelihood of hypotension, have well-controlled preoperative blood pressure, are taking multiple antihypertensive agents, and do not

have heart failure. Otherwise, patients should continue their ACE inhibitors and ARBs on the morning of surgery, and the anesthesiologist should be prepared for significant hypotension upon induction of anesthesia, alter anesthesia induction doses accordingly, have vasopressin handy, and avoid the temptation to treat hypotension with fluids or repeated doses of phenylephrine and ephedrine. The previous comment about concerns with ACE inhibitors and ARBs was in the context of *initiating* new therapies in the immediate preoperative period.

Question from the audience: Urinalysis is ordered for many patients undergoing orthopedic surgery, and invariably some bacteriuria is found. Can you comment on the value of urinalysis and subsequent treatment of abnormal results?

Dr. Cohn: I believe you should never order a urinalysis in an asymptomatic patient, with the exception of patients undergoing procedures that involve genitourinary or gynecologic instrumentation. Ordering a urinalysis before joint replacement has been promoted in the orthopedic literature on the theoretical grounds that bacteria might somehow seed and colonize the joint. Orthopedic surgeons like to do it, but I disregard their requests for it.

Dr. Sweitzer: One study showed that we'd need to spend $1.5 million on screening urinalysis for asymptomatic patients scheduled for joint replacement surgery in order to prevent one joint infection.[14]

Dr. Cohn: Also, patients are going to get their one dose of cephalosporin before surgery anyway, and that will probably knock out any bacteria that would be found on urinalysis.

Question from the audience: Can you clarify how the 2007 ACC/AHA perioperative guidelines define an active cardiac condition? The patient in your third case report had class III angina, or angina with less than usual activities, but nothing was presented to suggest that his symptoms were unstable. I would suggest that despite his class III symptoms, his angina was stable, and I would have continued down the algorithm rather than defining his cardiac condition as active and considering an intervention.

Dr. Cohn: An active cardiac condition is defined by the ACC as unstable coronary syndromes, which include acute (within the prior 7 days) or recent (within the prior 30 days) MI, unstable angina, and severe (class III or IV) angina.

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Both authors have indicated that they have no financial relationships with commercial interests that have a direct bearing on the subject matter of this article.

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Statins and noncardiac surgery: Current evidence and practical considerations

ABSTRACT

Vascular surgery is associated with a high risk of perioperative morbidity and mortality that is partly attributable to inflammatory stress induced by the surgical procedure. Preoperative initiation of a long-acting statin is a strategy intended to reduce the inflammatory stress response and the excess risk associated with vascular surgery. The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo III demonstrated significant reductions in perioperative myocardial ischemia and the composite end point of myocardial infarction or cardiovascular death with extended-release fluvastatin (relative to placebo) initiated 30 days prior to vascular surgery. These benefits were achieved with no increase in liver dysfunction, evidence of myopathy, or other side effects. Observational data suggest that perioperative statin use is associated with improved recovery from acute kidney injury after high-risk vascular surgery and with improved long-term survival in patients undergoing such surgery.

KEY POINTS

The inflammatory and oxidative stress induced by vascular surgery can be blunted by statin therapy.

Statin therapy started preoperatively can reduce the incidence of myocardial ischemia and the level of inflammatory markers in patients undergoing high-risk vascular surgery.

The purpose of perioperative statin use should be reduction of the inflammatory stress response to surgery, with the long-term goal being achievement of target lipid levels.

A long-acting statin is preferred preoperatively to best extend the anti-inflammatory effects into the postoperative period. Statin therapy should be continued postoperatively, if possible, to avoid deleterious acute withdrawal effects.

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Current uncertainty over the best approach for preventing fatal perioperative myocardial infarction (MI) lies in our inability, despite sophisticated testing methods, to detect unstable coronary plaque prior to surgery. Unstable plaque can be present in patients with coronary lumina that appear normal on coronary angiography. Therefore, reliance on medical therapy to blunt inflammation is currently the best practice for minimizing the risk that unstable plaque poses.

Perioperative use of statins is a cornerstone of such therapy. This article briefly reviews the rationale for perioperative statin use in the setting of noncardiac surgery, presents the latest evidence on the clinical effects of perioperative statin use, and considers the potential role for statins in promoting recovery from acute kidney injury after vascular surgery.

FATAL MI: ORIGINS AND APPROACHES TO RISK REDUCTION

Fatal perioperative MI has two potential origins.[1,2] One is a culprit coronary plaque that fissures and ruptures, causing a cascade of thrombogenic events (hemorrhage and thrombosis) inside the vessel wall, culminating in an MI. Less often, fatal perioperative MI results from long-lasting myocardial ischemia (a demand/supply mismatch of oxygen), typically as a consequence of a fixed coronary stenosis.

In nearly half of patients with fatal MI, coronary inflammation is a key contributor. In the perioperative setting, surgical stress induces the release of inflammatory cytokines that disrupt smooth muscle cells in the endothelium and contribute to disruption of a nonobstructing coronary plaque, predisposing to acute thrombus formation.

Risk reduction depends on pathophysiology

Strategies for minimizing the risk of perioperative MI depend on the pathophysiology involved. In the case of oxygen demand/supply mismatch as a result of flow-limiting stenosis, a beta-blocker and coronary revascularization, if possible, may be useful.

In the more common case of unstable plaque, a multifactorial strategy appears optimal, involving the following:

- Statin therapy to reduce coronary inflammation

- Aspirin to blunt the prothrombotic milieu postoperatively
- Chronic low-dose beta-blockade to decrease myocardial oxygen demand or inhibit plaque rupture.

A particular role for statins

Ridker et al found that patients with an acute coronary syndrome who experience a decline in high-sensitivity C-reactive protein (hsCRP) level after treatment with a statin have improved clinical outcomes compared with those whose hsCRP level remains high, regardless of their resultant low-density lipoprotein (LDL) cholesterol level.[3]

Among surgical patients, those most at risk for poor cardiovascular outcomes are those who undergo vascular surgery. In Europe, the cardiovascular death rate in such patients is approximately 2%.[4]

Retrospective cohort data and data from randomized clinical trials have demonstrated reductions in perioperative cardiac complications with statin use in patients undergoing various types of noncardiac vascular surgery.[5–9] In light of these data, my colleagues and I recently undertook a prospective study to examine the effect of perioperative statin use on cardiovascular complications in patients undergoing vascular surgery.[10] Key details and findings are surveyed in the following section.

DECREASE III: PROSPECTIVE EVIDENCE FOR ISCHEMIC BENEFIT FROM PERIOPERATIVE STATINS

The Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo III (DECREASE III) was conducted at a single center (Erasmus Medical Center, Rotterdam, the Netherlands) in a randomized, double-blind, placebo-controlled manner.[10]

Patients and study design

The study population included 497 statin-naïve patients who were scheduled for one of four noncardiac vascular surgical procedures (repair or revascularization for abdominal aortic aneurysm, abdominal aortic stenosis, lower limb arterial stenosis, or carotid artery stenosis). Patients with unstable coronary artery disease or left main disease were excluded.

Patients were randomized to placebo or extended-release fluvastatin (80 mg/day) starting on the day of randomization, which was a median of 37 days before surgery. Treatment was continued until 30 days after surgery.

Extended-release fluvastatin was chosen because its long half-life permits a bridge to the early postoperative period, during which oral medications are not permitted in patients undergoing high-risk vascular surgery.

The primary end point was the occurrence of myocardial ischemia as assessed by three methods:

- Holter monitoring during the first 72 postoperative hours
- Measurement of troponin T on days 1, 3, 7, and 30
- Additional electrocardiographic recordings on days 7 and 30.

The secondary end point was a composite of cardiovascular death and nonfatal MI during the first 30 postoperative days.

Baseline characteristics were similar between the two randomized groups, with a median age approaching 66 years. About three-fourths of the patients were male, one-fourth had a history of MI, one-fourth had angina pectoris, one-fifth had diabetes mellitus, and nearly 30% had a history of cerebrovascular accident or transient ischemic attack.

All patients were being treated with a beta-blocker, about 60% with antiplatelet therapy, more than one-fourth with anticoagulant therapy, nearly half with either an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and more than one-fourth with diuretics. There were no significant differences between the groups in the proportion of patients on each of these therapies.

Results: Reductions in inflammatory markers

Baseline levels of hsCRP and interleukin-6 (IL-6) were comparable between the groups. In patients randomized to placebo, the hsCRP level increased by 3%, from a median of 5.80 mg/L at randomization to 6.00 mg/L immediately prior to surgery. In contrast, the hsCRP level in patients randomized to extended-release fluvastatin decreased by 21%, from a median of 5.93 mg/L to 4.66 mg/L. The between-group difference in the change in hsCRP level was statistically significant ($P < .001$). There was also a significantly greater reduction from baseline in median level of IL-6 among fluvastatin recipients compared with placebo recipients (–33% vs –4%; $P < .001$).

The specificity of hsCRP for cardiac inflammation is not yet known, but measures of hsCRP and IL-6 can provide a fingerprint of inflammatory activity prior to surgery. Other inflammatory and noninflammatory markers are being investigated to better identify (prior to surgery) those high-risk patients most likely to benefit from perioperative statin use.

Results: Favorable effect on clinical end points

The incidence of the primary end point—myocardial ischemia 30 days after surgery—was significantly lower in the patients randomized to extended-release fluvastatin compared with placebo (10.9% vs 18.9%; $P = .016$), as was the incidence of the secondary end point of cardiovascular death or nonfatal MI (4.8% vs 10.1%; $P = .039$).

The number needed to treat (NNT) to prevent one occurrence of myocardial ischemia was 13; the NNT to prevent one nonfatal MI was 36; and the NNT to prevent one cardiovascular death was 42 **(Table 1)**.

TABLE 1
Outcomes in DECREASE III with extended-release fluvastatin vs placebo[10]

End point	Odds ratio	95% CI	Absolute risk reduction	NNT
Myocardial ischemia	0.53	0.32–0.88	28.0%	13
Nonfatal MI	0.55	0.24–1.27	22.8%	36
CV death	0.33	0.09–1.22	22.4%	42
CV death or nonfatal MI	0.48	0.24–0.95	25.3%	19

DECREASE III = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo III; CI = confidence interval; NNT = number needed to treat (to prevent one event); MI = myocardial infarction; CV = cardiovascular

TABLE 2
Safety end points in DECREASE III[10]

Measure	Placebo (n = 247)	Extended-release fluvastatin (n = 250)	*P* value
Discontinuation	7.3%	6.4%	0.7
CK > 10× ULN	3.1%	4.1%	0.8
Median CK (U/L)	113	141	0.2
ALT > 3× ULN	5.2%	3.1%	0.3
Median ALT (U/L)	23	24	0.8

DECREASE III = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo III; CK = creatine kinase; ULN = upper limit of normal; ALT = alanine aminotransferase

Safety: No effects on liver function or evidence of increased myopathy

No significant differences were seen between the study arms in safety end points, including discontinuation of study drug, the incidence of creatine kinase (CK) elevations above 10 times the upper limit of normal, median CK levels, the incidence of alanine aminotransferase (ALT) elevations above three times the upper limit of normal, and median ALT levels **(Table 2)**. Receipt of general anesthesia prevented monitoring for symptoms of myopathy and rhabdomyolysis.

We concluded that initiation of therapy with a long-acting statin should be considered in statin-naïve patients undergoing vascular surgery.

PERIOPERATIVE STATIN USE: PRACTICAL CONSIDERATIONS

Inflammation, not cholesterol, should be the target

The optimal statin choice and the target level of LDL cholesterol immediately prior to surgery remain controversial. It may be that the more potent statins induce more side effects during surgery, but any such claim is speculative since no comparative studies exist. Regardless, the purpose of perioperative statin use should be reduction of the inflammatory stress response to surgery, with the long-term goal being achievement of recommended target lipid levels.

In particular, patients with peripheral arterial disease should have a statin initiated prior to high-risk vascular surgery (if they are not already receiving one), to increase the odds of recovering renal function after surgery (see section below) and to improve long-term outcomes.

Who are the best candidates?

Patients with multiple cardiac risk factors represent an especially high-risk group that benefits the most from statin therapy prior to vascular surgery, as they are likely to have more extensive disease and more extensive inflammation in the coronary artery tree.

Given the low incidence of side effects associated with statins, initiating a statin in patients with multiple cardiac risk factors who are undergoing intermediate-risk surgery may seem appropriate, but no data from large randomized trials are available to support this practice. Caution is in order when extrapolating data from studies conducted in the high-risk vascular surgery context to other surgical settings, since statins may pose hidden side effects such as liver dysfunction and myopathy, which may be missed in patients under anesthesia.

My personal practice is to initiate a statin prior to high-risk surgery or in patients with multiple cardiac risk factors if the risk-factor profile presents a clear indication for long-term statin use. If no risk factors are present, I am more reluctant to initiate a statin because of a lack of supportive data.

Beware the rebound effect with statin withdrawal

Statin withdrawal for several days following surgery is a common practice, since statins are given orally and their pleiotropic effects are underappreciated.

A withdrawal effect leading to abrogation of clinical benefit has been observed with perioperative use of short-acting statins, whose anti-inflammatory properties do not effectively extend to the postoperative period. Acute withdrawal has been associated with an increase in markers of inflammation and oxidative stress, and an increase in cardiac events has been observed with acute withdrawal of statins during periods of instability when compared with continuation of statin therapy.[11]

For these reasons, a long-acting statin is preferred preoperatively in patients whose oral intake will be compromised for several days after surgery (eg, in gastric surgery). The optimal statin for preventing the with-

drawal effect is unknown. We chose extended-release fluvastatin in DECREASE III because its biological effect appears to last at least 4 days[12] even though analysis of serum levels of the drug indicates a shorter half-life.

ANOTHER POTENTIAL BENEFIT: ENHANCED RECOVERY OF KIDNEY FUNCTION

Postoperative renal dysfunction is an ominous sign

Renal ischemic reperfusion injury is inevitable after vascular surgery that requires aortic cross-clamping. This is significant, as renal dysfunction after surgery is an ominous long-term sign that indicates abundant atherosclerosis. Complete recovery after acute kidney injury portends an improved long-term outcome, whereas patients with persistent renal dysfunction after vascular surgery have poor long-term outcomes.

A benefit from statins?

Statins may offer an effective means of preventing or shortening the course of acute kidney injury after surgery. Statins have been reported to lengthen survival of chronic kidney disease patients with sepsis or infectious complications and to improve the course of acute kidney injury in aging rats.[13–15] These findings prompted my colleagues and I to conduct a retrospective study to evaluate whether statins may ameliorate reperfusion injury in the kidney after aortic cross-clamping.[16]

Promising findings from an observational review

We reviewed the records of all patients who had undergone vascular surgery at Erasmus Medical Center from January 1995 to June 2006 to examine the relation between preoperative statin use and renal function after suprarenal aortic cross-clamping.[16] Of the 1,944 patients who met inclusion criteria, 515 (26.5%) were statin users. Postoperative kidney injury was defined as more than a 10% reduction in creatinine clearance on postoperative day 1 or 2 compared with baseline. Recovery of kidney function was defined as a creatinine clearance of greater than 90% of the baseline value by postoperative day 3.

The clinical characteristics of the populations with and without kidney injury after aortic cross-clamping were similar, including baseline creatinine clearance and serum creatinine.

Acute kidney injury within 2 days of surgery occurred in 664 patients (34%), of which 313 (47%) had complete recovery of kidney function at postoperative day 3. Although the incidence of postoperative kidney injury was similar among statin users and nonusers, statin use was associated with an increased chance of complete recovery of kidney function at day 3 (odds ratio = 2.0; 95% CI, 1.0–3.8).

All-cause mortality was assessed during a mean follow-up of 6.24 years. Statin use was associated with improved long-term survival, regardless of any change in kidney function (hazard ratio for death = 0.60; 95% CI, 0.48–0.75). Among the four broad patient groups, survival was highest among statin users with no postoperative kidney injury, followed by statin users who had kidney injury, then by nonusers of statins with no kidney injury, and finally by nonusers of statins who had kidney injury.

We concluded that perioperative statin use was associated with clinically significant recovery from acute kidney injury after high-risk vascular surgery and, more importantly, with improved long-term survival regardless of the presence of kidney injury. These promising findings require confirmation in prospective trials.

SUMMARY

Vascular surgery carries a high risk of perioperative mortality. Perioperative use of extended-release fluvastatin is associated with a reduced incidence of myocardial ischemia and the composite of MI and cardiovascular death at 30 days following surgery. These beneficial clinical outcomes are achieved without an increase in the incidence of side effects, including liver dysfunction and myopathy. Preoperative initiation of a long-acting statin is a reasonable strategy for reducing the risks associated with vascular surgery, and offers a bridge to postoperative statin continuation to blunt the inflammatory stress of surgery. Ischemic reperfusion injury is a major cause of renal dysfunction following vascular surgery. Statin therapy appears to help restore kidney function after aortic cross-clamping in patients undergoing high-risk vascular surgery.

DISCUSSION

Question from the audience: The majority of patients randomized in DECREASE III had relatively normal cholesterol levels. Do you believe those patients are biologically different from patients with physiologic vascular disease and elevated cholesterol levels?

Dr. Poldermans: We enrolled patients with various baseline cholesterol levels, and we found that these levels were not related to postoperative outcome. It would be a good idea to examine inflammation status just prior to surgery in patients with lower cholesterol levels to see if they have different outcomes from those with high cholesterol.

Question from the audience: If a patient is already on a short-acting statin and we know that he or she won't be able to take a statin postoperatively, should we change to a long-acting statin just prior to surgery?

Dr. Poldermans: To be honest, this is a financial issue. If you have the opportunity, the best course would be

to prescribe a statin with a prolonged half-life or an extended-release formulation. Of course, it's not always possible to prescribe one particular statin. You have to negotiate what is feasible and hope to initiate the statin as early as possible to reduce risk.

Question from the audience: In studies conducted outside the perioperative setting, such as PROVE IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) and a substudy of REVERSAL (Reversing Atherosclerosis with Aggressive Lipid Lowering), it took about 30 days after statin initiation for hsCRP levels to minimize, and at least that long for halting of plaque progression to be detected by intravascular ultrasonography. Given that, does it make sense to delay nonurgent surgery in a patient in whom you're worried about a postoperative MI?

Dr. Poldermans: Rat studies show improved blood flow and reduced thrombosis within hours of statin initiation. In the perioperative setting, therefore, initiating a statin within 30 days may be appropriate, but nobody knows the exact timing for optimal effect. Since there are no data to answer this question, I would not postpone surgery for this reason.

DISCLOSURES

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The experts debate: Perioperative beta-blockade for noncardiac surgery—proven safe or not?

ABSTRACT

Guidelines on perioperative management of patients undergoing noncardiac surgery recommend the use of prophylactic perioperative beta-blockers in high-risk patients who are not already taking them, and their continuance in patients on chronic beta-blockade prior to surgery. These recommendations were challenged recently by results of the Perioperative Ischemic Evaluation (POISE), a large randomized trial of extended-release metoprolol succinate started immediately before noncardiac surgery in patients at high risk for atherosclerotic disease. While metoprolol significantly reduced myocardial infarctions relative to placebo in POISE, it also was associated with significant excesses of both stroke and mortality. The merits and limitations of POISE and its applicability in light of other trials of perioperative beta-blockade are debated here by two experts in the field—Dr. Don Poldermans and Dr. P. J. Devereaux (co-principal investigator of POISE).

NOTE: The individual co-authors in this debate-based article are responsible only for those views within their respective bylined subsections and those views ascribed to them in the rebuttals and discussion at the end.

Perioperative beta-blockade improves outcomes

By Don Poldermans, MD, PhD

It is my contention that perioperative beta-blockade improves mortality and cardiac outcomes in select high- and intermediate-risk patients undergoing noncardiac surgery. Patients on chronic beta-blocker therapy should have it continued perioperatively. For patients not already on beta-blockade who are at cardiac risk, initiation of low-dose beta-blocker therapy should be considered prior to surgery; such therapy should be started approximately 1 month before surgery, with dose titration to achieve hemodynamic stability. Reports of increased stroke rates with perioperative beta-blockade appear to be due to inappropriate acute administration of high-dose beta-blocker therapy.

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THE PHYSIOLOGIC RATIONALE FOR PERIOPERATIVE BETA-BLOCKADE

Perioperative myocardial infarction (MI) can occur by one of two mechanisms, both of which can be attenuated by beta-blockade:

- The stress induced by surgery can cause an asymptomatic coronary plaque to become unstable and rupture, resulting in complete occlusion of a portion of the coronary tree. This type of perioperative MI occurs typically in patients with multiple risk factors for MI absent a critical coronary stenosis. The perioperative risk associated with unstable plaque can be reduced pharmacologically with aspirin, statins, and chronic beta-blocker therapy.
- Alternately, a fixed coronary stenosis can predispose to a mismatch of oxygen demand and supply, leading to myocardial ischemia and infarction. The patient with a fixed coronary lesion typically presents with stable angina pectoris, and the at-risk stenosis is identified through a stress echocardiogram or nuclear scan. The risk conferred by flow-limiting stable plaque can be reduced by coronary revascularization and a short course of beta-blocker therapy prior to surgery.

INITIAL SUPPORTIVE DATA

Mangano and colleagues were the first to evaluate perioperative beta-blockade in a randomized, controlled fashion.[1,2] In their study of 200 surgical patients with or at risk for coronary artery disease, oral atenolol administered perioperatively was associated with a 50% reduction (compared with placebo) in the incidence of postoperative myocardial ischemia as measured by three-lead Holter monitoring.[2] During 2 years of follow-up, mortality was significantly lower in the atenolol group (10%) than in the placebo group (21%) ($P = .019$).[1]

In the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE I), my research group randomized 112 high-risk patients (as identified by dobutamine echocardiography) to standard perioperative care alone or standard perioperative care plus bisoprolol starting 30 days prior to major vascular surgery.[3] The dosage of bisoprolol was titrated to achieve a target heart rate of 60 to 70 beats per minute. Thirty days after surgery, the incidence of the primary end point—a composite of death from cardiac causes or nonfatal MI—was reduced from 34% in the standard-care group to 3.4%

in the bisoprolol group ($P < .001$). Thus, in this unblinded study in a population with proven coronary artery disease, beta-blockade clearly improved outcomes.

Additional studies of perioperative beta-blocker use have produced a wide range of outcomes, with most favoring beta-blockade, albeit usually not to a statistically significant degree.[4–13] Notably, only some of these trials were randomized, they used various beta-blocker regimens at various doses, they were conducted in patients with varying degrees of cardiac risk, and many had small sample sizes.

What emerged from these trials was the idea that perioperative beta-blockade in patients with coronary artery disease produces an effect similar to that of long-term beta-blockade in reducing the risk of cardiovascular events in post-MI patients and in those with coronary artery disease and heart failure.

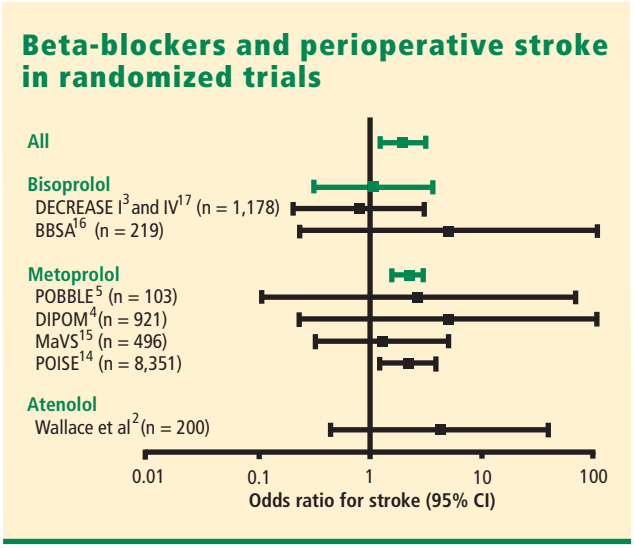

FIGURE 1. Pooled analysis of trials of perioperative beta-blockade shows no significant increase in perioperative stroke among studies using bisoprolol[3,16,17] or atenolol,[2] but pooled analysis of studies using metoprolol[4,5,14,15] shows a significant excess of stroke driven largely by results from POISE.[14] See text and References list for expansion of study abbreviations.

THE POISE STUDY AND ITS IMPLICATIONS

Results of the Perioperative Ischemic Evaluation (POISE) were published in 2008, in which 8,351 noncardiac surgery patients with or at risk of atherosclerotic disease were randomized to placebo or extended-release metoprolol succinate started 2 to 4 hours preoperatively and continued for 30 days.[14] Metoprolol was associated with a clear reduction in the primary end point, a composite of cardiovascular death, nonfatal MI, or nonfatal cardiac arrest (5.8% vs 6.9% with placebo; hazard ratio [HR] = 0.84 [95% CI, 0.70–0.99]; $P = .0399$), but this effect was offset by significant increases in total mortality and stroke incidence in the metoprolol group. Mortality was 3.1% with metoprolol versus 2.3% with placebo (HR = 1.33 [95% CI, 1.03–1.74]; $P = .0317$), and stroke incidence was 1.0% with metoprolol versus 0.5% with placebo (HR = 2.17 [95% CI, 1.26–3.74]; $P = .0053$). Cerebral infarction, not bleeding, explained most of the excess mortality with metoprolol.

Of the 60 strokes in POISE, 49 were ischemic in origin, 3 were hemorrhagic, and 8 were of uncertain etiology. Preoperative predictors of stroke were the use of clopidogrel and a history of stroke or transient ischemic attack. Postoperative predictors of stroke included intraoperative bleeding and intraoperative hypotension. These predictors suggest a diseased cerebrovascular tree or unstable hemodynamics during the intraoperative period in the patients who suffered a stroke.

Does dosing explain the rise in mortality and strokes?

Could the fatal outcomes associated with the beta-blocker in POISE be attributed to the dosage of metoprolol? In the study, 100 mg of metoprolol was started immediately prior to surgery, and an additional 100 mg could be given, depending on the hemodynamic response. Maintenance therapy (200 mg/day) was started on the same day, making it possible that a patient could have received as much as 400 mg of metoprolol the day of surgery. The starting dose of metoprolol used in POISE was two to eight times the commonly prescribed dose.

The initial 100-mg dose of metoprolol used in POISE has a similar beta$_1$-receptor blockade potency compared with the 5-mg dose of bisoprolol used in DECREASE I.[3] However, in DECREASE I, bisoprolol was initiated 30 days prior to surgery and was titrated, if necessary, according to heart rate. The maintenance dose of bisoprolol was half of the maintenance dose used in POISE. In the later DECREASE trials, the starting dose of bisoprolol was only 2.5 mg. Therefore, there was a huge difference in beta-blocker dosing between POISE and DECREASE.

Perioperative cardiac outcomes were similar in POISE and DECREASE I, with clear reductions in each trial among the patients randomized to the beta-blocker, as in other trials of perioperative beta-blockade. Stroke outcomes, in contrast, are inconsistent among trials of perioperative beta-blockade, with no increase in stroke observed in studies using low-dose titrated bisoprolol and an overall increase in stroke in studies of metoprolol, driven by the data from POISE[2–5,14–17] **(Figure 1)**. When interpreting the pooled analyses in **Figure 1**, it should be noted that DECREASE I[3] and IV[17] were open-label trials, not double-blind studies.

What about timing of beta-blocker initiation?

The POISE findings may also be explained in part by the timing of beta-blocker initiation. Whereas bisoprolol was carefully titrated for 30 days before surgery in

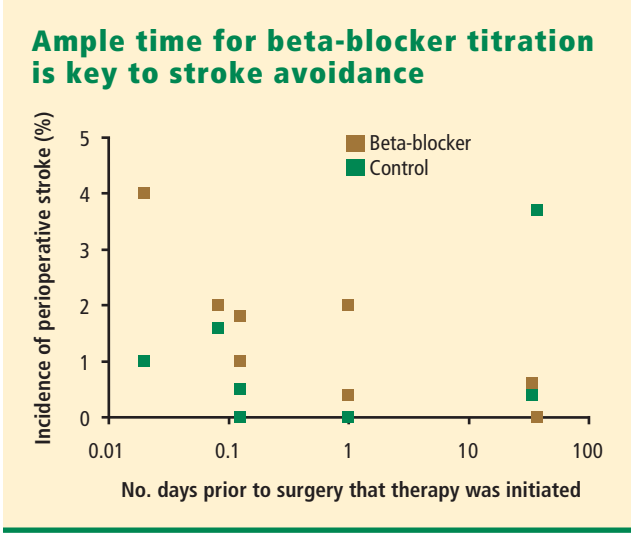

FIGURE 2. Relationship between timing of beta-blocker initiation (relative to surgery) and stroke incidence in controlled trials of perioperative beta-blockade. The lower incidence of stroke among patients on titrated chronic beta-blocker therapy suggests that ample time for titration may be necessary to achieve an optimal, stable hemodynamic condition.

DECREASE, metoprolol was initiated just before surgery in POISE, and the maximum recommended dose may have been prescribed during the first 24 hours, although subsequent dosing was 200 mg daily, which is 50% of the maximum daily therapeutic dose. This extremely narrow time window for titration may be important, since the beneficial effects of beta-blockade on coronary plaque stability are likely to take weeks to develop.

To determine whether there might be a relation between timing of beta-blocker initiation and postoperative stroke, we performed an analysis (in press) plotting stroke rates according to timing of beta-blocker initiation from eight studies of perioperative beta-blockade. As illustrated in **Figure 2**, patients on titrated chronic beta-blocker therapy (at least 10 days) had a low (< 1%) incidence of stroke, whereas patients in whom beta-blocker therapy was started immediately before surgery had a much higher incidence of stroke. This finding suggests that ample time for titrating the beta-blocker dose may be necessary to achieve an optimal, stable hemodynamic condition and thereby prevent hemodynamic aberrations that could raise the risk of stroke.

Reassurance from a large case-control study

My colleagues and I conducted a case-control study from among more than 75,000 patients who underwent noncardiac, nonvascular surgery at our institution, Erasmus Medical Center, from 1991 to 2001.[18] The cases were the 989 patients who died in the hospital postoperatively; the controls were 1,879 survivors matched with the cases for age, sex, the year the surgery was performed, and the type of surgery. The incidence of perioperative stroke was 0.5%, which is comparable to the rate found in the literature. Risk factors predictive of stroke were the presence of diabetes, cerebrovascular disease, peripheral arterial disease, atrial fibrillation, coronary artery disease, and hypertension. Notably, no relationship was found between chronic beta-blocker use and stroke.

WHAT ABOUT PATIENTS AT INTERMEDIATE RISK?

Because the effect of perioperative beta-blockade has traditionally been ill defined in surgical patients at *intermediate* risk of cardiovascular events, the DECREASE study group recently completed a study (DECREASE IV) to assess perioperative bisoprolol in terms of cardiac morbidity and mortality in intermediate-risk patients undergoing elective noncardiovascular surgery.[17] Enrollees had a score of 1 to 2 on the Revised Cardiac Risk Index of Lee et al,[19] which corresponds to an estimated risk of between 1% and 6% for a perioperative cardiovascular event.[17]

DECREASE IV also aimed to assess the effect of perioperative fluvastatin, so a 2 × 2 factorial design was used in which the study's 1,066 patients were randomized to receive bisoprolol, fluvastatin, combination treatment, or combination placebo control. Bisoprolol was initiated up to 30 days prior to surgery, and the 2.5-mg daily starting dosage was titrated according to the patient's heart rate to achieve a target rate of 50 to 70 beats per minute. Fluvastatin was also started up to 30 days prior to surgery. Patients who received bisoprolol (with or without fluvastatin) had a significant reduction in the 30-day incidence of cardiac death and nonfatal MI compared with those who did not receive bisoprolol (2.1% vs 6.0%; HR = 0.34 [95% CI, 0.17–0.67]; P = .002). Fluvastatin was associated with a favorable trend on this end point, but statistical significance was not achieved (P = .17).[17]

There was no difference among treatment groups in the incidence of stroke (4 strokes in the 533 patients who received bisoprolol vs 3 strokes in the 533 patients who did not),[17] which further suggests that the increased stroke rate seen with beta-blockade in POISE may have been due to dosage, timing of initiation, or both.

CONCLUSIONS

Dose-related hypotension may explain POISE findings

Our understanding of postoperative stroke is incomplete, but it appears that dosing of a beta-blocker can be a contributor, especially with respect to the potential side effect of hypotension during surgery. Keep in mind that the average age of patients in POISE was approximately 70 years and that patients were naïve to beta-blockers. Some may have had asymptomatic left ventricular dysfunction, and we know that starting a beta-blocker at a high dose in such patients may lead to hypotension. At

my institution we routinely perform echocardiographic screening of all patients scheduled for surgery, and we have found that more than half of the patients with heart failure have it uncovered only through this screening.

It is not the medicine alone that can cause perioperative hypotension; other factors may induce hypotension, requiring beta-blocker titration and careful monitoring of hemodynamics during surgery.

Advice: Start early and titrate dose; continue chronic beta-blockade

My advice is as follows:

- If a patient is on chronic beta-blocker therapy, do not stop it perioperatively. We have seen devastating outcomes in the Netherlands when patients had their beta-blockers stopped immediately before surgery. Consider adjusting the dose, but do not stop it entirely. If a beta-blocker is on board and the patient develops hypotension or bradycardia during surgery, treat the symptoms and check for sepsis.
- In a patient not on a beta-blocker, consider adding one if the patient is at intermediate or high risk of a cardiac event, but start at a low dosage (ie, 2.5 mg/day for bisoprolol and 25 mg/day for metoprolol). Treatment ideally should be started 30 days preoperatively; in the Netherlands, we have the chance to start well in advance of surgery so we can titrate the dose according to hemodynamics.
- If a beta-blocker is not started because of insufficient time for titration, do not add one to treat tachycardia that develops during surgery, since tachycardia may represent a response to normal defense mechanisms.

Safety of perioperative beta-blocker use has not been adequately demonstrated

By P. J. Devereaux, MD, PhD

I contend that perioperative beta-blockade is a practice not grounded in evidence-based medicine, and its overall safety has increasingly come into question as more data from large, high-quality trials have emerged. I will begin with a historical overview of perioperative beta-blocker use, review the results of the POISE trial (for which I was the co-principal investigator), explore the major questions raised by this trial, and conclude with some take-away messages.

THE HISTORY OF PERIOPERATIVE BETA-BLOCKADE

In the 1970s, physicians were encouraged to hold beta-blockers prior to surgery out of concern that these medications may inhibit the required cardiovascular response when patients developed hypotension, and could thereby lead to serious adverse consequences.

In the 1980s, new research associated tachycardia with perioperative cardiovascular events, leading to proposals to implement perioperative beta-blocker use.

In the 1990s, two randomized trials with a total sample size of 312 patients[1,3] suggested that perioperative beta-blockers had a large treatment effect in preventing major cardiovascular events and death. These small trials had several methodological limitations:

- One trial[3] was unblinded in a setting in which the vast majority of MIs are clinically silent.
- One trial[3] was stopped early—after randomizing only 112 patients—for unexpected large treatment effects.
- One of the studies[1] failed to follow intention-to-treat principle.

Nevertheless, guidelines developed at the time by the American College of Cardiology and the American Heart Association (ACC/AHA) recommended the use of perioperative beta-blockers on the basis of the physiological rationale and these two small clinical trials. That recommendation was retained in the latest (2007) update of the ACC/AHA perioperative guidelines.[20]

In 2006, two clinical trials with a total sample size of 1,417 were completed,[4,15] surpassing the total size of previous trials by more than fourfold. These two more recent trials did not suffer from the methodological limitations of earlier trials. These trials showed no benefit of perioperative beta-blocker use; in fact, there was a trend toward worse outcomes in the beta-blocker recipients.[4,15] Despite these new data, guidelines committees continued to recommend perioperative beta-blockade.[20]

THE POISE TRIAL

Study design

This was the context into which the POISE results were released in 2008. POISE was a randomized, controlled, blinded trial of patients 45 years or older scheduled for noncardiac surgery who had, or were at high risk of, atherosclerotic disease.[14] The intervention consisted of metoprolol succinate (metoprolol controlled release [CR]) or placebo started 2 to 4 hours preoperatively (if heart rate was ≥ 50 beats per minute and systolic blood pressure [SBP] was ≥ 100 mm Hg) and continued for 30 days. The target dosage of metoprolol was 200 mg once daily. No patients received the recommended maximum dosage of 400 mg over 24 hours. The main outcome measure was a 30-day composite of cardiovascular death, nonfatal MI, or nonfatal cardiac arrest.

We randomized 9,298 patients in a 1:1 ratio to metoprolol or placebo. We encountered data fraud at a number of centers that prompted exclusion of data from 474 patients allocated to metoprolol and 473 allocated to placebo. Therefore, the total number of patients available for the intention-to-treat analysis was 8,351, from 190 centers in 23 countries.

TABLE 1
Insights on negative outcomes from POISE[14]

	Metoprolol (N = 4,174)	Placebo (N = 4,177)	HR (95% CI)	*P*
Significant hypotension	625 (15.0%)	404 (9.7%)	1.55 (1.38–1.74)	< .0001

	HR (95% CI)	Population-attributable risk*
Hypotension as a predictor of death	4.97 (3.62–6.81)	37.3
Hypotension as a predictor of stroke	2.13 (1.15–3.96)	14.7

* Numbers in this column mean that hypotension potentially accounted for 37.3% of deaths in the study and 14.7% of strokes in the study.

HR = hazard ratio; CI = confidence interval

Results

The risk of the primary composite outcome was reduced by 16% (relative reduction) in recipients of metoprolol CR compared with placebo recipients (*P* = .0399). Significantly fewer nonfatal MIs occurred in the metoprolol CR group than in the placebo group (152 [3.6%] vs 215 [5.1%]; *P* = .0008), leaving little doubt that perioperative beta-blockade prevents MI.

In contrast, total mortality was increased in the beta-blocker group, with 129 deaths among those assigned to metoprolol CR and 97 among those assigned to placebo (*P* = .0317), and the incidence of stroke was also significantly greater in the metoprolol CR group (1.0% vs. 0.5%; *P* = .0053).

Consistency with findings from other trials

The POISE data are consistent with those from a 2008 meta-analysis of high-quality randomized controlled trials in noncardiac surgery patients, which showed a significantly greater risk of death among patients assigned to a beta-blocker than among controls who were not (160 deaths [2.8%] vs 127 deaths [2.3%]; odds ratio [OR] = 1.27 [95% CI, 1.01–1.61]).[21] This meta-analysis also found a significantly greater risk of nonfatal stroke in beta-blocker recipients compared with controls (38 [0.7%] vs 17 [0.3%]; OR = 2.16 [95% CI, 1.27–3.68]).

I also contend that the DECREASE IV trial supports the POISE findings in that although few strokes were encountered in DECREASE IV, the trend was in the direction of harm in the beta-blocker group, which had 4 strokes among 533 patients versus 3 strokes among 533 patients not receiving the beta-blocker.[17]

Predictive role of hypotension

Clinically significant hypotension (defined as systolic blood pressure < 90 mm Hg that required intervention) was common in POISE, developing in 9.7% of the placebo group and 15.0% of the metoprolol group.[14] On multivariate analysis, clinically significant hypotension was an independent predictor—in fact the dominant predictor—of both death and stroke **(Table 1)**. Hypotension was associated with a nearly fivefold increase in the risk of death and a doubling in the risk of stroke. The population-attributable risk of hypotension to death was 37.3, meaning that hypotension potentially accounted for 37.3% of deaths in the study. The population-attributable risk of hypotension to stroke was 14.7. In light of hypotension's role as the dominant predictor of death, I take issue with Dr. Poldermans' earlier contention that cerebral infarction explained most of the excess mortality with metoprolol in POISE.

The link between hypotension and death in POISE is consistent with findings from the largest beta-blocker trial undertaken, COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial), in which 45,852 patients with acute MI were randomized to metoprolol or placebo.[22] In COMMIT, metoprolol had no effect on 30-day all-cause mortality but significantly reduced the risk of arrhythmic death, a benefit that was countered by a significantly increased risk of death from shock with a beta-blocker in acute MI. Clinically significant hypotension is much more common in the perioperative setting than in acute MI, which may explain the excess number of deaths observed with metoprolol in POISE as opposed to metoprolol's neutral effect on mortality in COMMIT.

ANSWERING THE CRITICS

Several criticisms have been raised about POISE, as detailed below.

Beta-blocker dose

Some contend that a lower dose of beta-blocker would provide benefit and minimize risk, but this assertion must be supported by evidence from a large clinical trial. The targeted dosage of metoprolol in POISE represents 50% of the maximum daily therapeutic dose. Further, the protocol called for decreasing the dosage to 100 mg/day if SBP dropped to less than 100 mm Hg or if heart rate fell to less than 45 beats per minute.

The two small trials on which guideline recommendations for perioperative beta-blockade are primarily based[1,3] had a sample size that was 4% of that in POISE, which calls into question the reliability of their results. The study by Mangano et al used atenolol at a target dosage that was 50% of the maximum daily therapeutic dose,[1] the same as with metoprolol in POISE. DECREASE initiated bisoprolol at 25% of the maximum daily therapeutic dose, and allowed for titration to 50% of the maximum daily therapeutic dose.[3]

As the second largest study of perioperative beta-

blockade, the Diabetic Postoperative Mortality and Morbidity (DIPOM) trial enrolled 921 patients who were assigned to placebo or controlled-release metoprolol with a target dosage that was 25% of the maximum daily therapeutic dose.[4] The 30-day outcomes from DIPOM showed a trend toward an excess of death and stroke despite using only one-half the dosage in POISE and the same dosage as in DECREASE.

Timing of beta-blocker initiation

Another contention is that earlier beta-blocker initiation would be better. The issue with timing of initiation is not benefit, as POISE showed that starting a beta-blocker hours before surgery results in a reduction in the risk of MI. The issue is whether giving a beta-blocker earlier makes administering the drug safer. Nearly 10% of placebo recipients in POISE developed clinically significant hypotension, which suggests that the titrated dosage of a beta-blocker that appears effective preoperatively is unlikely to inform a safe dose *after* surgery, when hypotension is common.

The practicality of titrating the dose of beta-blocker prior to surgery also comes into play. Most patients referred to my institution for surgery are seen 1 to 2 weeks in advance, at the earliest. Real-world practice at present simply does not afford us the luxury of seeing patients three to four times before surgery in order to titrate the beta-blocker dose.

POISE did not address chronic beta-blocker therapy

It is important to remember that POISE excluded patients on chronic beta-blocker therapy and thus did not attempt to address the perioperative management of such patients who undergo noncardiac surgery. My suspicion is that perioperative continuation of beta-blockade in these patients is the best course of action, but this too has not been studied robustly, so we need a large controlled trial to confirm that this practice is indeed safe.

CONCLUSIONS

The POISE results suggest that for every 1,000 patients treated, perioperative metoprolol would:

- Prevent 15 MIs, 3 cardiac revascularizations, and 7 new cases of atrial fibrillation
- Result in 8 excess deaths, 5 strokes, 53 cases of clinically significant hypotension, and 42 cases of clinically significant bradycardia.

The central take-away message is that patients are unlikely to want a perioperative beta-blocker if they are unwilling to accept a probable increase in mortality or if they place three times more value on avoiding a perioperative stroke than on avoiding an MI.

It has been 10 years since the recommendation to use perioperatove beta-blockers was incorporated into perioperative practice guidelines. Assuming only 10% of physicians acted on this recommendation, 100 million patients have received a perioperative beta-blocker over this time as a result. If the POISE results are applicable, a full 800,000 of these patients died and another 500,000 suffered perioperative strokes as a result of being given a beta-blocker. This issue is not to be taken lightly, given the evidence to suggest harm.

Though it is possible that an alternative beta-blocker regimen to the one used in POISE may provide benefit without substantial harm, the data suggest this is not probable. The POISE data highlight the risk of making assumptions, as well as the importance of and need for large, high-quality randomized trials in the perioperative setting.

It is time for perioperative medicine to enter the age of evidence-based practice and embrace one of its central tenets: only large trials are reliable when it comes to therapeutic questions.

Rebuttals and discussion

POLDERMANS REBUTTAL: MORE TRANSPARENCY NEEDED IN POISE DOSING DATA

Dr. Poldermans: The initial paper describing the POISE trial design did indeed indicate that it was possible for a patient to receive 400 mg of metoprolol on the first day of treatment. We need to see the actual doses of metoprolol given to all patients in POISE who had a perioperative stroke. If you show me these data, the issue will be much easier to discuss.

Our data from randomized trials are consistent in showing that a titrated dosing regimen using bisoprolol reduces the incidence of postoperative cardiac events with no increase in the number of strokes.

My take-home message is that if you want to use beta-blockers, use them sensibly, use them carefully, and act during surgery. If many of your patients are developing hypotension, then you are doing something wrong.

DEVEREAUX REBUTTAL: A SHIFT IN THINKING IS REQUIRED

Dr. Devereaux: The data from POISE are fully available, and I take issue with Dr. Poldermans' contention that a patient could have received as much as 400 mg of metoprolol CR on the day of surgery; this was not an option according to protocol. I believe his statement is misleading in the same way that it is misleading to indicate that in the DECREASE trial patients may have received 20 mg of bisoprolol within 24 hours of surgery. It is possible that a patient in DECREASE could have gone to surgery at 2:00 PM and may have taken his or her bisoprolol at 10:00 AM that morning. The following morning (in the hospital), it is possible that the patient would have received his or her bisoprolol 10 mg at 7:00 or 8:00 AM (ie, 20 mg within 24 hours of surgery). Although this is possible and something similar

could have happened within POISE, it does not reflect a patient receiving an effective dose of metoprolol CR 400 mg or bisoprolol 20 mg over a 24-hour period.

I worry about the distortion of reality in perioperative medicine that leads so many of us to believe that randomization is magical despite small sample sizes. Small randomized trials are at profound risk of imbalance between the randomized groups, whether we see it or not, and the results are therefore simply not reliable.

Unless we shift our thinking, we make ourselves susceptible to overconfidence in the benefits of a certain intervention before the data from large clinical trials become available. In the meantime, as we have seen from POISE, an intervention may have negative consequences that are not apparent from small clinical trials.

The reality of excess stroke with perioperative beta-blockers is consistent across all the trials. It does not mean that we cannot find another way to give beta-blockers safely, but if we want to establish safety, we need a large trial that unequivocally demonstrates safety, as opposed to simply using observational data, retrospective cohorts, or comparisons between two nonrandomized trials. Until we have large data sets, it is very difficult to say that we can give beta-blockers safely.

DISCUSSION WITH THE AUDIENCE

Moderator*: Dr. Devereaux, was the hypotension in POISE related to the long-acting beta-blocker itself or to the large dose of if that was used? Similarly, were the strokes a result of the drug itself or of the hypotension?

Dr. Devereaux: I must take issue with your premise that the dose of metoprolol used in POISE was "large." As I noted, Mangano's study used its beta-blocker (atenolol) at 50% of its maximum daily therapeutic dose,[1] the same proportion used in POISE, and Dr. Poldermans' own DECREASE trial allowed titration of bisoprolol up to 50% of the maximum daily therapeutic dose.[3] The DIPOM trial used half the dose of metoprolol that we used, yet it too yielded a trend toward more death and stroke in the beta-blocker group.[4] So it's not that the dose we used was at some excessive level. At the same time, that does not mean that a smaller dose may not have achieved a similarly significant benefit in cardiac outcomes.

We can't explain most of the strokes. Because most strokes were ischemic, I suspect that the explanation may lie in the threshold used to define clinically significant hypotension. We used an SBP cutoff of less than 90 mm Hg, but we did not classify large drops in SBP, such as from 180 to 95 mm Hg, as clinically significant hypotension. The high incidence of clinically significant hypotension in the placebo group—about 10%—suggests that hypotension was likely the driving factor for stroke. The beta-blocker exacerbated the hypotension, but its more important effect may have been that it made it harder for the body to overcome the hypotension. That is the exact same signal observed in the COMMIT trial in the setting of acute MI.[22]

Dr. Poldermans: I'd like to see the intraoperative blood pressure data for the 60 patients who suffered strokes in POISE. We could then find out exactly when the hypotension occurred, what kind of hypotension it was, what the patient's initial blood pressure reading was, and so on. If we had access to this information, we could determine which occurred first—the hypotension or the stroke.

Dr. Devereaux: Although trials can indicate a signal, they can't explain with certainty the pathway through which the outcome occurred. For example, we know that beta-blockers prevent MI, but we don't know how. What's most impressive about the stroke issue is the consistency across all the perioperative beta-blocker trials: every one shows a direction of excess stroke with beta-blockers.

Question from the audience: The patient groups studied in DECREASE and POISE were different. DECREASE studied a very high-risk vascular surgery group with known coronary artery disease on the basis of echocardiography. POISE included patients undergoing emergency surgery and patients with sepsis. Can you describe the outcomes in POISE solely among the patients who underwent elective vascular surgery, similar to the patients studied in DECREASE?

Dr. Devereaux: In terms of the benefit to bisoprolol in very high-risk patients in DECREASE, remember that it was a study of 112 patients. That's far too small a trial to establish safety or efficacy. The benefit of perioperative beta-blockade in preventing MI is unequivocal because it's consistent across all trials. But the real issue is, was it safe?

Interestingly, in POISE, the groups at highest risk looked like they benefited the least, not the most. The notion of targeting high-risk people is not supported by POISE; if anything, the POISE results went in the direction of harm with beta-blockade in high-risk patients. That being said, the *P* value for interaction is not statistically significant, but it's heading in the direction of harm. So I wouldn't take comfort in believing that if we simply target high-risk patients, beta-blockers become safe.

Question from the audience: I believe that the seven or eight studies that showed higher stroke rates with beta-blockers all gave beta-blockade within 24 hours of surgery. Only in DECREASE was it given days and weeks in advance of surgery. Can you comment?

Dr. Poldermans: There's clearly a relation between the time of beta-blocker initiation and the incidence of stroke. If you look at the randomized trials, you see an increased

* Amir K. Jaffer, MD, University of Miami Miller School of Medicine, served as moderator of the debate and the discussion period.

incidence of stroke in patients in whom beta-blockers are started just prior to surgery but not in patients who are on chronic beta-blockers. In our case-control study,[18] we screened more than 185,000 patients for stroke and could not detect an increased incidence of stroke in those on chronic beta-blocker therapy. So stroke indeed has something to do with starting beta-blockers just before surgery.

Dr. Devereaux: In DECREASE IV, bisoprolol was started up to 1 month before surgery, yet there were 4 strokes in the bisoprolol group versus 3 in the control group.[17]

Dr. Poldermans: Yes, but that difference is not statistically meaningful.

Comment from the audience: I'm uncomfortable with the way Dr. Devereaux stresses the importance of significant findings from large randomized trials but then quibbles about a stroke rate of 4 versus 3, which is not statistically significant. Keep it scientific: either there is or there isn't a *P* value that achieves significance.

Though I congratulate you on a great trial, any resident in my program would be fired for pursuing your strategy of perioperative care in POISE, which included using an SBP of 100 mm Hg as the threshold for stopping the beta-blocker regardless of preoperative blood pressure. An SBP of 100 mm Hg is not the definition of hypotension. Most anesthesiologists and perioperative physicians peg the beta-blockade to a reasonable level based on the preoperative blood pressure. They titrate in fluids and titrate in the beta-blocker. Certainly the timing is an issue—we don't recommend giving it right before the operation.

Dr. Devereaux: I referred to the stroke rates in DECREASE IV because Dr. Poldermans has claimed that the excess in strokes has occurred in all trials but his, yet DECREASE IV was one of his trials and also one in which bisoprolol was started early. I'm not claiming statistical significance between the 3 versus 4 strokes in DECREASE IV, but the stroke trend is in the same direction as in the other trials, so it tells us nothing with regard to safety. My point is, has anyone proven safety? As much as we'd like to imagine that beta-blockers are safe perioperatively—and maybe they are—it has not been proven. The largest trials at present are consistent with a signal toward harm.

It's easy to criticize the methodology after a trial is done. A number of us came together and thought we had a reasonable protocol for POISE. We found a reduction in the incidence of MI but more strokes and higher mortality with perioperative metoprolol. Does this mean there is not a safe way to give a beta-blocker and derive the benefit? Of course not. But at the moment the evidence does not support a way to give a beta-blocker safely. Do we need to find a way to give it safely? Of course we do.

For example, the design of POISE II is factorial, looking at aspirin versus placebo as well as clonidine versus placebo. There are a number of factors about clonidine that suggest we might be able to achieve the benefits we saw in POISE and avoid the risk, but until we do a large trial, we're not going to know.

Comment from the audience: It's important that we clearly understand the conclusion from POISE. It's not that the administration of beta-blockers is not safe. It's that the administration of a beta-blocker, as your methodology applied it, was not totally safe. Those are two very different conclusions.

Dr. Devereaux: I would say the conclusion is that the way that beta-blockers are being given has not been proven to be safe. The result is consistent. It's even consistent with DECREASE IV.

Moderator: I believe in large clinical trials, but they must apply to real-life practice. POISE did not address the practices of many people in this room, particularly regarding the doses of metoprolol used. So it is hard for us to apply the findings in clinical practice. Those of you who design large trials need to think through your trial design very thoroughly, considering the millions of dollars that go into these trials. It's not fair to clinicians to do a study that may have little clinical relevance.

Dr. Devereaux: Investigators from 190 centers in 23 countries were involved in POISE, and all of them thought we had a reasonable approach and methodology. That doesn't mean it was perfect, yet the criticisms we are hearing now did not surface while the trial was ongoing.

Comment from the audience: My hospital in Australia contributed to the POISE study. When it started 6 or 7 years ago, the cardiologists were using beta-blockers liberally and haphazardly. It was a huge challenge to convince them that conducting the trial was justifiable—that the case for perioperative beta-blockers had not been absolutely and overwhelmingly proved. They wanted to put beta-blockers in the water supply at the doses we're talking about.

It would be interesting to do separate analyses of the data from the various countries involved in POISE. In Australia, the percentage of the population on chronic beta-blockers—who therefore would have been ineligible for the trial—is now quite high. Most patients who need to be on beta-blockers long term are on them, whereas that was not the case 15 years ago. The population is changing even while we're doing the trials. Australian cardiologists are no longer putting every patient on perioperative beta-blockers; they're thinking about it first.

Dr. Devereaux: A compelling feature of POISE as an international trial is its consistency of outcomes across the planet. No matter where we looked, the outcomes were consistent: in Asia, Europe, North America, and Australia.

Moderator: Would each of you summarize your take-

home message for clinicians?

Dr. Devereaux: I urge clinicians to actually read the trials themselves rather than just relying on the advice of guideline writers. It's important not to allow ourselves to become entrenched in a practice without evidence, just because we've done it for so long. If you told your patients the number of MIs prevented and the potential number of excess strokes and deaths, I suspect the average patient would conclude it's not a great trade-off.

Remember that two-thirds of MIs in the perioperative setting are clinically silent. That doesn't mean they're not important, but the strokes, in contrast, are profoundly devastating. One-third of patients with stroke in POISE were dead within 30 days, and of those who survived, 60% were incapacitated, needing help with everyday activities.

I encourage clinicians to read the POISE manuscript with a fresh perspective, regardless of how you've practiced until now. Then ask yourself whether you really are comfortable with the safety of perioperative beta-blockers at this time. Of course, that doesn't mean the evidence won't change in the future.

Dr. Poldermans: The main imperative is to improve postoperative care. We strongly believe that perioperative beta-blockers work in the general population. If you have a patient who needs to be on a beta-blocker after surgery, why not start it preoperatively? I believe that dosing and timing of initiation are important. If you have the opportunity to start the beta-blocker prior to surgery, do so at a reasonable dose and start early. Patients in whom beta-blockers are started immediately prior to surgery may be worse off, with a higher incidence of stroke.

DISCLOSURES

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Perioperative considerations for patients with liver disease

ABSTRACT

In surgical patients with underlying chronic liver disease, surgical outcomes correlate with hepatocellular function. The risk of surgery in such patients should be assessed preoperatively using the Child-Pugh or Model for End-Stage Liver Disease (MELD) severity scoring systems. Patients with severe liver disease (eg, Child-Pugh class C) should not undergo any elective surgery and should be evaluated for liver transplantation. In patients who can proceed with surgery, coagulopathy should be corrected preoperatively and careful fluid management is required intraoperatively to avoid hypotension. Renal insufficiency (as evidenced by elevated creatinine) may indicate that hepatorenal syndrome has developed and carries a poor prognosis.

KEY POINTS

Patients with acute hepatitis should delay elective surgery until after their hepatitis resolves.

Patients with chronic liver disease who have developed any index complication—variceal hemorrhage, ascites, hepatic encephalopathy, or jaundice—are at increased risk for postoperative complications and death.

The Child-Pugh and MELD scores appear to be comparably effective in predicting surgical outcomes in patients with liver disease.

Cardiac surgery with cardiopulmonary bypass and abdominal surgery are particularly high-risk procedures in patients with liver disease.

If cholecystectomy is indicated in a patient with compensated liver disease, laparoscopy should be the initial approach, with conversion to an open procedure only if necessary.

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Assessing patients with liver disease for surgery is one of the most common reasons for hepatology consultation in the hospital. This review focuses on practical aspects of evaluating patients with known or suspected liver disease and provides guidance for determining whether it is safe to proceed with surgery in such patients. I begin with a case study to introduce some common clinical challenges and then revisit the case—with relevant teaching points—at the end.

CASE: A MIDDLE-AGED MAN WITH LIVER DISEASE SCHEDULED FOR CARDIAC SURGERY

A 57-year-old man with a history of liver disease is referred for preoperative assessment. It is 6:30 PM, and the patient has just arrived in the hospital; he is scheduled for coronary artery bypass graft surgery (CABG) early tomorrow morning for ischemic heart disease. Ten years ago, he was diagnosed with hepatitis C virus infection; 2 years later, he had a cholecystectomy. He has a remote history of intravenous drug use.

The sub-intern asks for an assessment of operative risk as well as advice on the type of anesthesia to be used.

HEPATIC EFFECTS OF ANESTHESIA

Anesthesiologists are keenly aware of the hepatic effects of anesthesia and that they must carefully choose anesthetics for patients with liver disease. There are a number of at least theoretical concerns about using particular anesthetics:

- Inhaled anesthetics, such as isoflurane, cause systemic vasodilation and depress cardiac output. These effects are of concern since many patients with advanced liver disease already have a hyperdynamic circulation because of peripheral vasodilation.
- Spinal or epidural anesthetics may reduce mean arterial pressure, which is of concern for similar reasons.
- Nitrous oxide has less of a depressive effect unless the patient has concomitant hypercapnia.

Another consideration is the hepatic metabolism of anesthetic agents. Use of halothane, which is 20% metabolized by the liver, is now uncommon, particularly if there is any concern about liver disease. In contrast, enflurane is only 4% metabolized by the liver. Numerous other anesthetics—including isoflurane, desflurane,

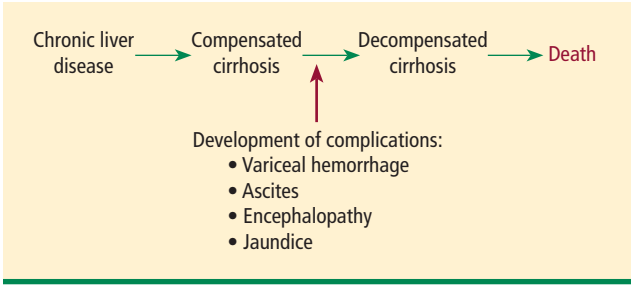

FIGURE 1. Natural history of chronic liver disease.

and sevoflurane—have only minimal hepatic metabolism (< 0.2%), which makes them, along with nitrous oxide, the best anesthetic choices for patients with liver disease.

ASSESSING OPERATIVE RISK

The more important issue in the consultation for our patient is the degree of operative risk associated with his underlying liver disease. A number of factors are pertinent, including the etiology and severity of the liver disease and the type of surgery planned.

Acute liver disease has higher operative risk

Literature dating back 40 years has associated acute viral and alcoholic hepatitis with poor outcomes in surgical patients. Major elective surgery for a patient with suspected acute hepatitis A, for example, should be deferred until the patient has recovered, barring some compelling reason for greater urgency, such as a perforated viscus.

In chronic liver disease, hepatocellular function predicts outcome

For patients with chronic liver disease, outcomes correlate with underlying hepatocellular function. Chronic liver disease tends to run a predictable course **(Figure 1)**. Patients with well-compensated cirrhosis may enjoy good health for many years. But once an index complication—such as variceal hemorrhage, ascites, hepatic encephalopathy, or jaundice—develops, prognosis rapidly worsens.[1]

When a patient with liver disease is evaluated for surgery, evidence should be sought to determine whether an index complication has already occurred. Because the patient in our case study had a cholecystectomy several years before, I would also ask, "What did the surgeon say your liver looked like? Did you have any bleeding problems afterwards? Did you develop ascites?"

It is also important to determine whether portal hypertension is present. For a patient with liver disease, otherwise unexplained thrombocytopenia is a useful indicator of portal hypertension.

Systems for scoring liver disease severity

Even a surgical patient with well-compensated liver disease is at risk for developing complications postoperatively, particularly if abdominal surgery is planned. Risk should be assessed in all patients with liver disease using either the Child-Pugh scoring system or the Model for End-Stage Liver Disease (MELD) scoring system.

The Child-Pugh score, which assigns 1 to 3 points according to the presence/absence and levels of each of five simple factors (bilirubin, albumin, prothrombin time/international normalized ratio [INR], ascites, and encephalopathy stage), has been used for decades to assess the severity of liver disease. Patients with Child-Pugh class A disease (score of 5–6) have well-compensated cirrhosis and good synthetic function, and therefore have essentially no restrictions for undergoing surgery. For patients in Child-Pugh class B (score of 7–9), the risk of perioperative complications and mortality is higher and any major hepatic surgery (such as hepatic resection) should be avoided. Patients with class C cirrhosis (score of 10–15) are not candidates for any major elective surgery and should be considered for liver transplantation referral.

The MELD scoring system was developed more recently and is used to prioritize eligibility for liver transplantation. Calculated using a mathematical formula that incorporates three objective patient variables—creatinine, bilirubin, and INR—the MELD score correlates very well with prognosis. The score can be calculated by an online MELD calculator such as the one at *www.unos.org/resources*.[2] A patient with a high MELD score is unlikely to survive for more than a few months without liver transplantation; a patient with a low MELD score is likely to survive for at least 12 months. Calculating the MELD score is now one of the first assessments in any patient suspected of having cirrhosis.

Risk factors for complications and death

In a retrospective study to identify factors associated with complications and mortality in surgical patients with cirrhosis, Ziser et al reviewed the records of 733 patients with cirrhosis who underwent surgical procedures (except liver transplantation) at the Mayo Clinic over an 11-year period (1980–1991).[3] The mortality rate within 30 days of surgery was 11.6%. Long-term follow-up showed that most deaths occurred within the first few months after surgery, when many patients succumbed to pneumonia or renal insufficiency.

Univariate analysis of the results identified many patient- and procedure-related factors that were predictive of complications and short- and long-term mortality. **Table 1** lists those factors that were found by multivariate analysis to be *independently* predictive of perioperative complications and of postoperative mortality.[3]

Risk factors have strong cumulative power

The study by Ziser et al also underscored the cumulative effect of risk factors, as the probability of developing a

perioperative complication increased dramatically with the number of risk factors (as identified by multiavariate analysis) that a patient had, as follows[3]:

- 9.3% risk of complications with 1 risk factor
- 14.5% risk with 2 factors
- 33.5% risk with 3 factors
- 63.0% risk with 4 or 5 factors
- 73.3% risk with 6 factors
- 100% risk with 7 or 8 factors.

Postoperative complications: Beware hepatorenal syndrome

The most common postoperative complications in the study by Ziser et al were pneumonia, other infections, ventilation dependency, and ascites.[3]

Possibly the most ominous perioperative complication in a patient with liver disease is the onset of renal insufficiency, which may be precipitated by a number of factors, including nephrotoxic drugs and intraoperative hypotension. Renal insufficiency is usually a predictor of markedly reduced survival and a sign that hepatorenal syndrome may have developed.

Hepatorenal syndrome, which occurred in 3.3% of patients in the analysis by Ziser et al,[3] is the presence of renal failure in a patient with cirrhosis. It is characterized by advanced liver failure and severe sinusoidal portal hypertension. The renal failure is said to be "functional" because significant histological changes are absent on kidney biopsy. Marked arteriolar vasodilation occurs in the extrarenal circulation with renal vasoconstriction leading to reduced glomerular filtration.

TABLE 1
Factors independently predictive of complications and mortality in cirrhotic patients undergoing surgery*

Predictors of complications	Predictors of mortality
Child-Pugh class B or C	Male gender
Ascites	Child-Pugh class B or C
Etiology of cirrhosis other than primary biliary cirrhosis	Etiology of cirrhosis other than primary biliary cirrhosis
Elevated creatinine	Ascites
Preoperative infection	Preoperative infection
COPD	Respiratory surgery
Preoperative upper GI bleeding	ASA physical status of 4–5
Invasiveness of surgical procedure	
Intraoperative hypotension	
ASA physical status of 4–5	

*According to multivariate analysis in a retrospective study of 733 patients.[3]
COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; ASA = American Society of Anesthesiologists

IMPORTANCE OF SURGICAL PROCEDURE TYPE

In addition to the patient-specific risk factors discussed above, certain surgical procedures deserve special consideration in patients with liver disease.

Cholecystectomy: Open vs closed

Patients with liver disease have the same indication for cholecystectomy as anyone else does: *symptomatic* gallstone disease. Patients with cirrhosis who are found to have incidental gallstones on ultrasonography should not undergo cholecystectomy unless the gallstones are symptomatic, as liver function may deteriorate after surgery.

For a patient with liver disease undergoing cholecystectomy, a common concern is whether an open or closed procedure should be done. Conventional wisdom had been that a patient with underlying liver disease (particularly cirrhosis) should have an open procedure so that the surgeon could more easily control bleeding, but that notion has changed in recent years with evidence supporting the safety of a laparoscopic approach in patients with liver disease.

One study supporting this new strategy is a retrospective review of 50 patients who had undergone cholecystectomy for symptomatic gallstone disease at the Mayo Clinic between 1990 and 1997.[4] The procedure was open in half of the patients and laparoscopic in the other half. All patients had Child-Pugh class A or B cirrhosis. The indications for surgery were acute cholecystitis, biliary colic, or pancreatitis, and the number of patients with each of these indications was comparable between the open-surgery and laparoscopy groups. Three patients who initially underwent laparoscopy were converted to open cholecystectomy: two for bleeding and one for poor access. The study found that laparoscopic cholecystectomy was associated with statistically significant reductions in operating room time, blood loss, and length of hospital stay. No deaths occurred in either group. The authors concluded that laparoscopic cholecystectomy is safe in patients with cirrhosis and offers several advantages over an open surgical approach.

In light of these findings and other recent evidence, laparoscopic cholecystectomy should be recommended for patients with liver disease unless they have ascites or other evidence of overt hepatic decompensation, in which case cholecystectomy itself is contraindicated.

Cardiac surgery with bypass poses extra risk

Patients with liver disease undergoing open heart surgery with cardiopulmonary bypass are at especially high risk because of the effect on hepatic hemodynamics. This risk was demonstrated in a retrospective review of all patients with cirrhosis who underwent cardiac surgery with car-

diopulmonary bypass at the Cleveland Clinic from 1992 to 2002.[5] Of the 44 patients identified, 12 (27%) developed hepatic decompensation and 7 (16%) died. Hepatic decompensation was a major factor in all the deaths.

The MELD and Child-Pugh scores correlated well with one another in this study and were highly associated with hepatic decompensation and death. The best cutoff values for predicting mortality and hepatic decompensation were found to be a score greater than 7 in the Child-Pugh system and a score greater than 13 in the MELD system. (For context, receipt of a donor liver via a transplant list in the United States requires a MELD score of at least 15.) The study confirmed that the Child-Pugh score, which is easy to determine at the bedside, remains a reliable predictor of poor outcomes.[5]

CASE REVISITED: POSTOPERATIVE LIVER FUNCTION DECLINE—HOW SERIOUS IS IT?

Our patient undergoes the CABG procedure, and 3 days later you are asked to see him. According to the subintern, although the surgery was successful, the patient is now "in liver failure." After hearing this news, the family is anxious to discuss liver transplantation.

On examination, the patient is alert and extubated, so he is clearly not encephalopathic. His wound is clean and shows no sign of infection. He appears to be mildly icteric, and he may have some ascites, based on mild flank dullness.

His laboratory test results are as follows:

- Bilirubin, 3.1 mg/dL (normal range, 0.3–1.2)
- INR, 1.2 (0.9–1.2)
- Alanine aminotransferase (ALT), 300 U/L (10–40)
- Creatinine, 0.9 mg/dL (0.6–1.2).

Although the bilirubin and ALT are elevated, it is notable that the creatinine is normal. This pattern is not uncommon after elective surgery in a patient with underlying cirrhosis. Renal dysfunction is the biggest concern in the perioperative management of a patient with liver disease, as it is an indicator that the patient may develop overt hepatic decompensation. Likely reasons for the patient's ALT elevation are the effects of cardiopulmonary bypass and possible intraoperative hypotension.

The family needs to be told that the patient is not in liver failure and that it is best to wait with the expectation that he will do fine unless other complications supervene.

You advise cautious diuresis, and the ALT falls over the next few days. The bilirubin declines to 2.0 mg/dL. At this point, you advise discharge planning.

One need not wait for the bilirubin to return to normal: after an acute hepatic insult such as ischemic hepatitis or intraoperative hypotension, bilirubin is the last indicator to improve. Bilirubin is in part albumin-bound, and the half-life of albumin is 18 days, so a patient can remain icteric for some time after the rest of the liver function tests have returned to normal.

DISCUSSION

Question from the audience: What are your recommendations regarding platelet transfusion if the platelet count is less than 50,000 in a patient with liver disease?

Dr. Martin: For patients with thrombocytopenia, it is prudent to get the platelet count above 60,000 before any procedure. We will not even do a blind liver biopsy in a patient with a platelet count of less than 60,000.

Question from the audience: A study from the *Annals of Surgery* concludes that patients with liver disease do poorly with a hemoglobin of less than 10 g/dL. Would you transfuse aggressively before surgery?

Dr. Martin: For a patient with anemia, I don't like to use aggressive transfusion if cirrhosis is present because the portal pressure may go up and increase the risk of variceal hemorrhage. If there is adequate time for a work-up, one can screen for varices by endoscopy. If there is evidence of overt hepatic decompensation and portal hypertension (esophageal varices, a palpable spleen, and thrombocytopenia), I wouldn't try to get the hemoglobin much above 10 g/dL.

Question from the audience: How would you modify prophylaxis for deep vein thrombosis following hip or knee replacement surgery in patients with liver disease?

Dr. Martin: I would base it on the INR. Patients who are already mildly coagulopathic tend to be very sensitive to warfarin in the long term. For immediate perioperative prophylaxis, I would not administer anything if the patient had a platelet count below 60,000; otherwise I would probably proceed as usual.

Question from the audience: You said that we shouldn't operate on patients with acute hepatitis, but we frequently encounter patients with drug-induced hepatitis, such as from anticholesterol drugs. These patients' ALT and aspartate aminotransferase (AST) levels can remain elevated for 2 or 3 months. How long should we delay surgery? For example, is it dangerous to proceed with a mastectomy a month after discontinuing the drug if the liver enzymes are still around 100 U/L?

Dr. Martin: It's worth noting that much of the literature on surgery in patients with acute viral hepatitis is 30 or 40 years old. If such a patient had a compelling reason to have surgery, you might wait until the liver enzymes were trending downward and you were confident that the patient was recovering.

Question from the audience: How do you manage

patients who have varices or have had variceal bleeding in the past? Many of them are on beta-blockers, such as propranolol, which can cause hypotension intraoperatively.

Dr. Martin: The standard of care is to prescribe beta-blockers for a patient with large varices, or to ablate the varices by endoscopy, which is my practice. In general, I would discontinue propranolol on the morning of surgery. If possible, however, I would have the patient undergo endoscopy before surgery to assess the likelihood of short-term variceal bleeding. If the varices look to be at low risk of bleeding, the beta-blocker can safely be stopped. If they look to be at high risk of bleeding, the surgery should be delayed for a few weeks, if possible, so that the varices can be ablated, which usually takes two or three sessions.

Question from the audience: I deal with many referrals, and I struggle with how aggressive a work-up I should do for patients undergoing elective surgery when a new abnormality is found in one of their liver function tests.

Dr. Martin: I would try to establish whether the abnormality is a chronic problem. Has the patient been told about an abnormal liver test in the past? Ask if the patient has been a blood donor, as measurement of ALT and some hepatitis serologies would have been required. Also ask if he or she has ever taken out a big life insurance policy, which also would have required liver function testing. If the abnormality is chronic, you may proceed with surgery if the bilirubin and INR are normal. In the absence of chronicity, surgery should be delayed for further work-up only in patients with indicators of significant liver disease—either markedly abnormal liver tests, thrombocytopenia, or coagulopathy.

Follow-up question: But patients rarely know whether they've had elevated liver enzymes in the past. You said not to worry about enzyme abnormalities unless they are markedly elevated, but how high is that?

Dr. Martin: AST and ALT are indicators of liver injury rather than of synthetic function. The true liver function tests are really albumin, bilirubin, and prothrombin time. Paradoxically, one of the best liver function tests is the platelet count. For me, a red flag for a patient with newly recognized liver disease is any degree of thrombocytopenia or coagulopathy or an elevation of bilirubin above the upper limit of normal. A patient with a platelet count of 90,000 and an INR above 1.2 has significant underlying liver disease, and I would be very concerned. Unless it's a dire emergency, such a patient would need further evaluation before proceeding with surgery. In contrast, a patient with an ALT of 89, an AST of 65, and normal prothrombin time and platelet count should be safe to proceed to surgery. But such a patient needs an evaluation for liver disease afterward.

Question from the audience: My institution performs many liver resections for metastases or primary liver cancers. Our liver surgeons routinely discontinue statins 2 to 3 weeks before liver surgery, but it has been said at this summit that is not necessary. What's your opinion?

Dr. Martin: I think that statins get a very bad rap in terms of hepatotoxity. Most patients with metabolic syndrome have hyperlipidemia, which can cause fatty liver disease and hepatic dysfunction. Statins help bring the lipid levels down. Hepatologists do not regard statins as major culprits in causing liver problems. I don't believe there's any particular indication to stop them before a patient undergoes hepatic surgery.

Question from the audience: I assess patients 1 or 2 weeks before surgery. For a patient with coagulopathy whom you suspect has underlying liver disease, is there any value in trying to treat the coagulopathy with vitamin K?

Dr. Martin: It can be worthwhile to try 10 mg subcutaneously for 3 days to see whether the situation improves, but if the patient has severe parenchymal liver disease, the vitamin K won't help much.

DISCLOSURES

Dr. Martin has indicated that he has no financial relationships with commercial interests that have a direct bearing on the subject matter of this article.

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Perioperative management of obstructive sleep apnea: Ready for prime time?

ABSTRACT

Obstructive sleep apnea (OSA) is associated with increased risks of cardiovascular disease and stroke and with elevated rates of postoperative complications (including cardiac ischemia and respiratory failure) in surgical patients. Additionally, the prevalence of OSA is higher in surgical patients than in the general population. Screening for OSA prior to surgery is recommended to identify patients at risk for postoperative complications. The presence of moderate or severe OSA calls for modified strategies of perioperative anesthesia, pain management, and postoperative monitoring to reduce the chance of OSA-associated complications.

KEY POINTS

OSA is more common than asthma in adults, affecting 4% and 2% of middle-aged men and women, respectively.

OSA is associated with serious health consequences, including increased risks for accidents, stroke, hypertension, coronary artery disease, atrial fibrillation, and postoperative complications.

Screening tools consisting of only a few questions are available to quickly and effectively identify risk for OSA prior to surgery.

For surgical patients deemed to be at high risk for OSA, and for whom surgery cannot be delayed for diagnostic tests and OSA treatment, the best course is to proceed with surgery but assume the patient has moderate to severe OSA.

Use of regional anesthesia, close attention to airway management, vigilant postoperative monitoring of pulse oximetry, and minimal use of opioids are recommended for patients with OSA.

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Obstructive sleep apnea (OSA) is characterized by repeated complete or partial collapse of the pharyngeal airway during sleep, causing cessation of airflow (apnea) or shallow breathing (hypopnea). Persons with OSA may have repeated arousals from sleep (to reestablish breathing) with each episode of apnea or hypopnea. The resulting sleep disruption often leads to daytime somnolence and compromised neurocognitive function.

This pattern of sleep arousal, coupled with intermittent hypoxemia, is associated with serious adverse cardiovascular outcomes, including stroke. Among surgical patients, OSA is associated with postoperative complications and the need for increased medical intervention. This review discusses why OSA is important in the perioperative setting, preoperative screening for OSA risk, and perioperative management of patients with likely or confirmed OSA.

OSA AT A GLANCE

Prevalence in the general population

Four percent of middle-aged men and 2% of middle-aged women meet minimal diagnostic criteria for OSA, according to a landmark cohort study from the 1990s.[1] This makes OSA more common than asthma among adults. Risk increases with age, as 24% of persons older than 65 years have OSA and up to 50% of nursing home residents have clinically significant OSA.[2]

Prevalence in the surgical population

The prevalence of OSA in the surgical population is higher than that in the general population, and it can vary widely according to the underlying medical condition. A study of 433 patients undergoing general surgery reported a 3.2% prevalence of OSA,[3] but this study excluded patients undergoing cardiac surgery, in whom the risk of OSA is higher. In contrast, the prevalence of OSA among obese bariatric surgery patients has been reported at greater than 70%.[4] Notably, the patients in the general surgery study[3] who appeared to be at risk for OSA based on screening questions were invited to participate in a sleep study, whereas all patients in the bariatric surgery study[4] were evaluated through sleep studies. It is likely that the prevalence of OSA among the general surgery study patients would

have been higher if all patients had been evaluated with polysomnography.

Pathophysiology

OSA can occur when any part of the upper airway does not function normally. Upper airway patency is determined by muscle activity, craniofacial and soft tissue structure, and sleep state. During sleep, upper airway muscles are relaxed, which reduces airway patency. Sleep is associated with pharyngeal narrowing and substantially increased inspiratory resistance even among persons without sleep apnea. A person who is awake can compensate for abnormal pharyngeal function through increased muscle activity. During sleep this muscle compensation fails, resulting in partial collapse and subsequent snoring, and sometimes prolonged obstructive hypoventilation. Complete closure results in apnea.

WHY OSA MATTERS

Health consequences of OSA

OSA is associated with serious health consequences, such as increased risk of motor vehicle accidents, stroke, and a number of cardiovascular conditions—hypertension, coronary artery disease, and atrial fibrillation.

Accidents. The daytime hypersomnolence resulting from OSA contributes to reduced vigilance and is likely responsible for an increased incidence of motor vehicle accidents. One study found that among a sample of men and women with unrecognized OSA undergoing polysomnography studies, the likelihood of motor vehicle accidents during the prior 5 years was significantly correlated with the subjects' apnea-hypopnea index (AHI) score, which reflects the number of apnea or hypopnea episodes per hour of sleep.[5] Other studies have demonstrated similar associations.

Stroke. Numerous observational studies have demonstrated an elevated prevalence of OSA among patients with stroke as compared with the general population, but these studies did not adjust for other cerebrovascular risk factors. A recent observational cohort study aimed to address this evidence gap by using proportional hazards analysis to determine the independent effect of OSA on the incidence of stroke or death from any cause among persons with no history of stroke or myocardial infarction.[6] Study participants were 1,022 consecutive patients who underwent polysomnography for evaluation of sleep-disordered breathing. OSA was identified in 68% of patients. During the 3.4-year follow-up period, 22 strokes and 50 deaths occurred among the 697 patients with OSA compared with 2 strokes and 14 deaths among the 325 patients without OSA. The probability of survival was significantly lower for patients with OSA compared with their counterparts without OSA ($P < .003$). After adjustment for other risk factors, OSA was significantly associated with stroke or death (hazard ratio = 1.97; 95% CI, 1.12–3.48).[6]

Hypertension. Four large studies involving a total of 10,708 patients evaluated for sleep-disordered breathing have established an association between OSA and hypertension risk.[7–10] In each study, the risk of hypertension rose linearly with AHI scores. Clinically significant OSA, defined as an AHI score greater than 15, roughly doubled the risk of hypertension compared with the absence of apnea/hypopnea episodes, with odds ratios ranging from 1.37 to 2.89 across the four studies.[7–10] Each apnea event per hour of sleep was estimated to increase the odds of developing hypertension by approximately 1%.[8] Notably, the effects of OSA on blood pressure are most pronounced in patients younger than age 50.[7]

Coronary artery disease. The Sleep Heart Health Study evaluated the association between sleep-disordered breathing and cardiovascular disease in 6,424 community-dwelling adults undergoing home polysomnography.[11] The population's median AHI score was 4.4. At least one cardiovascular event was reported by 16% of participants. Sleep-disordered breathing was associated with self-reported heart failure, stroke, and, more modestly, coronary artery disease. A linear relationship was noted between AHI and cardiovascular risk.

Snoring, which is often an indicator for OSA, has also been associated with cardiovascular risk. The Nurses' Health Study evaluated 71,000 women who completed medical questionnaires that included questions about snoring. Over 8 years of follow-up, the relative risks for cardiovascular disease were 1.46 among occasional snorers (95% CI, 1.23–1.74) and 2.02 among regular snorers (95% CI, 1.62–2.53) in comparison with nonsnorers. Snoring, even without a diagnosis of OSA, emerged as an independent risk factor for cardiovascular disease.[12]

Atrial fibrillation. OSA has been identified as a predictor of new-onset atrial fibrillation in a retrospective cohort study (hazard ratio = 2.18; 95% CI, 1.34–3.54).[13] In a prospective study, patients with atrial fibrillation but normal left ventricular function were found to have significantly higher AHI scores than matched normal controls.[14] After adjustment for relevant covariates, the odds ratio for an association between atrial fibrillation and significant sleep-disordered breathing (AHI score > 15) was 3.04 (95% CI, 1.24–7.46).[14] In another prospective trial, patients with atrial fibrillation and OSA who underwent cardioversion were at increased risk for a recurrence of atrial fibrillation if OSA was untreated (82% for untreated vs 42% for treated OSA; $P = .013$).[15]

An association with postoperative complications

OSA also has been shown to increase postoperative complication rates, increase the need for intensive care intervention, and prolong hospital stays.

TABLE 1
Factors to keep in mind in the evaluation for obstructive sleep apnea (OSA)

Factors that reduce upper airway size or predispose to upper airway collapse

- Obesity
- Male gender
- Menopausal status
- Hard-tissue craniofacial abnormalities (retrognathia, micrognathia, brachycephaly)
- Soft-tissue craniofacial abnormalities (large uvula, enlarged tonsils, macroglossia, long soft palate)
- Alcohol or sedative use (aggravates underlying OSA)

Symptoms and complaints that may be suggestive of OSA

Snoring	Personality change
Sleepiness	Morning confusion
Physically restless sleep	Intellectual impairment
Night sweats	Impotence
Morning dry mouth or sore throat	Morning headaches

Representative evidence. One of the first studies to characterize the postoperative risks of OSA was conducted by Mayo Clinic researchers who retrospectively reviewed 4 years of data for 101 patients with OSA who had had hip or knee replacement surgery within 3 years before (n = 36) or any time after (n = 65) their OSA diagnosis.[16] Outcomes were compared with those of 101 matched controls without OSA who underwent the same operations. Only half the patients with diagnosed OSA prior to their operation used continuous positive airway pressure (CPAP) therapy at home prior to hospitalization. Complications occurred among 39% of patients with OSA and among 18% of control patients (P = .001). Serious complications requiring intensive care unit transfer for cardiac ischemia or respiratory failure occurred in 24% of patients with OSA versus only 9% of controls (P = .004), and hospital stays were longer for patients with OSA compared with controls (P < .007). Most complications occurred during the first day after surgery, but a small number occurred as late as postoperative days 4 and 5.

In a separate study designed to evaluate OSA screening tools, postoperative complication rates were assessed in 211 patients who underwent polysomnography to determine the presence or absence of OSA prior to elective surgery.[17] Patients undergoing various elective procedures were included, but none were undergoing cardiac or bariatric procedures. The overall rate of postoperative complications was more than twice as high among patients with OSA compared with those without OSA (27.4% vs 12.3%; P = .02). The most common complication was oxygen desaturation (ie, level ≤ 90%), which occurred among 20.6% of patients with OSA versus 9.2% of patients without OSA (P < .04). There were no deaths or serious complications.

Potential causes of complications. In the immediate postoperative period, OSA-associated complications may be attributable to lingering effects of sedatives, which can often lead to respiratory problems. Later in the postoperative course, so-called REM rebound is more likely to be implicated in complications. Patients often experience sleep deprivation in the hospital due to constant interruptions. Once a patient does sleep, the amount of REM sleep increases to compensate for this deprivation. The REM stage is when most apneas and hypopneas occur, so the risk of hypoxemia is greatest in the REM stage. As a result, respiratory and cardiovascular complications such as arrhythmias can increase.

OSA AND THE PREOPERATIVE EVALUATION

Risk factors for OSA

The top portion of **Table 1** lists factors that reduce upper airway size or predispose to upper airway collapse and thereby increase risk for OSA. Fortunately, anesthesiologists are frequently aware of the craniofacial abnormalities listed in the table because they affect ease of intubation. The inclusion of menopausal status reflects the fact that women tend to catch up with men in their risk for OSA by the time they reach menopause.

Additionally, certain aspects of perioperative management can increase the risk of OSA in the perioperative setting. For example, general anesthesia can mimic the effects of sleep on the airway, reducing muscle tone and potentially leading to pharyngeal collapse. Normal response to hypercapnia is also diminished under general anesthesia and while patients remain sedated postoperatively, which subdues normal protective arousal mechanisms. This does not pose a problem while the patient remains intubated but highlights the need for respiratory monitoring in the extubated patient who is recovering from the residual effects of sedation.

History and physical examination

What to look for. A number of physical characteristics reveal potential risks for OSA. Obesity and hypertension are well established, as noted above. Large neck circumference (≥ 17 inches in men and ≥ 16 inches in women) is another characteristic associated with OSA. Examination of the upper airway can reveal obstruction due to tonsil enlargement, nasal obstruction, an elongated uvula, or macroglossia. Since retrognathia

or micrognathia can produce a narrowed oropharynx, attention to mandible size and position is advised.

Ask about sleep habits. Assessment of OSA risk in the preoperative evaluation need not be lengthy, but patients should be asked about snoring and waking habits, especially frequency of night wakening, to identify possible OSA. Patients generally do not volunteer information about sleep, so it is important to explicitly ask. Responses that suggest OSA include reports of tiredness or sleepiness during the day, or comments by a partner about the patient's snoring. A patient who reports having a dry mouth in the morning may have nasal congestion or obstruction that leads to mouth breathing. Severe sleep disruption can lead to sleep deprivation, causing personality changes, confusion, intellectual impairment, impotence, or morning headaches **(Table 1)**.

Preoperative screening tools. Screening tools can assist in identifying relevant questions about sleep. Three such tools for OSA have been validated for use in surgical patients: the Berlin questionnaire, the American Society of Anesthesiologists (ASA) checklist, and the STOP questionnaire.[17–20] The performance of these tools was evaluated in 177 surgical patients with OSA identified using polysomnography.[17] Each tool's sensitivity, specificity, and positive and negative predictive values were calculated according to polysomnography-based AHI severity. All three tools demonstrated moderately high sensitivity for detecting OSA.[17]

Use of any of these screening tools improves the likelihood of identifying OSA preoperatively. The quickest and simplest to use is the STOP questionnaire, which was recently modified to include questions about additional risk factors for OSA—body mass index, age, neck circumference, and gender; the modified tool is called the STOP-BANG questionnaire **(Table 2)**.[20] In a validation study, the addition of the "BANG" questions about these risk factors increased the questionnaire's specificity for moderate to severe OSA.[20] It is important to ask the questions as they are written **(Table 2)** to elicit the most complete response. For example, the question "Do you feel tired, fatigued, or sleepy?" may seem redundant, but all three terms should be included because men often complain of feeling sleepy while women are more likely to report feeling tired or fatigued.

Identifying levels of OSA severity. Physical examination and screening questions may be adequate to identify patients at risk for OSA prior to surgery. Mild OSA (AHI score of 5–15) can generally be managed after surgery, at the patient's leisure. In contrast, moderate OSA (AHI score of 15–30) and severe OSA (AHI score > 30) can affect perioperative management (see next section). If moderate to severe OSA is suspected, and if there is enough time before surgery to consult a sleep lab, polysomnography can provide a more complete diagnosis.

TABLE 2
STOP-BANG questionnaire*

STOP		
S (snore)	Do you *snore* loudly (louder than talking or loud enough to be heard through closed doors)?	Yes/No
T (tired)	Do you often feel *tired*, fatigued, or sleepy during daytime?	Yes/No
O (observed)	Has anyone *observed* you stop breathing during sleep?	Yes/No
P (blood pressure)	Do you have or are you being treated for high blood *pressure*?	Yes/No
BANG		
B (body mass index [BMI])	*BMI* > 35 kg/m^2?	Yes/No
A (age)	*Age* > 50 years?	Yes/No
N (neck)	*Neck* circumference > 40 cm?	Yes/No
G (gender)	*Gender* male?	Yes/No

Yes to ⩾ 3 questions = high risk of obstructive sleep apnea
Yes to < 3 questions = low risk of obstructive sleep apnea
*Adapted from Chung et al.[20]

PERIOPERATIVE MANAGEMENT OF OSA

When in doubt, proceed as if patient has OSA

Evidence of OSA's association with postoperative complications is emerging, as noted above, but more specific information about risks is needed to develop effective management procedures. For surgical patients who are deemed to be at high risk for OSA, and for whom surgery cannot be delayed for diagnostic tests and OSA treatment, the most prudent course is to proceed with surgery but assume the patient has moderate to severe OSA. Anesthesiologists should be informed when patients are likely to have OSA, as they may choose a different strategy for managing anesthesia during surgery for patients at high risk.

Management recommendations

The ASA published practice guidelines in 2006 for the perioperative management of patients with OSA.[19] In view of the paucity of data on the best management strategies, the guidelines were based mostly on expert opinion. Their key recommendations include the following:

- Surgical patients should be screened clinically to determine their OSA risk. Any of the aforementioned screening tools is effective for this purpose.
- For patients with a diagnosis of OSA or who are clinically determined to be at high risk, close attention to airway management is required, extubation should be

done when the patient is fully awake (to reduce residual effects of anesthesia and sedatives), and regional anesthesia should be used whenever possible.

- Postoperative pain management in patients with confirmed or suspected OSA should minimize the use of opioids and other sedatives. Such patients also should undergo close pulse oximetry monitoring in a step-down setting after surgery and receive postoperative CPAP therapy as soon as possible.

These ASA recommendations are broadly echoed by a 2003 clinical practice review report of the American Academy of Sleep Medicine, which recommends careful attention during the first 24 hours after surgery in patients with presumed OSA and also cautions that patient-controlled analgesia may not be appropriate.[21]

Future research questions

Even with the insights reviewed above, many questions about perioperative management of OSA remain, including the following:

- Will the early diagnosis and treatment of OSA—usually with CPAP—improve perioperative and postoperative outcomes?
- What are the costs associated with observed complications of OSA, and will immediate and continued use of CPAP postoperatively prove cost-effective?
- Where should patients with OSA be monitored postoperatively, and for how long?
- Which pain-control strategies are best for patients with OSA?

DISCUSSION

Question from the audience: Have studies of OSA-associated postoperative complications stratified results on the basis of AHI score?

Dr. Shafazand: Yes. In most studies, postoperative complications are more likely to occur among patients with AHI scores that indicate moderate to severe OSA. However, although the AHI is used extensively as a measure of OSA severity, it may not be the best measure. The degree and duration of oxygen desaturation are probably more relevant to the physiologic changes that occur than is the actual apnea or hypopnea event. The more severe the hypoxemia, the greater the risk of complications.

Comment from the audience: I want to reiterate the point from earlier in this summit that consultant physicians should avoid recommending a type of anesthetic in a preoperative consult. Despite the recommendations of the 2006 ASA guidelines,[19] many anesthesiologists prefer to use a minimal opioid technique or a general anesthetic for patients with OSA rather than risk losing the airway during the operation and having to perform an emergent intubation.

Dr. Shafazand: I agree. In my own consultations I never presume to make recommendations about the type of anesthesia to be used. The important thing is to have a discussion with the anesthesiologist about the best way to manage patients with OSA, but not in the intraoperative context because the patient is going to be intubated and the airway will be protected. The discussion is really more about how to manage patients once they are extubated.

Question from the audience: Should patients with OSA undergo surgery in outpatient facilities?

Dr. Shafazand: It depends on the type and duration of the procedure. If it is a quick procedure, which is likely for an outpatient facility, with minimal sedation and a period of respiratory observation to ensure that the patient is fully awake, the outpatient setting is probably acceptable, especially if the patient is using CPAP at home. It also depends on the severity of OSA. For patients with more severe OSA, an outpatient facility is not recommended. Unfortunately, data about OSA complications in outpatient facilities are sparse.

Question from the audience: What is the role of overnight pulse oximetry versus a sleep study?

Dr. Shafazand: That is the Achilles' heel of managing patients with OSA. Sleep labs are overbooked, so it is often not possible to order a sleep study for patients prior to surgery. Some studies have evaluated overnight pulse oximetry, noting the percentage of desaturation or the total time spent at less than 90% saturation during the night or per hour. This approach is probably adequate for screening for suspected severe OSA, but not all patients with OSA will have desaturations. Overnight pulse oximetry is at best a "poor man's" screening tool—if it is negative, OSA *cannot* be ruled out.

Question from the audience: What is your opinion of surgical treatments for sleep apnea such as uvulopalatopharyngoplasty (UPPP)?

Dr. Shafazand: For patients with an AHI score below 15 and no comorbidities, some surgical correction may be advisable. For patients with an AHI score above 15, surgery can be recommended in some circumstances—for example, if there is a clear blockage of the nasal passage. But patients with moderate to severe OSA usually continue to require CPAP therapy after surgery. CPAP is still the recommended treatment for moderate to severe OSA, though surgery might help the patient tolerate CPAP better in certain instances by lowering the pressure requirements.

Question from the audience: A minimal number of hospitals actually screen patients for OSA and treat them differently. Do you know why the Joint Commis-

sion dropped a proposed safety goal to screen patients for OSA upon admission and treat based on the results?

Dr. Shafazand: I think the biggest problem is that results from the literature are so variable in terms of risks that it's difficult to draw conclusions. Patients with desaturation are given oxygen to address the immediate problem, but there is no focus on complications. Depending on the study, there are true complications that affect patient safety but also add to the costs of care. Until there are more definitive results in the literature, there is not enough evidence to make and enforce recommendations.

DISCLOSURES

Dr. Shafazand has indicated that she has no financial relationships with commercial interests that have a direct bearing on the subject matter of this article.

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Nuts and bolts of preoperative clinics: The view from three institutions

ABSTRACT

Three directors of dedicated preoperative assessment clinics share their experience in setting up and running their programs. Standardizing and centralizing all or part of the preoperative evaluation process—obtaining patient records; the history and physical examination; the surgical, anesthesiology, and nursing assessments; ordering tests; and documentation and billing—increases efficiency. The savings achieved from minimizing redundancy, avoiding surgery delays and cancellations, and improved reimbursement coding offset the increased costs of setting up and running the clinic.

KEY POINTS

Standardizing the preoperative assessment process helps ensure that regulatory, accreditation, and payer requirements and guidelines are met.

Careful triage based on a patient's history can help avoid unnecessary assessment of low-risk patients and ensure that necessary assessments for higher-risk patients are completed before the day of surgery.

Perioperative assessment and management guidelines for various types of surgery and patient risk factors should be developed, continuously updated, and made available online to all providers within the institution.

Electronic medical records allow standardization of patient information, avoid redundancy, and provide a database for research.

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Weiner Center for Preoperative Evaluation at Brigham and Women's Hospital

By Angela M. Bader, MD, MPH

When organizing our preoperative clinic at Brigham and Women's Hospital, we had several goals. Overall, we wanted a standardized process to help us achieve a high level of excellence. We hoped that creating a new system would eliminate ambiguity about who was responsible for following up on a patient's abnormal laboratory test result—the surgeon, anesthesiologist, or primary care physician. We also wanted to better coordinate the various care teams involved throughout the perioperative period.

STANDARDIZATION HELPS MEET MANY GOALS

Standardization can occur at many levels:

- Performance of assessments and testing
- Organization of the patient chart and medical records
- Systems checks throughout the process to ensure that nothing is missed
- Team-to-team communication.

Documentation requirements apply regardless of institutional structure

When considering any system of preoperative assessment, keep in mind that the hospital must meet and appropriately document compliance with all regulatory, accreditation, and payer requirements and guidelines, such as those of the Joint Commission, the Centers for Medicare and Medicaid Services (CMS), and the National Surgical Quality Improvement Program. For example, the Joint Commission requires that a surgical history and physical examination be done within 30 days of a procedure. An anesthesiology assessment and a nursing assessment are also required. All of these assessments have mandatory elements, including documenting "never events" and ordering appropriate laboratory tests, electrocardiograms (ECGs), and radiographs.

Sometimes administrators of other hospitals say to me, "We can't afford a preoperative clinic, and we don't need one." My response is that regardless of whether a hospital has a preoperative clinic, the regulatory requirements and guidelines must be met: it is not an issue of

avoiding certain steps. Having a dedicated preoperative clinic simply shifts the work to a standardized, centralized system and avoids delaying these required steps until the day of surgery, when taking care of a problem involves the most inefficient use of resources.

Tailor system to institutional needs and characteristics

Within the regulatory framework, the organizational scheme of every institution must address issues of volume and acuity, the types of surgery performed, and the time frames required. A system must be able to deal with the preoperative needs of patients undergoing operations that are booked weeks in advance (often the case for orthopedic surgery) as well as those that may not be booked until a day before the procedure (eg, cancer surgery).

Our plan was developed for our very high-volume, tertiary care institution. In 2008, 24,000 patients used our clinic (roughly 100 patients per day).

DESIGN OF THE PREOPERATIVE CLINIC

A nurse practitioner–based model for 'one-stop shopping'

We decided that the clinic should offer all elements of the preoperative assessment and thereby give patients "one-stop shopping." Each patient sees a nurse practitioner, who performs the surgical history and physical examination as well as the anesthesiology and nursing assessments. The result is a multidisciplinary approach with a single assessment output. We shifted employees who had been responsible for preoperative assessment in the offices of various surgeons to a central clinic so that all assessments could be standardized, and we provided additional training to enable them to perform various assessments. The nurse practitioners are supervised by an on-site attending physician, as detailed below.

This model offers a number of advantages:

- Patients see a single provider.
- Assessment is facilitated for our surgeons, who may not be completely up-to-date on perioperative risk assessment and management.
- We have a central location for standardized education programs for our physicians, nurses, and residents.
- The clinic's standardized records and processes facilitate data generation for research and clinical practice improvement.

Independent budgetary and staffing structure

The preoperative clinic is a separate cost center under the leadership of the department of anesthesiology. Resources were shifted to a central location so that as volume increases, we can add resources to meet the additional volume. We contracted with the hospital administration to provide payment for two full-time-equivalent anesthesiologists per day, who serve as on-site attending physicians. The hospital is willing to do this because not only do these attending physicians supervise the anesthesiology assessment, they are the collaborating physicians for the entire perioperative assessment. They review every patient, order tests and write prescriptions as needed, and discuss issues with the primary care physicians and referring specialists.

The preoperative clinic has an anesthesiologist director (me) who reports directly to the hospital's vice president for surgical services on budget and staffing issues. I also report to the chairman of the department of anesthesiology, though he is not involved in budgetary functions (the hospital contracts with him to provide the anesthesiology staffing). The clerical and nursing staff work directly for the clinic.

The clinic is run in a self-contained area with a central waiting room and space for doing all the assessments and laboratory work internally, including 16 examination rooms and a room for chart organization.

MORE BENEFITS OF STANDARDIZATION

Standardized scheduling ensures reliability

The secretaries in each surgeon's office schedule appointments through a central computer system after registration and insurance precertification. Our computer system does not allow an operation to be scheduled without an evaluation also being scheduled. The evaluation can involve either a visit or a telephone screen; we provide algorithms so that the surgeons' secretaries know which is required. This system has substantially reduced the number of walk-ins, allowing for a more even distribution of patients and ensuring that medical records will be available when a patient is seen.

We watch our schedule carefully. Our computer system monitors the time that each patient is in our clinic to determine his or her waiting time and assessment time. It takes about 75 minutes to go through the whole process, including the time for a nurse practitioner to do the surgical history and physical examination and the anesthesiology and nursing assessments, a laboratory technician to do an ECG and laboratory tests if indicated, and completion of all required documentation. Accordingly, patients are scheduled in 75-minute blocks between 7:00 AM and 6:30 PM. We do not have evening or weekend hours because of the difficulty of contacting surgeons and primary care physicians when questions arise. It is simply not cost-effective to have to do that type of follow-up on a case after the patient leaves.

Only about 10% of our patients are screened by telephone, since most of our operations are complicated and require in-person assessment (most low-acuity procedures are done at other hospitals). Of the patients who visit the preoperative clinic, about 75% undergo the single assessment model for surgery, anesthesiology, and nursing as described above. The remaining 25% of

patients have their history and physical exam completed outside Brigham and Women's Hospital for insurance reasons; the remainder of their assessment is conducted in our preoperative clinic by a registered nurse and an anesthesiology resident.

Multiple systems checks

Our model also incorporates standardization in the form of multiple systems checks:

- **Case presentation.** Every case is presented to an attending anesthesiologist, who reviews the ECG (if ordered) before the patient leaves the clinic.
- **Post-visit chart check.** A registered nurse or nurse practitioner signs off on each chart after the visit, confirming test results and resolution of all paperwork issues.
- **Surgical checklist.** The end result is a checklist that serves as the front sheet of the operating room chart.

Our ability to use this system of checks to get the chart completed comprehensively and reliably and deliver it to the operating room when needed was key to securing institutional support and funding for the preoperative clinic.

ROLE OF THE ATTENDING ANESTHESIOLOGISTS

Two full-time attending anesthesiologists are present in the preoperative clinic each day. One is responsible largely for supervising the nurse practitioner assessments and reviewing case presentations, while the other also oversees the education and supervision of residents. Residents rotate through the clinic for 2 weeks (one or two at a time) and have a designated curriculum consisting of daily lectures and competencies in preoperative evaluation.

Because our anesthesiologists are expert in preoperative assessment, we require very few outside consults. We can communicate directly with the cardiologists and other physicians and order tests when indicated. We have a clerical assistant who obtains all necessary paperwork and prior testing from outside providers so that the clinicians need not waste time on this.

A GROWING CHALLENGE: ASSESSMENT FOR PROCEDURES IN AMBULATORY SETTINGS

Looking forward, a rapidly growing challenge facing our clinic stems from the tremendous growth in patients who require anesthesia for procedures performed outside the operating room. In these situations, the proceduralists need a system for deciding whether an anesthesiologist must be present for any given case.

We have started to develop appropriate screening processes to ensure that the proceduralists in multiple departments know which patients to refer for preprocedure assessment. We hope to soon develop protocols for high-risk patients and for various procedures such as implanting a pacemaker or defibrillator, catheter procedures, interventional radiology, and endoscopy.

Anesthesia Perioperative Medicine Clinic at University of Chicago

By BobbieJean Sweitzer, MD

Detsky and Naglie have argued that the costs and clinical outcomes associated with any intervention must be compared with those of alternate strategies for treating the same patients,[1] and I believe their point applies well to preoperative clinics. Although certain requirements of the Joint Commission and CMS must be met, as noted by Dr. Bader, they can be met in various ways. I will preface my comments by emphasizing that one size does not fit all: every institution must decide the best approach to preoperative assessment based on its patient population, the types of procedures it performs, and the volume it handles.

TRIAGE STREAMLINES THE PROCESS

Our preoperative clinic at the University of Chicago emphasizes triage. Not every patient should have to go to the trouble of coming in to see a provider. In the future, we will likely see more "virtual" preoperative assessments using devices in development, such as handheld ultrasonography machines. Just as patients can have their pacemakers and implantable cardiac defibrillators remotely checked via phone contact, more tools will one day be available for remote assessment.

Although not every surgical patient needs to come in to the preoperative clinic, every patient must have a physical examination. All patients will be seen on the day of surgery, so in some cases the physical exam may be able to wait until then. For example, an airway assessment need not be done ahead of time. Most anesthesiologists are prepared to manage airways on very short notice, so extensive advance planning is not always necessary.

Obtain basic info by questionnaire to save staff time

Information about the patient is key to triage, and it may be either paper- or computer-based. An initial priority should be to develop some mechanism for getting information from patients before the day of their procedure without a visit to the hospital or ambulatory surgery center.

We use a two-page paper questionnaire to obtain basic information from patients, including (among other pertinent questions) age, planned operation, names of the surgeon and primary doctor, past operations and medical history, allergies, a list of medications, social history (drug,

alcohol, tobacco use), whether they have ever taken steroids, whether they have high blood pressure, and whether they can comfortably walk up a flight of stairs. We provide the primary care physicians and surgeons with blank questionnaires, which their patients can fill out in their waiting rooms or take home and fax to us (or drop off) later. The questionnaire gives us a good deal of essential information without using staff time.

Various computer-based and Web-based systems are also available for collecting basic patient information. Smaller institutions need not purchase an entire electronic medical record system, which can be very expensive. Some Web-based tools operate on a pay-per-use basis and can be very helpful.

Review the information to guide triage

We then review the patient information to determine the extent of preoperative evaluation required. Some patients, especially those scheduled at an ambulatory surgery center, are healthy enough that they can just come in on the day of surgery for an examination and an update of their information. Others will need an appointment at the clinic before the day of surgery for more extensive preoperative evaluation. For other patients, review of their questionnaire responses may prompt a phone call or e-mail from the clinic for more information to determine whether a day-of-surgery exam will suffice or whether evaluation in advance is needed. When in doubt, concerns raised by the questionnaire should be explored before the day of surgery to avoid surprises and allow sufficient time for a consultation, if needed.

STANDARDIZED GUIDELINES KEEP CARE CONSISTENT

We encourage our staff to minimize preoperative testing and ECGs. A majority of diagnoses are made based on the history and physical exam.[2] Generally, a test should confirm what is already suspected and merely provide objective evidence when needed. Testing in this setting should *not* be done to "find out what is wrong" with a patient.

It is helpful to develop standardized guidelines for preoperative assessment and make them available to everyone in the institution via the Web. The guidelines should address recommended preoperative tests and management practices according to specific patient conditions or surgical procedures. The clear objective is to avoid disagreement about what a patient needs between the provider who evaluated the patient in advance and the surgeon or anesthesiologist who evaluates the patient on the day of surgery.

Our guidelines at the University of Chicago include recommendations for patients on long-term anticoagulant therapy, for patients with coronary stents, for medications that should be discontinued (and those that may be continued) on the day of surgery, and for numerous other conditions and issues. Our testing guidelines list indicated tests for various medical problems, which in turn link to other guidelines. Other links are based on the medications a patient is using or the type of operation that is planned.

We collaborated with our electrophysiology department to create guidelines for managing patients with pacemakers and defibrillators. Almost every patient with one of these devices has a little card associated with the device, and we ask the surgeons to copy the card and send it to the clinic if we will not be directly seeing the patient. Using a national database, the electrophysiology department can determine from the card the type of pacemaker or defibrillator a patient has, and they fax or e-mail us back a page of instructions to let us know whether the device requires special consideration during surgery, whether it should be checked preoperatively, and whether its battery needs replacing. With this system, we have markedly reduced problems on the day of surgery.

CONSULTS HAVE AN IMPORTANT ROLE

Consults should never be requested in order to "clear a patient for surgery." Consult requests should rather address specific issues, such as, "Is this patient medically optimized?" or "Please address this patient's hypertension." In turn, consult notes should provide meaningful information that can be used in a specific way. A clearance letter or simple risk assessment is not helpful.

If a patient has not seen a primary care doctor in a long time, a consult request should (in addition to requesting a global risk assessment) specify any particular concerns, such as, "The patient reports snoring; please address sleep apnea and cardiac risk."

Case study: Beware consult notes with no specifics

Consider a case we encountered of a 54-year-old man who had a preoperative cardiac risk assessment. The cardiology consultant completed a short form consisting of a multiple-choice check-off list indicating low, moderate, or high cardiac risk. The consultant checked that the patient had low cardiac risk but provided no other instructions or information other than his own contact information.

When we reviewed the patient's questionnaire, we saw that his medications included metoprolol, clopidogrel, and aspirin even though the patient did not mention that he had coronary artery disease. On this basis, we requested details about his cardiac evaluation from his cardiologist. It turned out that the patient had a history of four catheterizations with several cardiac stents placed. The most recent stent was implanted to overlap a previous stent that had been found "floating" in the blood vessel; this last stent was placed just 6 months before the cardiologist issued the consult note

TABLE 1
Surgery cancellations on day of scheduled surgery according to attendance in preoperative clinic[5]

Surgical setting	Cancellation rates: Pts seen in preop clinic	Cancellation rates: Pts *not* seen in preop clinic	*P* value
Ambulatory surgery center	98/1,164 (8.4%)	366/2,252 (16.3%)	< .001
General operating rooms	87/1,631 (5.3%)	192/1,477 (13.0%)	< .001

indicating "low cardiac risk."

The moral is to approach consult notes with caution, especially if they offer no specifics. It actually makes me nervous when a note states "low risk" because if something unexpectedly goes wrong in surgery, it appears that the perioperative team took poor care of the patient even if the complication actually may have stemmed from higher-than-recognized underlying patient risk.

PROVIDE, AND REINFORCE, CLEAR INSTRUCTIONS

We give patients written preoperative instructions that become part of our computerized records. We first verbally give explicit instructions for each medication—ie, whether it can be taken as usual or when it needs to be stopped before surgery (and why). Then we provide the same information in writing, after which we try to have the patient repeat the instructions back to the clinician. We include a phone number that patients can call if they need help understanding their preoperative instructions.

Web-based programs also can provide patients online instructions about their medications. Some services even customize information by providing, for example, lists of local surgeons who are willing to allow a patient to continue on aspirin therapy until the day of surgery.

USE THE RIGHT RESOURCES

Staffing

Our model at the University of Chicago relies mainly on residents in training and physician assistants, but advanced nurse practitioners are well suited to a preoperative clinic as well. These types of providers have background training in history-taking, physical examination, diagnostic testing, and disease management. Registered nurses have more limited abilities, although they may be appropriate for a clinic that deals primarily with healthy patients for whom only history taking and a list of medications is needed. Additionally, our clinic is staffed by one attending anesthesiologist at all times (from among a group of rotating anesthesiologists) as well as medical assistants and clerical staff.

Some clinics perform the surgical history and physical exam at the same time as the anesthesia assessment. I would urge caution with this practice. Just as primary care doctors should not be conducting the anesthesia assessment, nonsurgeons should not be conducting the surgical assessment; doing so puts them out on a limb from a medicolegal standpoint. Advanced nurse practitioners and physician assistants may do surgical assessments under the supervision of a surgeon, but only surgeons should ultimately decide—and document—whether an operation is necessary and what degree of examination is required in advance.

Computer technology for records, messaging, billing

Using electronic medical records and corresponding with colleagues by e-mail make preoperative care much more efficient. We have standardized computer forms for ordering tests and documenting the physical exam. Patients usually understand that electronic medical records are safe and more efficient, and they are often more accepting of their use than practitioners are. Many patients want e-mail access to doctors, to schedule appointments online, and to receive appointment reminders by e-mail.[3]

Electronic medical records also avoid redundancy. If a patient has been seen in our preoperative clinic and is later scheduled for another surgery (even if a different surgeon is involved), a return visit to our clinic may not be necessary. In some cases, we can send the old workup stamped "For information only," which can then be updated by the anesthesiologist on the day of surgery.

A central, standardized process also makes billing more efficient and helps to ensure that payment is received for all services provided. Standardized documentation makes it easier for coders to enter the correct evaluation and management codes and ensures that all required criteria are met.

THE PAYOFF: LIVES AND DOLLARS SAVED

A thorough and efficient preoperative assessment system is cost-effective. Every minute of operating room time is worth $10 to $15,[4,5] so delays should be avoided. Everything that is done ahead of time saves money for the whole enterprise by reducing unnecessary case setups and reducing "down time" due to lack of patient, equipment, or staff readiness. We routinely bill for preoperative evaluations when this service goes beyond a routine preoperative assessment based on CMS (and other insurance) requirements. However, a preoperative evaluation is required by CMS and most payers if one wants to be paid for any anesthesia-provided service. As a result, a cost is incurred without offsetting revenue if a case is cancelled on the day of surgery after one performs the anesthesia evaluation.

A study we published a few years ago showed that patients who were seen in our preoperative clinic were significantly less likely to have day-of-surgery cancellations than were patients not seen in our clinic, a finding that applied to both our ambulatory surgery center and our main operating rooms **(Table 1)**.[5] These findings held even after adjustment for American Society of Anesthesiologists severity class. In addition, the median delay in surgery start time was significantly less among patients who were seen in the preoperative clinic.

Yesterday I heard someone ask, "Do we really need all this preoperative evaluation? Does it really improve outcomes?" There is some evidence that it does. A study from 2000 based on data from the Australian Incident Monitoring Study found that 11% of the 6,271 critical incidents that occurred following operations were attributable to inadequate preoperative evaluation and that 3% were unequivocally related to problems with preoperative assessment or preparation. More than half of the incidents were deemed preventable.[6]

Preoperative clinics are good for patients and make good sense economically. We just need to demonstrate to our administrators and to payers that we are offering an excellent service.

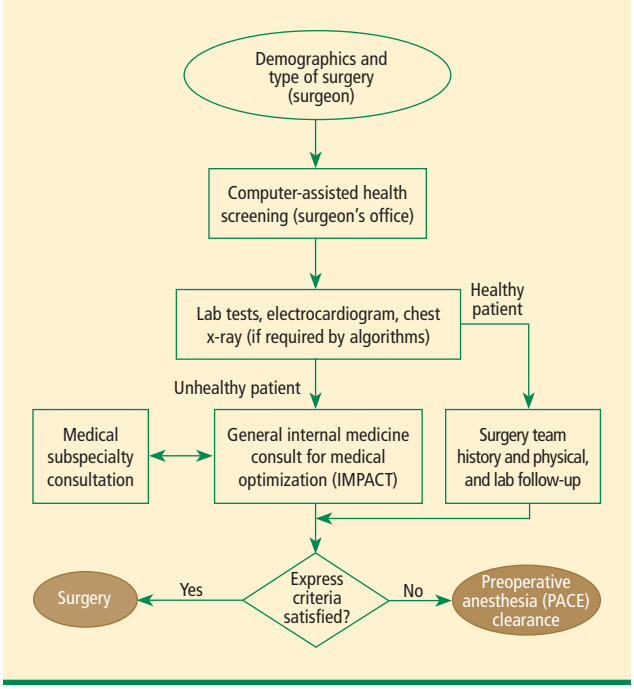

FIGURE 1. Flow chart of the preoperative evaluation process at Cleveland Clinic.

Cleveland Clinic IMPACT Center

By Ajay Kumar, MD

Cleveland Clinic is structured differently from most other institutions in that its surgeons, anesthesiologists, and hospitalists are all direct employees of the institution. Despite this unique structure, many aspects of our preoperative clinic—known as the Internal Medicine Preoperative Assessment, Consultation and Treatment (IMPACT) Center—are applicable to other institutions.

Cleveland Clinic is a busy surgical hospital whose preoperative optimization system is designed to provide high-quality care. The IMPACT Center is consulted for most complicated noncardiac surgery patients, and its referral sources include most of the institution's surgical specialties.

QUEST FOR A BETTER PATIENT EXPERIENCE

When the IMPACT Center was created in 1997, the aim was to focus on the same objectives highlighted by Drs. Bader and Sweitzer: safety, a positive patient experience, enhanced communication, better continuity of care, effective use of resources, and improving throughput by standardizing care.

A prime motivator was the desire to move away from the tendency for presurgical consults to simply "clear the patient for surgery," and we have indeed evolved considerably from that point. The focus of our perioperative care program today is to comprehensively evaluate risk by taking into account patient-, procedure-, and anesthesia-related factors.

We offer "one-stop shopping," and our priority is for efficient throughput. We are located in a 12-story building that includes outpatient, preoperative, and surgical clinics and offices. The IMPACT Center is on the first floor along with the preoperative anesthesia consultation and evaluation (PACE) clinic, the laboratory, and ECG and stress-test labs. Patients can undergo radiographic studies on the second floor.

The patient experience counts for a lot. Many of our patients are from another state or country, so efficiency and convenience are especially important. Patients can usually get all assessment and testing done in a single day.

A TIGHTLY MANAGED PROCESS

A 'smart' questionnaire starts the process

Our process **(Figure 1)** begins in the surgeons' offices, where a patient is seen by a surgeon and an operation is deemed necessary. There the patient is asked to fill out a computer-assisted health screening questionnaire available online. The questionnaire is very sophisticated: based on the patient's answers, it asks further pertinent questions and requests details if the history is complicated. A patient with multiple health problems may take 20 minutes to complete it, while a healthy patient may take only 3 minutes.

A computerized report based on the questionnaire

guides the surgical office in scheduling the patient to specific areas according to algorithms. Based on case complexity and clinical needs, patients are scheduled for the IMPACT Center along with the PACE clinic; if needed (based on the algorithms), patients also are scheduled for laboratory tests or imaging. This standardized approach helps create a safe passage for patients through the preoperative process with less confusion.

Patient is given a personalized binder

Once all appointments and tests are scheduled, the patient is given a binder containing specific information about the procedure and preoperative instructions. The medical appointment at the IMPACT Center is usually scheduled before the PACE clinic appointment. Patients receive an itinerary for all preoperative appointments and surgical office appointments before the planned surgery. The itinerary is planned so that if additional testing is requested, it can be accommodated on the same day.

At the end of the preoperative assessment, the patient receives printed information with specific preoperative instructions, including which medications to continue or stop.

Standardized, computer-based medical records

Our systems and processes have undergone a good deal of evolution. We have integrated our medical records and use a standard outside medical record retrieval process. The template for the history and physical exam is standard for all Cleveland Clinic patients and is used for all presurgical assessments before all noncardiac surgeries. The template is comprehensive, including the history of the present illness, the review of systems, the physical exam, and anesthesia-related issues. All outside documents are scanned into our electronic medical record system and are available for viewing prior to surgery from any computer connected to the system.

Our preoperative assessment guidelines are also kept updated at a central online location so that all providers have access to them.

Staff keeps process running efficiently

The IMPACT Center is managed by the department of hospital medicine and supported by at least 5.5 full-time physicians every day. We also have two registered nurses, two assistants who help with scheduling and testing, and three secretaries who support the doctors, obtain records, and make arrangements with outside doctors for testing if a patient wants to return home before our testing can be completed.

A secretary also keeps a log for each patient seen in the clinic, tracking all pending issues. The day before surgery, the secretary contacts the appropriate office for anything that is still pending. If she gets no response, the matter is transferred to one of our doctors so that the problem can be resolved at once. This strategy allows us to achieve a nearly 0% rate of surgery delay or cancellation attributable to unavailable test results.

Our patient volumes have increased significantly since we started in 1997. Last year more than 15,000 patients visited the IMPACT Center and now we have expanded our services to regional hospitals within the Cleveland Clinic Health System.

INTERDEPARTMENTAL COMMUNICATION IS CRITICAL

Interdepartmental communication is a must for patient safety, so we encourage a culture of communication between the hospitalist and the surgical team. The location of most of our surgical clinics within the same building as the IMPACT Center further facilitates communication, as does the proximity of the PACE clinic. Additionally, one of our IMPACT Center physicians is accessible around the clock to answer to our surgeon or anesthesiologist colleagues as needed.

We regularly assess our process and seek feedback from surgeons and anesthesiologists. We also conduct yearly patient experience surveys to make sure we are providing patients with the highest quality of care.

Discussion

Question from the audience: Our anesthesia assessment department was approached by our surgeons to do both the anesthesia and surgical assessments, but we felt that would put us in a potential legal conflict if a patient who was assessed that way developed problems. Can you comment?

Dr. Bader: Although we do surgical assessments at our preoperative clinic, we don't make any decisions about whether or not to proceed with an operation. We get an office note from the surgeon that is directed specifically toward the need for surgery, indications for surgery, and surgical consent. We perform the surgical history and physical examination. Our process is essentially the same as when surgeons have a physician assistant do the history and physical examination in their office. Our practitioners are employed by the hospital, so there is no conflict of interest there.

Comment from the audience: I'm a strong believer in hands-on patient contact. Over my 15 years of practice, we have encountered a lot of unexpected problems during the preoperative exam—aortic stenoses, infections, ventricular septal defects—all of which would never have been detected from a screening form.

Dr. Sweitzer: I agree that we pick up many things by seeing the patient in person. I've picked up more cases of aortic stenosis as an anesthesiologist in the preoperative clinic than I ever did as an internist, because the popula-

tion is high-risk. But patients who have such problems tend to have risk factors and be in certain age groups. Studies indicate that the history is more important than the physical exam: the history suggests about 75% of conditions that are present. The physical exam adds only a little more—perhaps another 15%. Our recommendations are very much consistent with the American College of Cardiology and American Heart Association guidelines on preoperative cardiac evaluation.[7] It is more important to identify whether a patient has risk factors for coronary artery disease than to find out whether a stress test or ECG is normal. One needs to do a really good history, but it can be done remotely. Based on certain risk factors identified, high-risk patients can be selected who need to come in and have a physical exam.

Question from the audience: Could you elaborate on the electronic medical record system used at the University of Chicago? I've heard there's a steep learning curve when implementing these kinds of systems. They also are very expensive—I've heard that some cost $40 to $80 million. Has enhanced revenue flow offset the costs?

Dr. Sweitzer: We have a home-grown system developed with FileMaker Pro by a computer programmer at our institution. It was a lot easier to develop than people tend to think. There are many savvy computer programmers out there; I've had medical students assist me with updating it. We're now considering developing it as a commercial system. Many systems are available for purchase, including Epic, Pyxis, one from General Electric, and many others. They are very expensive, so smaller institutions might want to use a pay-for-service system.

There definitely is a learning curve to switching to electronic medical records, but it is not nearly as steep as many believe. The extra time it takes a clinician to initially make a computer entry rather than write on paper is vastly recouped downstream: the electronic medical record is legible and organized, and it doesn't get lost or need to be redone. You can bring up a patient record from 6 months before and reuse it as a template.

Dr. Bader: The discussion of cost savings from preoperative clinics usually focuses on savings from avoiding surgery cancellations and delays and from more efficient laboratory testing, but the biggest savings for an institution is better reimbursement through better diagnosis-related groups (DRG) coding. That's an important reason our institution is funding our clinic. Electronic medical records allow standardization of information so that coders know exactly where to look for the comorbidities and other pertinent information. This increases payments for DRGs, which can be documented for the hospital. This literally runs into millions of dollars a year and more than offsets the costs of the system.

Question from the audience: Dr. Bader, I'm impressed with the number of patients going through your preoperative clinic. How many patients are seen per nurse practitioner in your clinic?

Dr. Bader: The nurse practitioners have 10-hour shifts and see one patient every 75 minutes. The process of seeing a patient takes a lot less time now than with the old system, in which patients saw an anesthesiologist plus a nurse. Our current system eliminates redundancy: questions need to be asked only once.

Question from the audience: My compliance office says that preoperative assessments for early-morning admission patients are good for only 7 days. Is that true?

Dr. Bader: There are sometimes differences between Joint Commission requirements and those of certain insurance companies. That kind of issue needs to be discussed with your hospital compliance office. We program rules into our scheduling system to accommodate different insurance policies and other requirements so that a patient is not scheduled beyond the allowable period.

DISCLOSURES

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Perioperative management of anemia: Limits of blood transfusion and alternatives to it

ABSTRACT

Perioperative anemia is associated with excess morbidity and mortality. Transfusion of allogeneic blood has been a long-standing strategy for managing perioperative anemia, but the blood supply is insufficient to meet transfusion needs, and complications such as infection, renal injury, and acute lung injury are fairly common. Further, data suggest that mortality and length of stay are worsened with liberal use of transfusion. Medical alternatives to transfusion include iron supplementation and erythropoiesis-stimulating agents (ESAs). Though ESAs reduce the need for perioperative blood transfusion compared with placebo, they are associated with an increased risk of thrombotic events in surgical patients. Cleveland Clinic has been developing a blood management program aimed at reducing allogeneic blood exposure for greater patient safety; the program has achieved some reduction in blood utilization in its first 7 months.

KEY POINTS

Anemia is a potent multiplier of morbidity and mortality risk, including in the perioperative setting.

The Joint Commission plans to implement a performance measure on blood management in the near future.

While the safety of the blood supply has improved markedly from the standpoint of infection transmission, other risks from transfusion persist, including transfusion-related acute lung injury and emerging infections.

The preoperative evaluation should elicit a history of bleeding tendencies, previous transfusions, and symptoms of anemia. Medications should be reviewed with an eye toward those that may need to be stopped to avoid a predisposition to bleeding (eg, antiplatelets, anticoagulants).

Use of ESAs minimizes the need for blood transfusion in patients undergoing orthopedic and other surgeries, but they raise the risk of thromboembolism in the absence of prophylactic anticoagulation.

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Anemia is a potent risk factor for mortality and morbidity in surgical patients, and its management has begun to shift away from allogeneic blood transfusion in recent years. This article reviews the clinical importance of perioperative anemia, the role and shortcomings of blood transfusion, and the pros and cons of alternative approaches to managing perioperative anemia. I conclude with an overview of a program for perioperative blood product use at my institution, Cleveland Clinic.

SIGNIFICANCE OF PERIOPERATIVE ANEMIA

Prevalence depends on many factors

The reported prevalence of anemia in surgical patients varies widely—from 5% to 76%[1]—and depends on the patient's disease and comorbidities, the surgical procedure and associated blood loss, and the definition of anemia used. The prevalence of preoperative anemia increases with patient age and is higher in women than in men.[2]

A multiplier of risk

Anemia is an important multiplier of mortality risk. For example, the presence of anemia raises the relative risk of 2-year mortality from 2.05 to 3.37 in patients with chronic kidney disease, from 2.86 to 3.78 in patients with heart failure, and from 4.86 to 6.07 in patients with concomitant heart failure and chronic kidney disease.[3]

Adverse effects of anemia have been demonstrated specifically in the perioperative setting as well. A large retrospective cohort study showed that a preoperative hemoglobin concentration of less than 6 g/dL increases the risk of death 30 days after surgery by a factor of 26 relative to a concentration of 12 g/dL or greater in surgical patients who declined blood transfusion for religious reasons.[4] The anemia-associated mortality risk was especially pronounced among patients with cardiovascular disease.[4] Other studies have demonstrated perioperative anemia to be associated with increases in the risk of death,[5] cardiac events,[6] pneumonia,[7] and postoperative delirium.[8]

IS BLOOD TRANSFUSION THE ANSWER?

The use of allogeneic blood transfusion to manage anemia and blood loss is a concept that originated several centuries ago and has changed little over the years.

Blood supply challenges

Blood collection has historically lagged demand, resulting in a blood supply insufficient to meet transfusion needs. According to the federal government's 2007 National Blood Collection and Utilization Survey Report, 6.89% of US hospitals reported that they cancelled elective surgery on 1 or more days in the prior year because of a lack of blood availability, and 13.5% experienced at least 1 day in which nonsurgical blood needs could not be met.[9] Unless practices are changed to increase blood donation, these unmet tranfusion needs may grow.

Joint Commission set to measure blood management

In response to this challenge, an advisory panel formed by the Joint Commission has identified 17 performance measures related to blood conservation and appropriate transfusion.[10] These measures are currently in development, and we expect to see some types of metrics in the near future. Such metrics are likely to further prioritize blood management for US hospitals.

Safety of the blood supply: Viral transmission down, TRALI risk persists

The safety of the blood supply has improved markedly. Sophisticated testing and public demand have led to a dramatic decline in the risk of transfusion-related transmission of HIV, hepatitis C virus, and hepatitis B virus.[11]

Despite this progress, the risk of transfusion-related acute lung injury (TRALI) has persisted in recent years. TRALI is characterized by acute onset of noncardiogenic pulmonary edema within 6 hours of blood product transfusion. Believed to be immune-mediated, TRALI is thought to occur as antibodies to human leukocyte antigens develop, inducing capillary leak syndrome.[12] The patients most commonly affected are those who receive plasma from multiparous female donors. A recent evaluation of transfusion-related fatalities reported to the US Food and Drug Administration (FDA) revealed a continual rise in fatal TRALI cases in the United States from 2001 to 2006.[13–15] TRALI was implicated in more than half of all transfusion-related fatalities reported to the FDA in 2006, a higher number than for any other single cause.[13]

At the same time, there is evidence that hemovigilance can reduce TRALI risk. In the United Kingdom, the Serious Hazards of Transfusion Steering Group introduced in late 2003 a policy of using plasma from male donors as much as possible, in view of the association of TRALI with plasma from multiparous female donors. The effort appeared to pay off: whereas TRALI accounted for 6.8% of all transfusion-related adverse events reported in the United Kingdom during the period 1996–2003,[16] this proportion declined to just 1.9% in 2006.[17]

Finally, despite the progress in screening blood for more established infections like HIV and the hepatitis viruses, some additional infections now must be considered when assessing blood supply safety. These include diseases newly recognized as being transmissible by blood, or for which blood donor screening is not currently available, or that are newly emergent infections for which the potential for spread by transfusion is unknown. For such diseases—which include malaria and West Nile virus—the risk of transmission through transfusion is low, as they are much more likely to be acquired by other means.

Transfusion and outcomes: Not a strong record

Transfusion has never undergone safety and efficacy evaluation by the FDA. Given the challenges of conducting a randomized study of transfusion in the perioperative setting, we may never have high-quality data to assess transfusion in this setting.

A few studies merit mention, however. The Transfusion Requirement in Critical Care (TRICC) trial was conducted in 838 critically ill patients in the intensive care setting.[18] Patients were randomized to a strategy of either liberal transfusion (begun when hemoglobin fell below 10 g/dL) or restrictive transfusion (begun when hemoglobin fell below 7 g/dL). Thirty-day mortality was similar between patients in the two strategy groups, but the restrictive strategy was associated with significantly lower mortality in at least two subgroups: patients with myocardial infarction and patients with pulmonary edema. Further subgroup analysis found no benefit of early or aggressive transfusion in patients with coronary artery disease or in those requiring mechanical ventilation.

Rao et al performed a meta-analysis of three large international trials of patients with acute coronary syndromes to determine whether blood transfusion to correct anemia in this setting was associated with improved survival.[19] They found significantly higher mortality among patients who underwent transfusion compared with those who did not, prompting them to urge caution in the use of transfusion to maintain arbitrary hematocrit levels in stable patients with ischemic heart disease.

Similarly, a risk-adjusted, propensity-matched analysis of 6,301 patients undergoing noncardiac surgery found that receipt of 4 U of blood or more was a predictor of greater mortality, higher risk of infection, and longer hospital stay.[20] Moreover, in an observational cohort study of 11,963 patients who underwent isolated coronary artery bypass graft surgery, each unit of red blood cells transfused was associated with an incrementally increased risk of adverse outcome (eg, mortality, renal injury, need for ventilator support, lengthened hospital stay, infection).[21] The latter study found that transfusion was the single factor most reliably associated with increased risk of postoperative morbidity.

Additional studies have echoed these findings—ie, that perioperative blood transfusion has been associated with a host of adverse outcomes, including increased

Work-up for suspected anemia in patients undergoing elective surgery

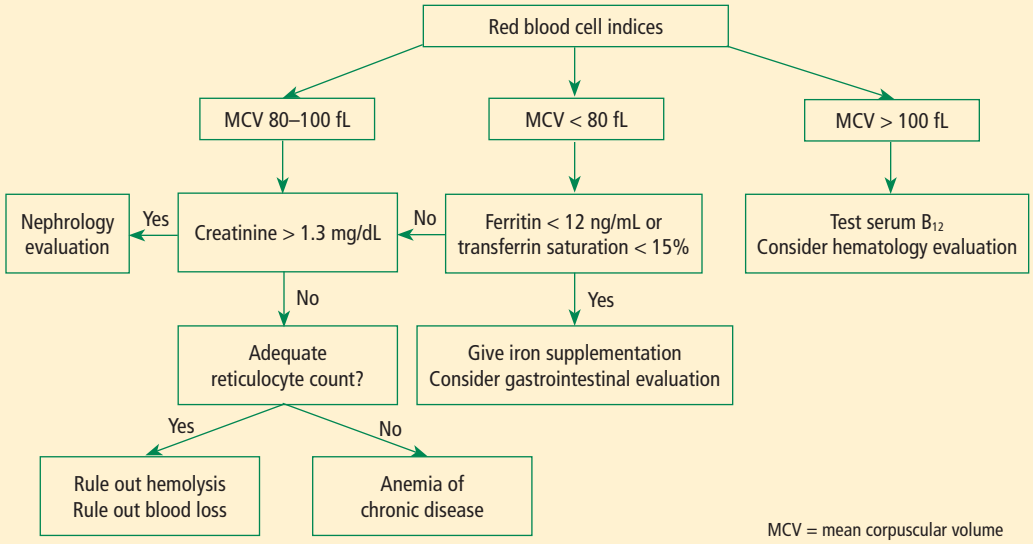

FIGURE 1. Clinical care pathway for identifying and evaluating anemia in patients with abnormal hemoglobin levels undergoing elective surgery.

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morbidity and length of stay, increased rates of postoperative infection, as well as immunosuppression, viral transmission, and acute transfusion reactions.[5,22,23]

Outcomes and duration of blood storage

An interesting factor in the relation between transfusion and outcomes is the shelf life of the blood being transfused. The FDA currently allows storage of blood for a maximum of 42 days, but a recent study of patients who received red blood cell transfusions during cardiac surgery found that those who received "older blood" (stored for > 14 days) had significantly higher rates of sepsis, prolonged intubation, renal failure, in-hospital mortality, and 1-year mortality compared with those who received "newer blood" (stored for ≤ 14 days).[24]

These differing outcomes are generally attributed to the so-called storage defect: as blood gets older, it loses components such as 2,3-DPG and adenosine disphosphate, its red cells lose deformability, and it undergoes buildup of cytokines and free hemoglobin. Increased demand for newer blood in light of the storage defect could further intensify pressures on the blood supply.

MANAGEMENT OF PERIOPERATIVE ANEMIA

In light of these shortcomings of blood transfusion, how should anemia be managed perioperatively to reduce or avoid the need for transfusion?

Preoperative evaluation

Vigilance for anemia and related issues in the preoperative evaluation is fundamental. The evaluation should elicit a history of bleeding tendencies, previous transfusions, and symptoms of anemia. Medications should be reviewed with an eye toward any that may predispose to perioperative bleeding and anemia, such as aspirin, clopidogrel, and anticoagulants. During the physical examination, alertness for pallor and petechiae is key, as is attentiveness to symptoms of anemia such as shortness of breath and fatigue.

The laboratory work-up begins with a measure of hemoglobin: anemia is defined as hemoglobin less than 13 g/dL in males and less than 12 g/dL in females. If anemia is present and is associated with another hematologic abnormality, the patient should be referred to a hematologist for bone marrow examination. If no other hematologic abnormality exists, the ensuing work-up relies on red blood cell indices as detailed in **Figure 1**.[25] The goal is to identify those conditions for which intervention in the short term is possible—namely, anemia of chronic disease, iron deficiency, and vitamin B_{12} deficiency. Findings suggestive of other conditions require further evaluation at a preoperative center.

Overview of management options

Once the cause of anemia is identified, the choice for optimal medical management can be made. Choices broadly consist of pharmacologic and technological options. The former include iron supplements and erythropoiesis-stimulating agents. Among other pharmacologic options are thrombin, collagen, fibrin glue, tranexamic acid, and aminocaproic acid, but these agents are less well studied and will not be discussed here. Technological options include preoperative autologous blood donation, cell salvage, and acute normovolemic hemodilution.

In addition to these options, careful management of anticoagulant and antiplatelet medications should be provided, including discontinuation or substitution of drugs that could hamper clotting perioperatively.

PHARMACOLOGIC OPTIONS

Iron supplementation

Oral iron is available in four preparations: ferrous sulfate, ferrous gluconate, ferrous fumarate, and iron polysaccharide. Gastrointestinal side effects may limit these preparations' tolerability. Iron supplements with a high elemental value will require fewer pills and fewer doses, reducing the risk or frequency of side effects.

Intravenous (IV) iron preparations are much safer now than they were years ago, when anaphylactic reactions were a concern. The ones generally used in the perioperative setting are iron sucrose and iron gluconate. Unlike the older IV preparations, the use of iron sucrose and iron gluconate often requires a second dose. The effect on hemoglobin levels usually occurs starting at 1 week, with the maximum effect achieved at 2 weeks. Hypotension, arthralgia, abdominal discomfort, and back pain are potential side effects of IV iron.

Efficacy and safety of iron supplementation. Evidence of the efficacy of preoperative iron supplementation is mounting. A study of 569 patients undergoing colorectal cancer surgery found that among the 116 patients who were anemic, intraoperative transfusion was needed in a significantly lower proportion of those who received 2 weeks of preoperative oral iron supplementation (200 mg) compared with those who received no iron therapy (9.4% vs 27.4%; $P < .05$).[26] Similarly, in an uncontrolled study, 10 days of IV iron sucrose starting 4 weeks preoperatively significantly increased hemoglobin levels in 20 patients with iron-deficiency anemia prior to elective orthopedic surgery.[27]

Risks of infection and cancer progression have been concerns with IV iron therapy. However, no significant association between IV iron therapy and bacteremia was identified in a prospective study of 985 patients receiving chronic hemodialysis.[28] The effect of IV iron administration on tumor progression has not been prospectively studied.

In general, IV iron, especially the newer forms, is a safer alternative to blood transfusion. Death occurs at a much lower rate with iron than with blood transfusion (0.4 per million vs 4 per million, respectively), as do life-threatening adverse events (4 per million vs 10 per million, respectively), according to a systematic review by the Network for Advancement of Transfusion Alternatives.[29]

Erythropoiesis-stimulating agents

Erythropoiesis-stimulating agents (ESAs) include epoetin alfa (erythropoietin), first approved by the FDA in 1989, and the more recently introduced darbepoetin alfa. They are approved to treat anemia in several patient populations, but only epoetin alfa is approved by the FDA explicitly for use in patients undergoing major surgery (to reduce the need for blood transfusions). The ESAs have come under intense scrutiny in recent years over their risk-to-benefit ratio, as detailed below.

The preoperative dosing schedule for epoetin alfa is usually three weekly doses (plus a fourth dose on the day of surgery) if the surgery is scheduled 3 or more weeks in advance. However, daily dosing can be used effectively if the preoperative period is less than 3 weeks, provided that it is continued until 4 days after surgery. Oral iron is necessary throughout the course of epoetin alfa therapy.

Efficacy in reducing transfusions. In a systematic review published in 1998, epoetin alfa was shown to minimize perioperative exposure to allogeneic blood transfusion in patients undergoing orthopedic or cardiac surgery.[30] Its benefit was greatest in patients at the highest risk of requiring transfusion. It was effective whether given daily or weekly, and did not significantly increase the risk of thrombotic events when used in surgical patients, although some studies did find an excess of thrombotic events with its use.

In three randomized trials conducted in patients undergoing joint arthroplasty (hip or knee), epoetin alfa was associated with substantial and significant reductions in perioperative blood transfusion compared with placebo or preoperative autologous blood donation.[31–33] Rates of deep vein thrombosis (DVT) did not differ significantly between the epoetin alfa and placebo groups.

Concerns over perioperative thromboembolic risk. In early 2007, the FDA was made aware of preliminary results of an open-label study in which 681 patients undergoing elective spinal surgery who did not receive prophylactic anticoagulation were randomized to epoetin alfa plus standard-of-care therapy (pneumatic compression) or standard-of-care therapy alone.[34,35] The incidence of DVT was 4.7% in patients treated with epoetin alfa compared with 2.1% in those not receiving epoetin alfa. It is important to note that the available ESAs are prothrombotic and increase thrombotic risk significantly, especially in populations like this one in which pharmacologic DVT prophylaxis is not routinely used.

Based in part on this study, the FDA in 2007 required a boxed warning to be added to the ESAs' package inserts to specify the increased risk of DVT with their use in surgical patients not receiving prophylactic anticoagulation. The warning urges consideration of the use of DVT prophylaxis in surgical patients receiving an ESA.[34,35]

TECHNOLOGICAL OPTIONS AND OTHER STRATEGIES

Autologous blood donation: A practice in decline

In cases of elective surgery, autologous blood donation can be used to protect against disease transmission and

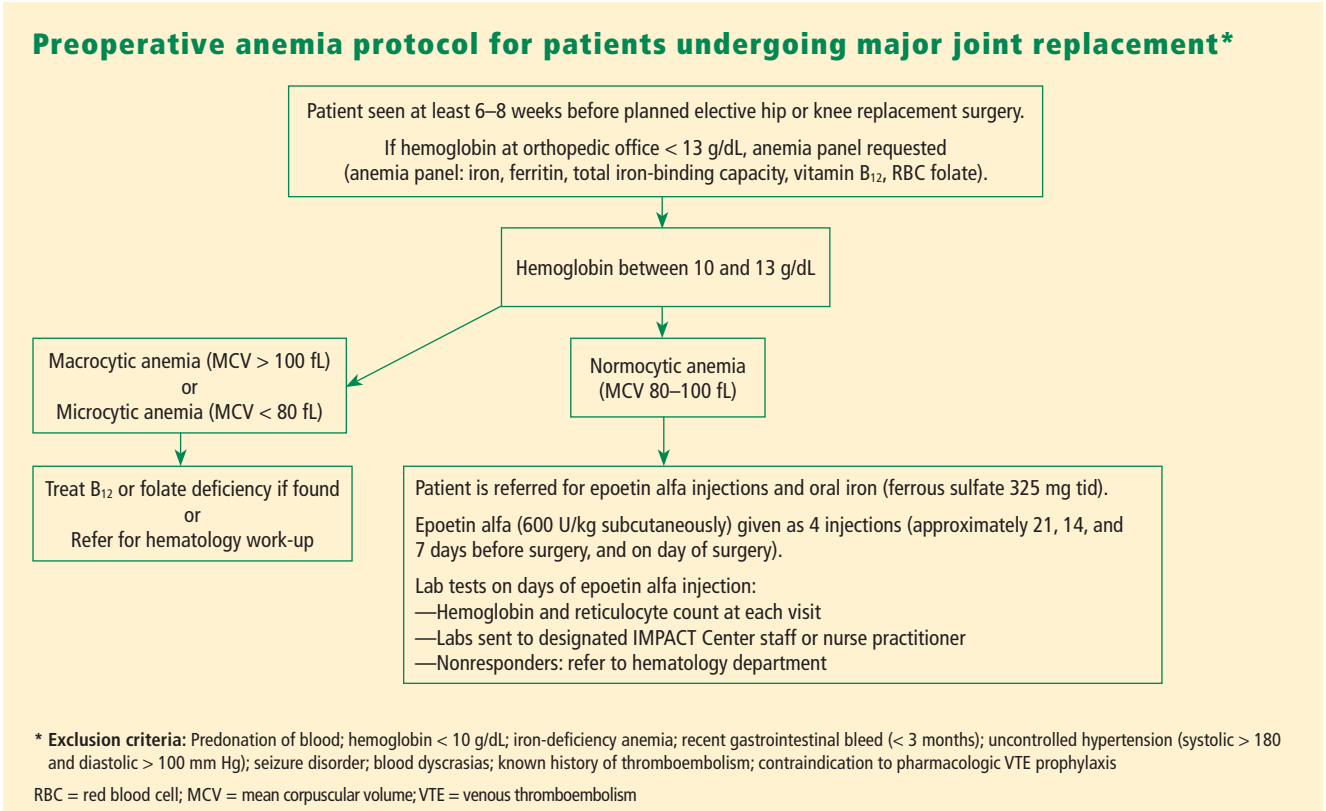

FIGURE 2. Cleveland Clinic's anemia protocol for patients undergoing major joint replacement surgery. Management starts with an assessment of hemoglobin 6 to 8 weeks before the planned procedure. Decision points are based on red blood cell indices.

overcome the challenge of blood type compatibility. Preoperative autologous donation of blood has been a prevalent practice, but its use is declining. One reason is that waste is high (approximately 50% at Cleveland Clinic), which makes this practice more costly than is often realized. Also, autologous blood donation increases the likelihood that the patient will be anemic on the day of surgery, so that he or she may still need allogeneic blood after all, defeating the initial purpose. Despite these limitations, preoperative autologous blood donation remains a useful option for a subset of patients with multiple antibodies for whom donor blood may be difficult to obtain.

Cell salvage

Cell salvage is an innovative technology that recovers the patient's own blood (after being shed from the surgical incision) for transfusion after filtering and washing. It is particularly well suited to procedures that involve massive blood loss. Cell savage requires technical expertise, however, and involves costs associated with both the machine and disposables.

Restricted postoperative phlebotomy

Phlebotomy accounts for a significant amount of blood loss, especially in intensive care patients with arterial lines. The equivalent of 30% of total blood transfused has been reported to be lost to phlebotomy during an intensive care unit stay.[36] Triggers for transfusion cannot be assigned universally based on blood loss from phlebotomy but must consider the patient's hemodynamic status, cardiac reserve, and other clinical characteristics.

PROMOTING RESPONSIBLE BLOOD PRODUCT USE

Blood is expensive, and in recent years hospitals have experienced increases in the cost of blood and blood products. To promote responsible blood use, we have developed a multipronged approach to blood management at Cleveland Clinic. The program's cornerstone is increased awareness of the risks associated with blood transfusions. The emphasis is on educating staff physicians and other caregivers about the appropriate use of blood products. We also have implemented a new policy requiring staff authorization for all blood requested in nonemergency situations. Additionally, requests for blood components require adherence to an indication-based ordering process. Finally, data about blood use are shared transparently among physicians, encouraging good clinical practice.

Our program has also involved development and

implementation of a preoperative anemia protocol to explicitly define the indications for use of ESAs, iron therapy, and vitamin B_{12} therapy in patients undergoing joint arthroplasty **(Figure 2)**.

In the first 7 months of the program, we observed decreased utilization of blood products in the inpatient setting. Notably, the reduction in blood use was significantly greater in the surgical population than in the medical population.

CONCLUSIONS

Anemia is associated with increased morbidity and mortality in the perioperative setting. Perioperative blood transfusion is one method of raising hemoglobin levels in anemic surgical patients, but it increases perioperative morbidity in the form of acute transfusion reactions, immunosuppression, postoperative infection, and longer hospital stays. Moreover, blood collection continues to lag blood demand. For these reasons, most relevant major medical organizations—including the Association of Blood Banks, the American Red Cross, and the FDA—advise that red blood cell–containing components should not be used to treat anemias that can be corrected with medications. These medical alternatives—all of which can be used in the perioperative setting—include iron supplementation, vitamin B_{12}, and ESAs in select patient groups.

DISCUSSION

Question from the audience: Are there risks involved with autologous blood donation? Are different hemoglobin thresholds used when a patient's own blood is used?

Dr. Kumar: As I mentioned, preoperative autologous donation is a technique that is less frequently used in our hospital. Autologous transfusion is considered safe only for patients who come to the clinic with normal hemoglobin values. Some patients may not have recovered from their blood loss by the time they come to surgery, so you end up needing to give them more blood because they started out anemic.

Question from the audience: Is there risk to giving patients back their own blood? Do you have to worry about transfusion-induced lung injury, sepsis, or other complications?

Dr. Kumar: As with allogeneic blood, the risk of clerical or clinical error exists with autologous blood: it too needs to be kept on the shelf, taken out, and infused, and the risk of sepsis remains the same.

DISCLOSURES

Dr. Kumar has indicated that he has no financial relationships with commercial interests that have a direct bearing on the subject matter of this article.

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Medicolegal issues in perioperative medicine: Lessons from real cases

ABSTRACT

Medical malpractice lawsuits are commonly brought against surgeons, anesthesiologists, and internists involved in perioperative care. They can be enormously expensive as well as damaging to a doctor's career. While physicians cannot eliminate the risk of lawsuits, they can help protect themselves by providing competent and compassionate care, practicing good communication with patients (and their families when possible), and documenting patient communications and justifications for any medical decisions that could be challenged.

KEY POINTS

The standard to which a defendant in a malpractice suit is held is that of a "reasonable physician" dealing with a "reasonable patient."

In malpractice cases, the plaintiff need only establish that an allegation is "more likely than not" rather than the "beyond a reasonable doubt" threshold used for criminal cases.

Plaintiffs typically seek damages (financial compensation) for economic losses as well as for pain and suffering. Awarding punitive damages against an individual physician for intentional misconduct is rare, and such damages are usually not covered by malpractice insurance.

Settling a case is often cheaper and easier than going to court, but the physician's reputation may be permanently damaged due to required reporting to the National Practitioner Data Bank.

Informed consent should involve more than a patient signing a form: the doctor should take time to explain the risks of the intervention as well as available alternatives, and document that the patient understood.

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If this is a typical audience of physicians involved in perioperative care, about 35% to 40% of you have been sued for malpractice and have learned the hard way some of the lessons we will discuss today. This session will begin with an overview of malpractice law and medicolegal principles, after which we will review three real-life malpractice cases and open the floor to the audience for discussion of the lessons these cases can offer.

MALPRACTICE LAWSUITS ARE COMMON, EXPENSIVE, DAMAGING

If a physician practices long enough, lawsuits are nearly inevitable, especially in certain specialties. Surgeons and anesthesiologists are sued about once every 4 to 5 years; internists generally are sued less, averaging once every 7 to 10 years,[1] but hospitalists and others who practice a good deal of perioperative care probably constitute a higher risk pool among internists.

At the same time, it is estimated that only one in eight preventable medical errors committed in hospitals results in a malpractice claim.[2] From 1995 to 2000, the number of new malpractice claims actually declined by approximately 4%.[3]

Jury awards can be huge

Fewer than half (42%) of verdicts in malpractice cases are won by plaintiffs.[4] But when plaintiffs succeed, the awards can be costly: the mean amount of physician malpractice payments in the United States in 2006 (the most recent data available) was $311,965, according to the National Practitioner Data Bank.[5] Cases that involve a death result in substantially higher payments, averaging $1.4 million.[4]

Lawsuits are traumatic

Even if a physician is covered by good malpractice insurance, a malpractice lawsuit typically changes his or her life. It causes major disruption to the physician's practice and may damage his or her reputation. Lawsuits cause considerable emotional distress, including a loss of self-esteem, particularly if the physician feels that a mistake was made in the delivery of care.

CATEGORIES OF CLAIMS IN MALPRACTICE LAW

Malpractice law involves torts, which are civil wrongs causing injury to a person or property for which the plain-

tiff may seek redress through the courts. In general, the plaintiff seeks financial compensation. Practitioners do not go to jail for committing malpractice unless a district attorney decides that the harm was committed intentionally, in which case criminal charges may be brought.

There are many different categories of claims in malpractice law. The most common pertaining to perioperative medicine involve issues surrounding informed consent and medical negligence (the worst form being wrongful death).

Informed consent

Although everyone is familiar with informed consent, details of the process are called into question when something goes wrong. Informed consent is based on the right of patient autonomy: each person has a right to determine what will be done to his or her body, which includes the right to consent to or refuse treatment.

For any procedure, treatment, or medication, patients should be informed about the following:

- The nature of the intervention
- The benefits of the intervention (why it is being recommended)
- Significant risks reasonably expected to exist
- Available alternatives (including "no treatment").

If possible, it is important that the patient's family understand the risks involved, because if the patient dies or becomes incapacitated, a family that is surprised by the outcome is more likely to sue.

The standard to which physicians are held in malpractice suits is that of a "reasonable physician" dealing with a "reasonable patient." Often, a plaintiff claims that he or she did not know that a specific risk was involved, and the doctor claims that he or she spent a "typical" amount of time explaining all the risks. If that amount of time was only a few seconds, that may not pass the "reasonable physician" test, as a jury might conclude that more time may have been necessary.

Negligence and wrongful death

Negligence, including wrongful death, is a very common category of claim. The plaintiff generally must demonstrate four elements in negligence claims:

- The provider had a duty to the patient
- The duty was breached
- An injury occurred
- The breach of duty was a "proximate cause" of the injury.

Duty arises from the physician-patient relationship: any person whose name is on the medical chart essentially has a duty to the patient and can be brought into the case, even if the involvement was only peripheral.

Breach of duty. Determining whether a breach of duty occurred often involves a battle of medical experts. The standard of care is defined as what a reasonable practitioner would do under the same or similar circumstances, assuming similar training and background. The jury decides whether the physician met the standard of care based on testimony from experts.

The Latin phrase *res ipsa loquitur* means "the thing speaks for itself." In surgery, the classic example is if an instrument or a towel were accidentally left in a patient. In such a situation, the breach of duty is obvious, so the strategy of the defense generally must be to show that the patient was not harmed by the breach.

Injury. The concept of injury can be broad and often depends on distinguishing bad practice from a bad or unfortunate outcome. For instance, a patient who suffered multisystem trauma but whose life was saved by medical intervention could sue if he ended up with paresthesia in the foot afterwards. An expert may be called to help determine whether or not the complication is reasonable for the particular medical situation. Patient expectations usually factor prominently into questions of injury.

Proximate cause often enters into situations involving wrongful death. A clear understanding of the cause of death or evidence from an autopsy is not necessarily required for a plaintiff to argue that malpractice was a proximate cause of death. A plaintiff's attorney will often speculate why a patient died, and because the plaintiff's burden of proof is so low (see next paragraph), it may not help the defense to argue that it is pure speculation that a particular event was related to the death.

A low burden of proof

In a civil tort, the burden of proof is established by a "preponderance of the evidence," meaning that the allegation is "more likely than not." This is a much lower standard than the "beyond a reasonable doubt" threshold used for criminal proceedings. In other words, the plaintiff has to show only that the chance that malpractice occurred was greater than 50%.

Three types of damages

Potential damages (financial compensation) in malpractice suits fall into three categories:

- **Economic**, or the monetary costs of an injury (eg, medical bills or loss of income)
- **Noneconomic** (eg, pain and suffering, loss of ability to have sex)
- **Punitive**, or damages to punish a defendant for willful and wanton conduct.

Punitive damages are generally not covered by malpractice insurance policies and are only rarely involved in cases against an individual physician. They are more often awarded when deep pockets are perceived to be involved, such as in a case against a hospital system or an insurance company, and when the jury wants to punish the entity for doing something that was believed to be willful.

REDUCING THE RISK OF BEING SUED

Physicians tend to get sued when a bad outcome occurs that can be associated with substandard care or poor communication. Steps can be taken to reduce the risk of being sued, which can be simplified to the "four Cs": competence, communication, compassion, and charting **(Table 1)**.

Regardless of the circumstances, communication is probably the most important factor determining whether a physician will be sued. Sometimes a doctor does everything right medically but gets sued because of lack of communication with the patient. Conversely, many of us know of veteran physicians who still practice medicine as they did 35 years ago but are never sued because they have a great rapport with their patients and their patients love them for it.

The importance of careful charting also cannot be overemphasized. In malpractice cases, experts for the plaintiff will comb through the medical records and be sure to notice if something is missing. The plaintiff also benefits enormously if, for instance, nurses documented that they paged the doctor many times over a 3-day period and got no response.

CASE 1: PATIENT DIES DURING PREOPERATIVE STRESS TEST FOR KNEE SURGERY

A 65-year-old man with New York Heart Association class III cardiac disease (marked limitation of physical activity) is scheduled for a total knee arthroplasty and is seen at the preoperative testing center. His past medical history includes coronary artery disease, chronic obstructive pulmonary disease, hypertension, and prior repair of an abdominal aortic aneurysm. He is referred for a preoperative stress test.

Dobutamine stress echocardiography is performed. His target heart rate is reached at 132 beats per minute with sporadic premature ventricular contractions. Toward the end of the test, he complains of shortness of breath and chest pain. The test is terminated, and the patient goes into ventricular tachycardia and then ventricular fibrillation. Despite resuscitative efforts, he dies.

Dr. Michota: From the family's perspective, this patient had come for quality-of-life–enhancing surgery. They were looking forward to him getting a new knee so he could play golf again when he retired. The doctor convinced them that he needed a stress test first, which ends up killing him. Mr. Donnelly, as a lawyer, would you want to be the plaintiff's attorney in this case?

Mr. Donnelly: Very much so. The family never contemplated that their loved one would die from this procedure. The first issue would be whether or not the possibility of complications or death from the stress test had been discussed with the patient or his family.

TABLE 1
The 'four Cs' for reducing medicolegal risk

Competence: practice competent care

Communication: communicate expectations, risks, and treatment alternatives, and include the patient's family when possible

Compassion: treat patients with compassion

Charting: document communications and reasons for management decisions

Consent must be truly 'informed' and documented

Dr. Michota: How many of our audience members who do preoperative assessments and refer patients for stress testing can recall a conversation with a patient that included the comment, "You may die from getting this test"? Before this case occurred, I never brought up this possibility, but I do now. This case illustrates how important expectations are.

Comment from the audience: I think you have to be careful of your own bias about risks. You might say to the patient, "There's a risk that you'll have an arrhythmia and die," but if you also tell him, "I've never seen that happen during a stress test in my 10 years of practice," you've biased the informed consent. The family can say, "Well, he basically told us that it wasn't going to happen; he'd never seen a case of it."

Dr. Michota: Are there certain things we shouldn't say? Surely you should never promise somebody a good outcome by saying that certain rare events never happen.

Mr. Donnelly: That's true. You can give percentages. You might say, "I'm letting you know there's a possibility that you could die from this, but it's a low percentage risk." That way, you are informing the patient. This relates to the "reasonable physician" and "reasonable patient" standard. You are expected to do what is reasonable.

Is a signed consent form adequate defense?

Dr. Michota: What should the defense team do now? Let's say informed consent was obtained and documented at the stress lab. The patient signed a form that listed death as a risk, but no family members were present. Is this an adequate defense?

Mr. Donnelly: It depends on whether the patient understood what was on the form and had the opportunity to ask questions.

Dr. Michota: So the form means nothing?

Mr. Donnelly: If he didn't understand it, that is correct.

Dr. Michota: We thought he understood it. Can't we just say, "Of course he understood it—he signed it."

Mr. Donnelly: No. Keep in mind that most jurors have been patients at one time or another. There may be a perception that physicians are rushed or don't have time to answer questions. Communication is really important here.

Dr. Michota: But surely there's a physician on the jury who can help talk to the other jurors about how it really works.

Mr. Donnelly: No, a "jury of peers" is not a jury box of physicians. The plaintiff's attorneys tend to exclude scientists and other educated professionals from the jury; they don't want jurors who are accustomed to holding people to certain standards. They prefer young, impressionable people who wouldn't think twice about awarding somebody $20 million.

Who should be obtaining informed consent?

Question from the audience: Who should have obtained informed consent for this patient—the doctor who referred him for the stress test or the cardiologist who conducted the test? Sometimes I have to get informed consent for specialty procedures that I myself do not understand very well. Could I be considered culpable even though I'm not the one doing the procedure? I can imagine an attorney asking, "Doctor, are you a cardiologist? How many of these tests do you do? Why are you the one doing the informed consent? Did the patient really understand the effects of the test? Do *you* really understand them?"

Dr. Michota: That question is even more pertinent if the patient is referred to another institution covered under different malpractice insurance. You can bet the other provider will try to blame you if something goes wrong.

Mr. Donnelly: In an ideal world, both the referring physician and the physician who does the test discuss the risks, benefits, and alternatives, and answer all questions that the patient and family have. The discussion is properly documented in the medical record.

Question from the audience: Can you address the issue of supervision? What is the liability of a resident or intern in doing the informed consent?

Mr. Donnelly: The attending physician is usually responsible for everything that a resident does. I would prefer that the attending obtain the informed consent.

Dr. Michota: But our fellows and second-year postgraduate residents are independent licensed practitioners in Ohio. Does letting them handle informed consent pose a danger to a defense team's legal case?

Mr. Donnelly: It's not necessarily a danger medically, but it gives the plaintiff something to talk about. They will ignore the fact that an independent licensed practitioner obtained the informed consent. They will simply focus on the fact that the physician was a resident or fellow. They will claim, "They had this young, inexperienced doctor give the informed consent when there were staff physicians with 20 years of experience who should have done it." Plaintiffs will attempt to get a lot of mileage out of these minor issues.

Question from the audience: At our institution, the physician is present with the technician, so that when the physician obtains consent, the technician signs as a witness. The bottom of the long form basically says, "By signing this form, I attest that the physician performing the test has informed me of the benefits and risks of this test, and I agree to go ahead. I fully understand the implications of the test." Does that have value in the eyes of the law?

Mr. Donnelly: That's a great informed consent process and will have great value. That said, you can still get sued, because you can get sued for anything. But the jury ultimately decides, and odds are that with a process like yours they will conclude that the patient knew all the risks and benefits and alternatives because he or she signed the form and the doctor documented that everything was discussed.

Confidentiality vs family involvement

Comment from the audience: I'm struck by the comments that informed consent is supposed to be with the family so that there will be living witnesses in case the patient dies. According to Health Insurance Portability and Accountability Act (HIPAA) regulations, we have to be very careful to maintain confidentiality. For a competent patient, medical discussions are private unless specific permission has been obtained to involve the family.

Mr. Donnelly: Yes, we've assumed that the patient gave permission to discuss these issues with his family. If the patient does not want that, obviously you can't include the family because of HIPAA regulations.

Question from the audience: Should we routinely ask a patient to involve the family in an informed consent in case something goes wrong?

Mr. Donnelly: No. In general, it's appropriate only if the family is already present.

Dr. Michota: Keep in mind that there's nothing you can do to completely prevent being sued. You can do everything right and still get sued. If you're following good clinical practice and a patient doesn't want to involve

the family, all you can do is document your discussion and that you believed the patient understood the risks of the procedure.

Question from the audience: Do you consider a patient's decision-making capacity for informed consent? Should physicians document it prior to obtaining consent? A plaintiff can always claim that an elderly patient did not understand.

Mr. Donnelly: I have never seen specific documentation that a patient had capacity to consent, but it's a good idea for a borderline case. For such a case, it's especially important to involve the family and document, "I discussed the matter with this elderly patient and her husband and three daughters." You could also get a psychiatric consult or a social worker to help determine whether a patient has the capacity to make legal and medical decisions.

CASE 2: FATAL POSTSURGICAL MI RAISES QUESTIONS ABOUT THE PREOP EVALUATION

A 75-year-old man with rectal cancer presents for colorectal surgery. He has a remote cardiac history but exercises regularly and has a good functional classification without symptoms. The surgery is uneventful, but the patient develops hypotension in the postanesthesia care unit. He improves the next morning and goes to the colorectal surgery ward. Internal bleeding occurs but initially goes unrecognized; on postoperative day 2, his hemoglobin is found to be 2 g/dL and he is transferred to the intensive care unit, then back to the operating room, where he suffers cardiac arrest. He is revived but dies 2 weeks later. Autopsy reveals that he died of a myocardial infarction (MI).

Dr. Michota: The complaint in this case is that the patient did not receive a proper preoperative evaluation because no cardiac workup was done. As the hypothetical defense attorney, do you feel this case has merit? The patient most likely had an MI from demand ischemia due to hemorrhage, but does this have anything to do with not having a cardiac workup?

Mr. Donnelly: You as the physician are saying that even if he had an electrocardiogram (ECG), it is likely that nothing would have been determined. The cardiac problems he had prior to the surgery in question were well controlled, occurred in the distant past, and may not have affected the outcome. Maybe his remote cardiac problems were irrelevant and something else caused the MI that killed him. Nevertheless, the fact that the ECG wasn't done still could be a major issue for the plaintiff's attorney. After the fact, it seems like a no-brainer that an ECG should have been done in a case like this, and it's easy for the plaintiff to argue that it might have detected something. The defense has to keep reminding the jury that the case cannot be looked at retrospectively, and that's a tall order.

Dr. Michota: This case shows that even in the context of high-quality care, such things can happen. We have spent a lot of time at this summit talking about guidelines. But at the end of the day, if somebody dies perioperatively of an MI, the family may start looking for blame and any plaintiff's attorney will go through the record to see if a preoperative ECG was done. If it wasn't, a suit will get filed.

The four Cs offer the best protection

Question from the audience: Even if the physician had done the ECG, how do you know the plaintiff's attorney wouldn't attack him for not ordering a stress test? And if he had done a stress test, then they'd ask why he didn't order a catheterization. Where is it going to end?

Dr. Michota: You make a good point. The best way for physicians to protect themselves is to follow the four Cs mentioned earlier: competent care, communication, compassion, and charting. After I learned about this case, the next time I was in the clinic and didn't order an ECG, I asked the patient, "Did you expect that we would do an ECG here today?" When he responded that he did, I talked to him about how it wasn't indicated and probably would not change management. So that level of communication can sometimes prevent a lawsuit that might stem from a patient not feeling informed. I'm not suggesting that you spend hours explaining details with each patient, but it's good to be aware that cases like this happen and how you can reduce their likelihood.

Battles of the experts

Question from the audience: Exactly what standard is applied when the "standard of care" is determined in a court? For instance, my hospital may routinely order stress tests, whereas the American College of Cardiology and American Heart Association (ACC/AHA) guidelines are more restrictive in recommending when a stress test is indicated. Which standard would apply in court?

Dr. Michota: It's easy to find a plaintiff's expert who will say just about anything. If you claim that everybody gets a stress test at your community hospital and a patient dies during the stress test, the plaintiff's team will find an expert to say, "That was an unnecessary test and posed an unnecessary risk." If you're in a setting where stress tests are rarely done for preoperative evaluation, they'll find an expert to say, "Stress testing was available; it should have been done."

This is when the battles of the experts occur. If you have a superstar physician on your defense team, the plaintiff will have to find someone of equal pedigree who can argue against him or her. Sometimes cases go

away because the defense lines up amazing experts and the plaintiffs lose their stomach for the money it would take to bring the case forward. But usually cases do not involve that caliber of experts; most notables in the field are academic physicians who don't do this type of work. Usually you get busy physicians who spend 75% of their time in clinical practice and seem smart enough to impress the jury. Although they can say things that aren't even factual, they can sway the jury.

Question from the audience: I would not have ordered a preoperative ECG on this healthy 75-year-old, but one of the experts at this summit said that he would get a baseline ECG for such a case. How are differences like these reconciled in the legal context?

Dr. Michota: The standard to which we are held is that of a reasonable physician. Can you show that your approach was a reasonable one? Can you say, "I didn't order the ECG for the following reasons, and I discussed the issue with the patient"? Or alternately, "An ECG was ordered for the following reasons, and I discussed it with the patient"? The jury will want to know whether the care that was provided was reasonable.

Costs and consequences of being sued

Question from the audience: What does it cost to mount a defense in a malpractice trial?

Mr. Donnelly: You can easily spend more than $100,000 to go through a trial. Plaintiffs typically have three or four experts in various cities across the country, and you have to pay your lawyers to travel to those cities and take the depositions. And delays often occur. Cases get filed, dismissed, and refiled. A lot of the work that the lawyers did to prepare for the trial will have to be redone for a second, third, or fourth time as new dates for the trial are set. There are many unforeseen costs.

Dr. Michota: Let's say the physician who did the preoperative evaluation in this case was not affiliated with the hospital and wasn't involved in the surgery or any of the postoperative monitoring and management, which we see may have been questionable. This physician might get pulled into the case anyway because he didn't order an ECG in the preoperative evaluation. Although an ECG wasn't recommended in this case by the ACC/AHA guidelines, this doctor is looking at spending considerable time, energy, and money to defend himself. What if his attorney recommends that he settle for a nominal amount—say, $25,000—because it's cheaper and easier? Are there repercussions for him as a physician when he pays out a settlement under his name?

Mr. Donnelly: Absolutely. He will be reported to the National Practitioner Data Bank, and when he renews his license or applies for a license to practice in another state, he must disclose that he has been sued and paid a settlement. The new consumer-targeted public reporting Web sites will also publicize this information. It is like a black mark against this doctor even though he never admitted any liability.

CASE 3: A CLEAR CASE OF NEGLIGENCE—WHO IS RESPONSIBLE?

A 67-year-old man undergoes a laminectomy in the hospital. He develops shortness of breath postoperatively and is seen by the hospitalist team. He is started on full-dose weight-adjusted low-molecular-weight heparin (LMWH) for possible pulmonary embolism or acute coronary syndrome. His symptoms resolve and his workup is negative. It is a holiday weekend. The consultants sign off but do not stop the full-dose LMWH. The patient is discharged to the rehabilitation unit by the surgeon and the surgeon's assistant, who include all the medications at discharge, including the full-dose LMWH. The patient is admitted to a subacute nursing facility, where the physiatrist transfers to the chart all the medications on which the patient was discharged.

The patient does well until postoperative day 7, when he develops urinary retention and can't move his legs. At this point, someone finally questions why he is on the LMWH, and it is stopped. The patient undergoes emergency surgery to evacuate a huge spinal hematoma, but his neurologic function never recovers.

Dr. Michota: I think most of us would agree that there was negligence here. I bet a plaintiff's attorney would love to have this case.

Mr. Donnelly: Absolutely. The patient can no longer walk, so it's already a high-value case. It would be even more so if we supposed that the patient were only 45 years old and a corporate executive. That would make it a really high-value case.

Dr. Michota: What do you mean? Does a patient's age or economic means matter to a plaintiff's attorney?

Mr. Donnelly: Of course. For a plaintiff's attorney, it's always nice to have a case like this where there's negligence, but the high-dollar cases typically involve a likable plaintiff who is a high wage earner with a good family. A plaintiff's lawyer will take a case that may not be so strong on evidence of negligence if it's likely that a jury will like the plaintiff and his or her family. Kids always help to sway a jury—jurors will feel sorry for them and want to help them. This case even has two surgeries, so the family's medical bills will be especially high. It's a great case for a plaintiff's attorney.

Who's at fault?

Dr. Michota: Let's look at a few more case details. Once the various doctors involved in this case realized what

happened, they got nervous and engaged in finger-pointing. The surgeons felt that the hospitalists should have stopped the LMWH. The hospitalists claimed that since they had signed off, the surgeons should have stopped it. The physiatrist said, "Who am I to decide to stop medications? I assumed that the hospital physicians checked the medications before sending the patient to the rehab facility."

Interestingly, a hospitalist went back and made a chart entry after the second surgery. He wrote, "Late chart entry. Discussion with surgeon regarding LMWH. I told him to stop it." Does that make him free and clear?

Mr. Donnelly: Actually, the hospitalist just shot his credibility, and now the jury is really angry. The dollar value of the case has just gone up.

Dr. Michota: Okay, suppose the hospitalist wouldn't do something that obvious. Instead, he goes back to the chart after the fact, finds the same color pen as the entry at the time, and writes, "Patient is okay. Please stop LMWH," and signs his name. Is there any way anyone is going to be able to figure that out?

Mr. Donnelly: All the other doctors and nurses will testify that the note was not in the chart before. The plaintiff will hire a handwriting expert and look at the different impressions on the paper, the inks, and the style of writing. Now the hospitalist has really escalated the situation and is liable for punitive damages, which will come out of his own pocket, since malpractice insurance doesn't cover punitive damages. His license may be threatened. The jury will really be angered, and the plaintiff's lawyer will love stoking the situation.

DISCLOSURES

Dr. Michota has indicated that he has relevant financial relationships with the following commercial interests: advisory board member for Sanofi-Aventis, Scios, and Johnson & Johnson; consultant to Sanofi-Aventis and Genentech; and speakers' bureaus of Sanofi-Aventis and Genentech. Mr. Donnelly has indicated that he has no financial relationships with commercial interests that have a direct bearing on the subject matter of this article. All conflicts of interest have been resolved.

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Perioperative medication management: General principles and practical applications

ABSTRACT

An extensive medication history, including the use of nonprescription agents and herbal products, is the foundation of effective perioperative medication management. Decisions about stopping or continuing medications perioperatively should be based on withdrawal potential, the potential for disease progression if therapy is interrupted, the potential for drug interactions with anesthesia, and the patient's short-term quality of life. In general, medications with withdrawal potential should be continued perioperatively, nonessential medications that increase surgical risk should be discontinued before surgery, and clinical judgment should be exercised in other cases.

KEY POINTS

Common drugs that have been associated with withdrawal symptoms when discontinued preoperatively include selective serotonin reuptake inhibitors (SSRIs), beta-blockers, clonidine, statins, and corticosteroids.

In general, most nonsteroidal anti-inflammatory drugs should be stopped at least 3 days before surgery.

Although ACE inhibitors and angiotensin receptor blockers intensify the hypotensive effects of anesthesia, it may be prudent to continue them perioperatively unless their only indication is for hypertension and the patient's blood pressure is well controlled.

Herbal medications should be stopped at least 7 days before surgery, owing to the uncertainly over their actual contents.

Among psychotropics, SSRIs, tricyclic antidepressants, benzodiazepines, and antipsychotics are generally safe to continue perioperatively.

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As a hospitalist who practices in a perioperative clinic, I probably spend more of my time with patients reviewing and discussing the medications they are taking than on any other single subject. Surgical patients—many of whom are elderly—commonly are on multiple medications, have renal or hepatic disease that can alter drug metabolism, and may not be adequately educated about their medication regimens.

Patient safety is the overriding concern behind perioperative medication management, consistent with the medication-related objectives in the Joint Commission's 2009 National Patient Safety Goals.[1] The increasing surgical burden that comes with an aging population, along with rising expectations for functional recovery, has likewise elevated the importance of perioperative medication management.

Despite these demands, there is scant evidence from randomized controlled trials to directly guide perioperative medication management. For this reason, recommendations in this area rely largely on other forms of evidence, including expert consensus, case reports, in vitro studies, recommendations from pharmaceutical companies, and other known data (pharmacokinetics, drug interactions with anesthetic agents, and effects of the agent on the primary disease and on perioperative risk).

This article reviews general principles of perioperative medication management and then presents four case vignettes to explore perioperative recommendations for a number of common medication classes. It is not intended as a comprehensive review of the perioperative management of all medications, as numerous classes (antiplatelets, beta-blockers, oral hypogycemic agents, insulin, statins) are discussed in detail elsewhere in this proceedings supplement.

GENERAL CONSIDERATIONS IN MEDICATION MANAGEMENT

A comprehensive medication history is fundamental

Effective perioperative management of medications requires an understanding of the patient and his or her comorbidities so that the risk of perioperative decompensation can be gauged. This understanding stems from

a thorough medical history that includes a comprehensive medication history to provide a complete inventory of the following:

- All prescription medications
- All over-the-counter (OTC) agents (including nonsteroidal anti-inflammatory drugs [NSAIDs])
- All vitamins
- All herbal medications.

When to stop, when to resume?

Guidance on stopping and resuming medications in the perioperative period is relatively absent from the literature. General considerations include the following:

- The potential for withdrawal when stopping a medication
- The progression of disease with interruption of drug therapy
- The potential for interactions with anesthetic agents if the medication is continued.

Withdrawal potential

Abrupt discontinuation of some drugs may lead to unnecessary complications due to the potential for withdrawal. Common medications that have been associated with withdrawal symptoms are selective serotonin reuptake inhibitors (SSRIs), beta-blockers, clonidine, statins, and corticosteroids.[2] A recent systematic literature review concluded that continuation of chronic corticosteroid therapy without supplemental (stress) doses of corticosteroids is appropriate unless patients have primary disease of the hypothalamic-pituitary-adrenal axis, in which case perioperative stress dosing is recommended to avoid acute adrenal insufficiency (addisonian crisis).[3]

Patients on chronic drugs are more likely to have complications

In a medication survey of 1,025 patients admitted to a general surgery unit, Kennedy et al reported that 49% of the patients were taking medications (other than vitamins) unrelated to their surgical procedure.[4] Even while this percentage is considerably lower than what I observe in my practice, this study showed that medication use has important perioperative consequences[4]:

- The odds ratio for a postoperative complication was 2.7 (95% CI, 1.76–4.04) if patients were taking a drug unrelated to their surgery.
- The risk of a complication was particularly elevated if patients were taking cardiovascular drugs or agents that act on the central nervous system; if patients were on NPO ("nothing by mouth") orders for more than 24 hours before surgery; and if the operation was more than 1 hour in duration. These findings could reflect destabilization of the disease processes for which the patients were taking chronic medications that required interruption.

Unintended discontinuation of chronic drugs

Stopping a chronic medication for a surgical procedure raises the possibility that its resumption could be overlooked, especially since medical errors are particularly common in the transition between health care settings following hospital discharge. A population-based cohort study among all elderly patients discharged from Ontario, Canada, hospitals over a 5½-year period found that 11.4% of patients undergoing elective surgery did not resume their indicated chronic warfarin therapy within 6 months after its presurgical discontinuation.[5] Although 6-month rates of unintended failure to resume therapy were lower for statins (4%) and ophthalmic beta-blocker drops (8%),[5] these findings underscore that drug discontinuation always carries a risk that therapy might not be resumed as indicated.

Additional considerations

Stress response to surgery. Decisions about perioperative drug therapy should always take into account the stress response to surgery and the challenge it presents to homeostasis in the face of increased sympathetic tone and release of pituitary hormones.

Unreliable absorption of oral medications. Surgery and the postoperative state can lead to unreliable absorption of oral drugs for any of a number of reasons: villous atrophy, diminished blood flow to the gut, edema, mucosal ischemia, diminished motility from postoperative ileus, and use of narcotics.[6]

Take-away general principles

The following principles can be applied to guide perioperative medication management in a general sense[7]:

- **Continue** medications with withdrawal potential
- **Discontinue** medications that increase surgical risk and are not essential for short-term quality of life
- **Use clinical judgment** when neither of the above two principles applies, but be mindful that many other medications are given in the narrow perioperative time window and that metabolism and elimination of chronic drugs may be altered.

CASE 1: A PATIENT ON A NONPRESCRIPTION NSAID FOR SEVERE ARTHRITIS

A 55-year-old man with severe osteoarthritis is scheduled for total hip arthroplasty in 2 days. He stopped his aspirin (325 mg/day) 1 week ago but continued taking ibuprofen 600 three times daily with food, explaining that "no one told me to stop." His last dose was yesterday evening.

Question: What should you do?

A. Call the surgeon and cancel the surgery

B. Call the surgeon to notify, and tell the patient to stop the ibuprofen now

C. Check his bleeding time and proceed if normal
D. Just tell the patient to stop the ibuprofen now
E. Proceed to the operating room regardless of the ibuprofen dose

The best approach would be to notify the surgeon and tell the patient to stop the ibuprofen now. NSAIDs such as ibuprofen reversibly inhibit platelet cyclooxygenase (COX), diminish thromboxane A_2 production, diminish platelet aggregation, and can increase bleeding time measurement and overall bleeding risk. They can induce renal failure in combination with other drugs, especially in the setting of hypotension.[8,9] COX-2 inhibitors have less effect on platelet function but retain the potential for renal toxicity and also confer well-known cardiovascular risks.

In the past, NSAIDs were typically held for 7 days before surgery, but this practice was not supported with much evidence. In vitro assessment indicates that platelet function normalizes within 24 hours after cessation of regular ibuprofen or dexibuprofen in healthy individuals.[10,11]

Since NSAIDs vary in their effect on bleeding time, which does not correlate well with elimination half-life, a general recommendation is to stop most NSAIDs at least 3 days before surgery.

CASE 2: A PATIENT ON MULTIPLE CARDIOVASCULAR DRUGS

A 67-year-old man with dilated cardiomyopathy and an ejection fraction of 25% (well compensated) is scheduled for a laparoscopic cholecystectomy tomorrow. He is taking lisinopril (40 mg/day), irbesartan (150 mg/day), and furosemide (80 mg/day).

Question: What is your advice?

A. Call the surgeon and cancel the surgery
B. Call the surgeon to notify, and tell the patient to stop his medications now
C. Hold all of the above medications on the morning of surgery
D. Proceed to the operating room with the usual doses of his medications on the morning of surgery

The best approach is to withhold these medications on the morning of surgery.

Diuretics are typically held on the morning of surgery because of the potential for hypovolemia and electrolyte depletion.

Angiotensin-converting enzyme (ACE) inhibitors intensify the hypotensive effects of anesthesia induction. Because angiotensin II plays a key role in maintaining circulating volume in response to stressors, volume deficits can occur in ACE inhibitor-treated patients as angiotensin II cannot compensate for venous pooling of blood, resulting in diminished cardiac output and arterial hypotension. However, continued renin-angiotensin system suppression may protect regional circulation, as has been demonstrated by reduced release of cardiac enzymes with ACE inhibitor continuation (compared with interruption) in cardiac surgery patients. ACE inhibitors also have a renal protective effect, preserving glomerular filtration rate in patients undergoing aortic abdominal aneurysm repair or coronary artery bypass graft surgery. Hypotension with ACE inhibition is treatable with sympathomimetics, alpha-agonists, and intravenous fluids.[12–15]

If a patient's ACE inhibitor is stopped, be prepared for rebound postoperative hypertension. The probability of postoperative atrial fibrillation is also increased with ACE inhibitor interruption.[14] In patients with left ventricular dysfunction undergoing noncardiac vascular surgery, continued ACE inhibition is associated with reduced mortality.[16] These data argue, at the very least, for prompt resumption of ACE inhibitors after surgery.

Angiotensin receptor blockers (ARBs) have largely the same clinical benefits as do ACE inhibitors. These agents also increase the risk of hypotension upon induction of anesthesia, and this hypotension is not as responsive to conventional vasopressors such as ephedrine and phenylephrine; a better response is achieved with vasopressin.[15] In light of the long half-life of ARBs, current thinking is to withhold them 24 hours before surgery.

Rosenman et al recently published a meta-analysis of five studies assessing the effects of continuing or withholding ACE inhibitors and ARBs in the preoperative period.[17] They found a statistically significant increase in the incidence of perioperative hypotension in patients in whom the drugs were continued compared with those in whom the drugs were withheld (relative risk = 1.50; 95% CI, 1.15–1.96), but there was no significant difference in the rate of perioperative MI between the two groups. Notably, the indication for ACE inhibitor or ARB use in all of the studies was hypertension, not heart failure.

My approach to the perioperative management of ACE inhibitors and ARBs is to withhold them on the morning of surgery (in the case of ARBs, 24 hours prior to surgery) if their only indication is for hypertension and if the patient's blood pressure is well controlled. If the patient has another indication for these agents or has hypertension that is not well controlled, I am inclined to continue these agents but will first discuss the decision with the anesthesiologist.

CASE 3: A PATIENT TAKING HERBAL MEDICATIONS

A 68-year-old woman with a history of hypertension, osteoarthritis, and osteoporosis is scheduled for total hip replacement in 7 days. Her medications include atenolol, hydrochlorothiazide, and alendronate. She also reports taking some natural herbal medications. She does not recall their names initially but calls back with

the names: ginkgo biloba for her memory and echinacea for her immune system.

Question: What are your recommendations?

A. *Stop all medications now except atenolol and proceed to surgery*
B. *Stop the herbals now but take all other medications on the morning of surgery*
C. *Stop the herbals now and take only atenolol on the morning of surgery*
D. *Continue all medications now and take atenolol and the herbals on the morning of surgery*
E. *Cancel the surgery and call an herbalist for guidance*

The best strategy is to stop the herbals now and tell her to take only atenolol (a beta-blocker) on the morning of surgery.

Up to one third of patients scheduled for surgery take herbal medications,[18] and many do not report that they are taking them without prompting, which requires that the consultant specifically ask about herbals. Often this failure to report use of herbals stems from patients' misperception that herbals are inherently safe because they are "natural." Yet common herbal medications have been implicated in perioperative complications including MI, stroke, bleeding, prolonged anesthetic action, inadequate anesthetic action, and interference with other medications.[18] **Table 1** profiles potential perioperative effects specific to eight common herbal medications.

Because the US Food and Drug Administration (FDA) does not regulate herbal products, the contents of these products can vary widely. For example, an analysis using mass spectrometry of 50 commercial ginseng products from 11 countries found that the ginseng content varied from 0% (six preparations) to 9%.[19] Catecholamine-type compounds were found in some of the products.[19]

Because of the uncertainty over their actual contents, herbal medications should be stopped at least 7 days prior to surgery. If a patient is still taking herbal supplements on the day before surgery, I typically alert the anesthesiologist and surgeon.

TABLE 1
Potential perioperative effects of common herbals*

Ginseng	• Hypoglycemia • Inhibits platelet aggregation (may be irreversible) • Inhibits PT/PTT in animals • Increases anticoagulation effect of warfarin
Ephedra	• Myocardial infarction, cerebrovascular accident • Depletes endogenous catecholamine stores, which can cause intraoperative hemodynamic instability • Life-threatening interaction with MAO inhibitors
Garlic	• Inhibits platelet aggregation (may be irreversible) • Increases fibrinolysis • Increases risk of bleeding • Equivocal blood pressure lowering
Ginkgo biloba	• Inhibits platelet-activating factor, leading to increased bleeding risk
Kava	• Sedation, anxiolysis • Increases sedative effect of anesthetics • Potential for addiction, tolerance, withdrawal
St. John's wort	• Many drug–drug interactions via induction of CYP 450 enzymes
Echinacea	• Activates cell-mediated immunity • Allergic reactions • Immunosuppression
Valerian	• Increases sedative effect of anesthesia • Withdrawal • May increase anesthesia requirements

*Adapted from Ang-Lee et al.[18]
PT/PTT = prothrombin time/partial thromboplastin time; MAO = monoamine oxidase

CASE 4: A PATIENT ON MULTIPLE PSYCHOTROPICS

A 38-year-old woman with a history of severe major depression is scheduled for a mastectomy for breast cancer the next day. Her medications include fluoxetine, lorazepam, and phenelzine, all of which she has been taking for many years.

Question: What is your course of action?

A. *Call the surgeon and cancel the surgery*
B. *Call the surgeon and notify the day-of-surgery anesthesiologist that the patient is taking these agents*
C. *Stop all the medications now and proceed to the operating room*
D. *Request a psychiatric consult for an alternative drug regimen*
E. *Proceed and advise the patient to take all of these agents on the morning of surgery*

My approach would be to notify the day-of-surgery anesthesiologist, specifically about the phenelzine, which is a monoamine oxidase (MAO) inhibitor (see below). The other two agents can be taken on the morning of surgery, although fluoxetine has a long half-life, so missing a dose should not be problematic, and lorazepam can be given intravenously if needed.

SSRIs, including fluoxetine, are generally safe perioperatively. Serotonin depletion from platelets, however, increases the risk of bleeding, especially gastrointestinal bleeding, when SSRIs are used with NSAIDs.[20–22] A neurosurgical procedure may therefore be especially risky in patients who have not stopped their SSRI if they are also taking an NSAID or an herbal medication

that may increase the risk of bleeding. The caveat to stopping SSRIs is the potential for a minor withdrawal syndrome.

Tricyclic antidepressants inhibit the reuptake of norepinephrine and serotonin and may increase the action of sympathomimetics. Although arrhythmias are thought to be a concern with tricyclics, there are no reported cases of association in the literature. In general, I advise continuing triclyclics perioperatively, especially in patients who are on high doses.

Benzodiazepines, including lorazepam, are safe to use perioperatively, and a potential for withdrawal symptoms (hypertension, agitation, delirium, seizures) argues against their discontinuation. Chronic benzodiazepine use may increase anesthetic requirements.

Antipsychotic agents, which include haloperidol, olanzapine, risperidone, and ziprasidone, have multiple routes of administration—intramuscular, oral, sublingual, and intravenous. These agents are generally safe to use in the perioperative period.

MAO inhibitors, including phenelzine, are no longer commonly used and are typically reserved for the treatment of refractory depression. But they merit attention, as their use can cause accumulation of biogenic amines in the central and autonomic nervous systems. There are two types of MAO reactions—excitatory and depressive. Excitatory reactions lead to serotonin syndrome. Depressive reactions induce inhibition of hepatic microsomal enzymes, leading to narcotic accumulation and increased sedation.[23]

MAO inhibitors are also of concern because of their many drug interactions. When used with indirect sympathomimetics such as ephedrine, they promote a massive release of stored norepinephrine, leading to severe hypertension. When used with opioids like meperidine and dextromethorphan, MAO inhibitors are associated with a serotonin syndrome characterized by agitation, headache, fever, seizures, coma, and death.

Discontinuing MAO inhibitors before the day of surgery is no longer universally recommended, due to the risk of precipitating an exacerbation of major depression. Safe anesthetic regimens in the setting of MAO inhibitors involve avoidance of meperidine (morphine and fentanyl are safe) and use of only direct-acting sympathomimetics.

CONCLUSIONS

A good medication history that includes herbal and OTC products is essential for safe induction of anesthesia and optimization of outcomes during and following surgery. In general, medications with the potential to induce withdrawal symptoms should be continued. The use of nonessential medications that can increase surgical risk should be discontinued. If neither of these conditions applies, consider the patient's risk profile and the risk of the procedure when making perioperative management decisions. Be mindful of withdrawal syndromes and resume medications with the potential for such syndromes as soon as possible.

DISCUSSION

Comment from the audience: In regard to your comment that diuretics are typically held on the morning of surgery, my institution recently completed a randomized placebo-controlled trial (publication is pending) in which we studied the effect of continuing or not continuing furosemide preoperatively. We found no difference in the occurrence of intraoperative hypotension between the two groups. It will be interesting to see if these findings change practice over time.

Dr. Whinney: It's good to know that hypotension is not a concern with furosemide, but the issue here is not just blood pressure but electrolyte abnormalities that could predispose to arrhythmias. The patients who concern me are those who haven't been seen by a physician for a while and may be on high doses of furosemide. I would scrutinize such patients closely.

Question from the audience: We see a number of patients on methotrexate and other disease-modifying rheumatologic drugs. Can you comment on the perioperative management of these medications?

Dr. Whinney: Methotrexate has caused some anxiety over the risk of infection, but the literature does not support such concern.[24] In fact, it appears that continuing methotrexate is probably advisable because the risk of decompensation of the disease may be worse than the potential infectious risks. The only caveat is the patient with renal insufficiency, in whom the recommendation is to withhold methotrexate for 2 weeks before surgery. While most rheumatologists favor withholding disease-modifying drugs perioperatively, a recent systematic review showed no increased risk of either total or infectious complications with use of immunomodulators including infliximab, azathioprine, and cyclosporine.[25] It is still reasonable and prudent to discuss this issue with the patient's rheumatologist. Hydroxychloroquine is safe to continue.

Comment from the audience: First, I would like to urge everyone to be mindful of medication-related indications for preoperative testing. There are many psychotropic drugs that prolong the QT interval and thus constitute an indication for a baseline electrocardiogram prior to surgery. Second, I believe there is a mythology in the perioperative community about the bleeding risk associated with omega-3 fatty acids and vitamin E. Can you comment on the bleeding risks associated with each?

Dr. Whinney: There are few data; the fear is based purely on the potential of these compounds to cause bleeding. Neither is beneficial for short-term quality of life or for chronic prevention, and there's no withdrawal syndrome from either. So I generally withhold them, but if the patient is still taking them up to the day of surgery, it doesn't merit postponing surgery. I generally let the surgeon or the nurse know, and it tends not to be a big deal.

Question from the audience: Do you stop herbal teas, energy drinks, and diet medications such as phentermine prior to surgery?

Dr. Whinney: You need to know which diet medications the patient is taking. The problem with many of the OTC products is that they may or may not be considered drugs, so they may not be approved by the FDA and thus you don't know what the patient is actually taking. For the most part, a diet medication does not contribute to short-term quality of life. My aim is to get the patient through surgery as safely as possible, so if a patient is taking an agent with ingredients, known or unknown, with an interaction potential, then I will stop it.

The two types of diet agents are those that block the absorption of fat, which could interact with other oral agents given at the same time, and those that act via the gastrointestinal tract. I generally withhold the fat-absorption blockers the day before surgery. Phentermine has the potential for catecholinergic reactions or sympathomimetic actions. I would put it in the category of herbal-type medicines and withhold it for at least 7 days.

Question from the audience: Can you comment on combination drugs such as losartan/hydrochlorothiazide on the morning of surgery?

Dr. Whinney: The ARB losartan may have more physiologic benefit than the diuretic, so I would prescribe a single dose of losartan the morning of surgery if I had decided to continue this class of medication for uncontrolled hypertension or concern over heart failure decompensation. The same is true for a beta-blocker/diuretic combination product; I will prescribe the beta-blocker component individually and tell the patient to take it the morning of surgery.

Question from the audience: I'm confused by the recommendation to stop hydrochlorothiazide. It's a far less potent diuretic than furosemide. Does the risk of stopping it, with resulting blood pressure elevation, outweigh the risk of a mild hypotensive response because of a mild diuretic effect? I'm aware of no data on the risk of stopping hydrochlorothiazide—are you?

Dr. Whinney: There are no data. Again, the recommendation is based on the physiology of the drug, as well as on expert consensus and opinion. Since anesthesia has a vasodilatory effect with a hypotensive response, it's probably reasonable to hold hydrochlorothiazide if its only indication is for hypertension. That's the logic behind the recommendation. If you continue it the day of surgery, it may not necessarily hurt, but we're not certain.

Question from the audience: The implication from your third case study was that alendronate should be held. What's the basis of that recommendation?

Dr. Whinney: First, the patient has to be upright for 30 minutes after taking alendronate, which could be a problem on the morning of surgery. Also, withholding it will not impair short-term quality of life; it's a weekly medication, so the patient can take her next dose once she's up and ambulatory.

Question from the audience: What do you for young women on oral contraceptives? I'm lucky if I see them within 7 days of surgery.

Dr. Whinney: You're bringing up the concern with exogenous hormones and the risk of venous thromboembolism (VTE), a risk that clearly is increased with the hypercoagulable milieu of surgery. The recommendation is to stop hormone therapy 30 to 45 days prior to surgery in these patients. As you note, however, we don't get the chance to see patients during that window of opportunity. So the question is whether stopping hormones within a shorter time period results in an incremental benefit. And that is not necessarily the case. These patients should be seen as being at risk for VTE and be given appropriate VTE prophylaxis. In fact, in the similar context of menopausal hormone therapy, a study among women undergoing orthopedic surgery showed that as long as they received appropriate VTE prophylaxis, there was no significant difference in VTE rates between the women whose hormone therapy was withheld versus those who continued it.[26]

Question from the audience: Are there concerns about withdrawal in patients with peripheral vascular disease treated with cilostazol or pentoxifylline?

Dr. Whinney: It's not particularly well studied. Guidelines from the American College of Physicians suggest to hold these agents for elective surgeries.[27] With respect to antiplatelet therapies, O'Riordan et al did a systematic review of 99 articles pertaining to antiplatelet agents in the perioperative period and concluded that aspirin should not be stopped in patients going for surgery.[28] In vascular surgery, antiplatelet agents may help promote graft patency.

DISCLOSURES

Dr. Whinney has indicated that he serves on the speakers' bureau of Sanofi-Aventis. All conflicts of interest have been resolved.

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