New developments in the preoperative evaluation and perioperative management of coronary artery disease in patients undergoing vascular surgery

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Background: Preoperative evaluation and perioperative management of cardiac disease in patients undergoing vascular surgery (VS) is important for patients and vascular surgeons. Recent evidence has emerged that has allowed us to develop current paradigms for evaluating and managing coronary artery disease in VS patients perioperatively. Methods: The utility of stress testing, the role of preoperative coronary revascularization, the optimal use of β-blockers and statins, and the role of antiplatelet therapy in VS patients were reviewed in the literature. Results: The revised Lee cardiac risk index, based on the number of risk factors (high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, insulin-dependent diabetes mellitus, renal failure, hypertension, and age >75) quantitates cardiac risk. Stress testing is not predictive of myocardial ischemia/infarction (MI) or death and is only recommended in patients with unstable angina or an active arrhythmia. Stress testing for patients with 0 to 2 risk factors delays VS up to 3 weeks. In high-risk patients (≥3 risk factors), it helps to identify patients who may develop myocardial ischemia and would benefit from a 30-day period to optimize medical therapy before VS. Stress testing and coronary catheterization do not predict which coronary artery to revascularize to prevent MI or death. Revascularization does not decrease MI or death rates at 1 month or 6 years. Although β-blocker treatment decreases cardiac risk with VS, timing and dosage (titration) influence outcomes, improper usage may increase stroke and death rate, and not all VS patients should be taking these drugs. Patients with ≥1 risk factor should be considered to begin a low dose β-blocker 1 month before VS. Preoperative statin use sharply decreases MI, stroke, and death perioperatively and long-term postoperatively. Conclusion: Routine stress testing should not be performed before VS. The Lee index should be used to stratify risk in patients undergoing VS. Patients with ≥3 risk factors or active cardiac conditions should undergo stress testing, if VS can be delayed. All VS patients, except those with 0 risk factors, should be started for a β-blocker (bisoprolol, 2.5-5 mg/d started 1 month before VS, titrated to a pulse <70 beats/min and a systolic blood pressure ≥120 mm Hg). Intermediate risk factors may not require aggressive heart rate control but simply maintenance on a low-dose β-blocker. Statins should be started (ideally 30 days) before all VS using long-acting formulations such as fluvastatin (80 mg/d) for patients unable to take oral medication. (J Vasc Surg 2010;51:242-51.)

Preoperative evaluation and perioperative management of coronary artery disease (CAD) in patients undergoing vascular surgery (VS) is a fundamental consideration in the practice of this specialty. In 1996, the American College of Cardiology (ACC) and the American Heart Association (AHA) introduced guidelines to identify and manage patients at risk for cardiac complications after VS. Recently, however, new evidence has recently emerged that suggests a decreased role for an extensive coronary preoperative work-up and raises questions about preoperative coronary revascularization. Some of this evidence led the ACC/AHA to update their identification and management guidelines in 2007. Furthermore, recent reports have added to this evidence and questioned the timing, dosage, and safety of some of the drugs that constitute optimal medical therapy.

The purpose of the present article is to review this new information as it relates to VS patients and use it to clarify the current management of these patients preoperatively and perioperatively with regard to clinical risk stratification, stress testing, coronary revascularization, and the optimal usage of β-blockers, statins, and antiplatelet therapy after coronary stenting. We have made these recommendations based on our interpretation of all currently available evidence.

PATHOPHYSIOLOGY OF THE PERIOPERATIVE MYOCARDIAL INFARCTION: THE SCIENTIFIC FOUNDATION FOR THE UPDATED RECOMMENDATIONS

A new understanding of the fundamental pathophysiology of perioperative myocardial infarctions (MIs) provides an explanation why recent evidence and the resulting altered 2007 ACC/AHA guidelines differ from those in the past. Patients with pre-existing CAD who undergo VS are now thought to be at increased risk for perioperative MI because of a process known as acute coronary syndrome (ACS) that is enhanced by the systemic stress response associated with the VS. ACS is due to the instability of an atherosclerotic plaque leading to rupture, thereby exposing a prothrombotic surface that causes platelet adherence and vessel thrombosis.1-2 Atherosclerotic plaque rupture is no longer considered to result solely from excess lipid accumu-
lation but is now thought to be the result of an inflammatory reaction and repeated cycles of wounding and healing associated with breakdown of the overlying diseased endothelium.\(^1\)\(^4\)\(^5\) ACS can occur from any atherosclerotic plaque and does not necessarily involve the most stenotic plaques that cause a positive stress test.\(^2\)\(^3\) Some authors have suggested that primary MIs in unoperated-on patients are most likely caused by stenoses of <50%.\(^1\)\(^3\)

ACS is also enhanced by the stress response from surgery, which includes a surge in catecholamines that leads to increased ionotropic and chronotropic effects on the heart. This increase in heart rate and contractility causes an increase in oxygen demand that cannot be supplied by the diseased coronary arteries. Furthermore, the increased catecholamines lead to a systemic prothrombotic state with vasospasm, increased platelet activity, and decreased fibrinolytic activity.\(^6\) The combination of the random rupturing of the unstable plaques causing ACS and the enhancement of ACS by the systemic stress induced by surgery indicates that the most effective prevention of perioperative MI would come from systemic treatment to stabilize plaques and unburden the heart rather than from a local myocardial revascularization procedure.

Short-term β-adrenergic blockade decreases the stress response on the heart, and its long-term effects result in decreased inflammatory mediators, which may stabilize atheromatous plaques in the coronary arteries.\(^1\)\(^7\)\(^-\)\(^14\) Statins also decrease inflammatory cytokines and stabilize atheromatous plaques, further decreasing the risk of ACS.\(^1\)\(^2\)\(^15\)\(^-\)\(^20\)

### RISK STRATIFICATION BASED ON CLINICAL FACTORS

The ACC/AHA guidelines for risk stratification and management recommend using a clinical risk index to identify patients at risk for a perioperative MI when the functional capacity is unknown, which is often the case in VS procedures. Several risk indices have been developed to stratify surgical patients by using criteria to categorize patients into low, intermediate, or high risk. Historically, patients of intermediate or high risk were recommended to undergo an extensive CAD work-up.

The ACC/AHA guidelines were based on the Eagle criteria for evaluating risk,\(^2\)\(^21\)\(^22\) which included age >70 years, diabetes mellitus, angina, the presence of Q-waves on preoperative electrocardiogram (ECG), ventricular arrhythmia, and a history of congestive heart failure (CHF). Unlike the Eagle criteria, however, the 1996 ACC/AHA guidelines for risk assessment and management also included the patient’s functional capacity, and this was important because many VS patients have poor functional capacity, making it difficult to assess myocardial ischemic potential from their history.\(^5\) In addition, instead of using the preoperative ECG and the presence of Q-waves to determine prior coronary ischemic events, the 1996 ACC/AHA guidelines used a history of MI. This was a more sensitive indicator because less significant cardiac ischemic events were considered, such as asymptomatic cardiac enzyme leaks detected on laboratory assays.\(^2\) Patients who met ≥2 of the 1996 ACC/AHA criteria were categorized as intermediate risk.\(^2\)\(^21\)

The more recent studies evaluating preoperative CAD risk and management are based on a similar but different risk classification derived from Goldman et al\(^23\) that was developed in 1977. It was replaced in 1986 by the modified cardiac risk index.\(^24\) In 1999, Lee et al published the Revised Cardiac Risk Index, or Lee index, which has been used in many of the recent studies to assess cardiac risk in surgical patients when functional capacity is poor or unknown (Table I).\(^1\)\(^2\)\(^14\)\(^-\)\(^25\) This index uses six predictors of major cardiac complications: high-risk surgery, ischemic heart disease, CHF, cerebrovascular disease, insulin-dependent diabetes mellitus, and renal failure (creatinine >2.0 mg/dL).\(^24\) High-risk surgery in VS specifically includes open aortic surgery and open infrainguinal revascularization procedures. The 30-day incidence of cardiac complications in these procedures is reported to be as high as 6.2%.\(^26\)\(^-\)\(^27\)

Although open aortic surgery and open infrainguinal revascularization are considered the high-risk VS procedures in the literature, judgment is essential when determining risk of other VS procedures. VS procedures should be thought of as a continuum, with procedures done under local anesthesia and low physiologic insult, such as toe amputations and arteriovenous fistulas, being low-risk, followed by intermediate-risk procedures, such as carotid endarterectomy (CEA) and endovascular procedures, and then to the high-risk procedures that require general anesthesia and major dissections with possible significant estimated blood loss.

The risk of a major cardiac complication is estimated according to the presence of 0, 1, 2, or ≥3 Lee index risk factors, with the estimated risk of 0.4%, 0.9%, 7%, 11%, respectively.\(^24\) VS patients can be stratified into low-risk (0 risk factors), intermediate-risk (1 to 2 risk factors), and high-risk (≥3 risk factors) categories.\(^28\)\(^29\)

The Lee index does not account for age. A recent study demonstrated that the prognostic value of the Lee index is reduced in patients aged >75 years; therefore, adding age improves the accuracy. The same study also found that a history of hypertension enhances the accuracy of predicting cardiac risk.\(^30\) This is recognized in the adapted Lee index and has been shown to be predictive of cardiovascular death in elderly patients.\(^23\) Although the adapted Lee index is
more predictive, recent studies analyzing preoperative screening and perioperative CAD management, as well as the current ACC/AHA guidelines, use the original Lee index, and our recommendations will be based on this index.

OVERVIEW OF ACC/AHA 2007 GUIDELINES UPDATE

The updated 2007 ACC/AHA guidelines for the preoperative identification and perioperative management of patients undergoing VS include recommendations for the use of preoperative noninvasive stress testing, coronary revascularization, adrenergic β-blockade, and the duration of dual antiplatelet therapy after implantation of coronary stents. The management guidelines are classified into three categories of strength according to the current level of evidence (Table II).

It is important for the physician reviewing and applying these guidelines to realize that not all of the guidelines carry equal weight and their strength depends on the evidence they are based on. This makes the ACC/AHA guidelines confusing, and it is important to understand the differences so appropriate judgment can be used when applying them. Class I and III guidelines are clear: class I guidelines are based on valid evidence clearly demonstrating the benefit of the treatment, and class III guidelines are based on evidence that the intervention is ineffective and in some cases may be harmful. Ambiguity occurs in class II, where there is conflicting evidence or divergence of opinion, or both, amongst experts. This class is subdivided into two categories. In class IIa the weight of evidence is in favor of the effectiveness of a treatment and its use is suggested; and in class IIb the effectiveness of a treatment is less well established and there maybe a role for it, but its use is not generally recommended.

The 1996 ACC/AHA guidelines recommended that all patients scheduled for VS who were at an increased cardiac risk according to the clinically derived risk stratification (see below) undergo noninvasive cardiac stress testing to detect CAD. A patient with a positive stress test was recommended to undergo coronary angiography and be considered for a coronary revascularization procedure.

The 1996 guidelines reflected earlier evidence that screening coronary angiography demonstrated 30% of VS patients (including aortic aneurysm repair, lower extremity revascularizations, and extracranial arterial surgery) had severe CAD that warranted myocardial revascularization before the intended VS procedure. Furthermore, half of the patients undergoing VS who were screened with preoperative coronary angiography had positive history of cardiac disease or abnormal ECG results did indeed have severe CAD.

Further older data examining the role of noninvasive stress testing suggested that noninvasive stress testing was superior to clinical assessment and a safer screening modality than coronary angiography to determine cardiac risk during VS. However, more recent data have questioned the need for an aggressive screening and myocardial revascularization protocol in asymptomatic or stable CAD patients undergoing VS, and in 2007 the guidelines were updated accordingly (Fig 1).

Noninvasive stress testing. Recent studies have questioned the role and value of noninvasive stress testing for detection of CAD before VS. A reversible defect on a noninvasive cardiac stress test was considered a predictor of a postoperative adverse cardiac event, and coronary angiography with possible revascularization was recommended in 1996. However, a prospective study assessed reversible defects found during cardiac stress testing and showed they were of no value as a predictor of adverse events in low-risk and intermediate-risk VS patients. Other studies found cardiac event rates that were 0% and 0.9% for VS patients in the low-risk and intermediate-risk categories who were receiving perioperative β-blockers. These authors concluded that β-blockers were sufficient to decrease cardiac risk and preoperative stress testing was not needed in patients of low or intermediate risk.

Table II. American College of Cardiology/American Heart Association guidelines classification scheme, which is based on the level of evidence on the treatment

<table>
<thead>
<tr>
<th>Class</th>
<th>Level of evidence</th>
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<tr>
<td>Class I</td>
<td>Valid evidence demonstrates benefit of the treatment</td>
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<tr>
<td>Class II</td>
<td>Conflicting evidence or divergence of opinion</td>
</tr>
<tr>
<td>IIa</td>
<td>Evidence favors treatment</td>
</tr>
<tr>
<td>IIb</td>
<td>Effectiveness of treatment is less well-established</td>
</tr>
<tr>
<td>Class III</td>
<td>Evidence demonstrates treatment is ineffective and maybe harmful</td>
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Their Dutch Echocardiographic Cardiac Risk Evaluation (DECREASE-II) study prospectively reviewed the value of noninvasive stress testing in intermediate-risk patients who were receiving β-blocker therapy with strict heart rate control (60 to 65 beats/min). There was no statistically significant difference in the 30-day incidence of MI or cardiac death between those who underwent stress testing and those who were not. This study concluded there was no benefit to noninvasive cardiac stress testing in intermediate-risk patients provided they were receiving β-blocker therapy with a therapeutic heart rate of 60 to 65 beats/min. This study also found that noninvasive stress testing delayed VS for 3 weeks, with possible added risk to patients from aneurysm rupture or progression of ischemic disease during the period of delay.

As a result of these newer data, the ACC/AHA provided updated guidelines in 2007 for noninvasive cardiac stress testing in patients undergoing VS. The most recent guidelines is a class I recommendation that only patients with active cardiac conditions, such as unstable coronary syndromes, decompensated heart failure, significant arrhythmias, or severe valvular disease, undergo cardiac stress testing. The evidence also favors preoperative testing (class IIa recommendation) in patients defined as high-risk by the Lee index. Newer evidence confirms that preoperative testing delayed VS for 3 weeks, with possible added risk to patients from aneurysm rupture or progression of ischemic disease during the period of delay.

As a result of these newer data, the ACC/AHA provided updated guidelines in 2007 for noninvasive cardiac stress testing in patients undergoing VS. The most recent guidelines is a class I recommendation that only patients with active cardiac conditions, such as unstable coronary syndromes, decompensated heart failure, significant arrhythmias, or severe valvular disease, undergo cardiac stress testing. The evidence also favors preoperative testing (class IIa recommendation) in patients defined as high-risk by the Lee index. Newer evidence confirms that preoperative testing delayed VS for 3 weeks, with possible added risk to patients from aneurysm rupture or progression of ischemic disease during the period of delay.

The three noninvasive methods of cardiac testing to detect myocardial ischemia are treadmill test, dobutamine stress echocardiography, and myocardial perfusion scintigraphy:

- The treadmill stress test is a functional test that detects ischemia by ST segment changes on the ECG during exercise. This test is often not feasible in VS patients because of their limited exercise capacity, presence of claudication, arthritis, or chronic obstructive pulmonary disease.
- Dobutamine stress echocardiography uses increasing dobutamine dosage to induce myocardial ischemia in regions supplied by diseased arteries. The ischemic changes cause wall motion abnormalities that can be assessed by echocardiography.
- Myocardial perfusion scintigraphy involves the intravenous administration of a nuclear tracer, and images are obtained at rest and after stress with a vasodilator, such as dipyridamole (Persantine, Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, Conn). CAD induces differences in blood flow to a region of the myocardium, with stress causing perfusion defects.

Studies have not directly compared dobutamine echocardiography with myocardial scintigraphy. Although there is evidence that slightly favors dobutamine echocardiography, it is recommended that the test of choice depends on the experience of the institution.

In summary, clinical risk factors alone may identify intermediate- or low-risk patients and they should be simply optimized with medical therapy (see below) without the need for noninvasive cardiac stress testing. High-risk patients, as defined by the Lee index, should be considered for stress testing with the intention to identify patients at increased risk for myocardial ischemia induced by the stress response of VS. This information can be used to intensify medical therapy and possibly modify the operative approach to avoid high-risk surgery in favor of lesser procedures. In asymptomatic patients this is no longer an indication for coronary revascularization.

Role of coronary revascularization. The most recent and substantial change in the way VS patients should be treated relates to the role of revascularization before the intended procedure. The Coronary Artery Revascularization Prophylaxis (CARP) study randomized 510 patients to revascularization vs medical therapy without revascularization before VS. There was no statistically significant difference in the 30-day incidence of MI, death, or length of stay. The change in mortality at 6 years was 22% for revascularization and 23% for medical therapy, which was not significant. This study was limited to patients that had only one- or two-vessel disease with preserved left ventricular function. However, patients with three-vessel disease were examined in a recent study with similar results.

As a result of these studies, the ACC/AHA revised the guidelines and no longer recommends revascularization before surgery in patients with stable CAD. Indications for coronary revascularization are the same as they would be in the general population not undergoing VS, which include unstable angina, MI ≤30 days, left ventricular systolic dysfunction, positive screening stress test, and in preparation for valve replacement surgery.

It is important to emphasize that the most recent reports do not recommend coronary angiography or revascularization in patients without symptoms of CAD even if there is a positive stress test before VS. Two other points should also be emphasized. First, our current review does not address the management of patients with a positive screening stress test in the general population. Second, all circumstances are not fully covered by the current literature, and judgment by the vascular surgeon and the cardiologist must be applied in some cases depending on the indications for the VS procedure and the severity of the CAD.

Elements of Optimal Perioperative Medical Therapy

Status of β-adrenergic blockers. Increasing evidence and a new understanding of the pathophysiology of the perioperative MI suggest that a systemic approach with optimal medical therapy is more appropriate than coronary revascularization in preventing an MI in asymptomatic patients. Optimal medical therapy specifically includes controlling hypertension, smoking cessation, strict glycemic control, β-blocker therapy, antiplatelet agents, and perhaps most important, the administration of statin drugs (see below).
compared with placebo, the metoprolol group also had a
to their systolic blood pressure (SBP) went
30 days. Patients were maintained on this regimen unless
the procedure and continued at a dose of 200 mg daily for
2 to 4 hours before
of oral extended-release metoprolol 2 to 4 hours before
and hypotension requiring treatment was more frequent in
the metoprolol group. This study concluded that routine
therapy in VS patients. In the MaVS (Metoprolol after
Surgery) study, 496 patients were randomized to
receive placebo vs metoprolol on the day of surgery and
continued for the hospital stay. The results demonstrated
that although perioperative
surgery and coronary revascularization
in deaths; however, the most common cause of death in the
metoprolol group was sepsis. The authors concluded that
the increase risk of nonfatal stroke was due to
the hypotension and bradycardia in the metoprolol
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sion and bradycardia could have accounted for the increase
in deaths; however, the most common cause of death in the
metoprolol group was sepsis. The authors concluded that
the β-blockers may have been a contributing factor to this
by preventing tachycardia causing a delay in the recognition
of infection and the initiation of antibiotics and preventing
the normal hemodynamic response required to sustain
organ perfusion and deliver the antibiotics to tissue.41
The POISE study raises questions about the safety,
appropriate dosage, timing of the medication, and the type
of β-blocker used. The safety is likely related to the dosage,
because these patients were maintained on metoprolol at
200 mg/d, with dose adjustment only being made at a SBP
≤100 mm Hg or heart rate ≤50 beats/min. The threshold of
100 mm Hg for SBP is likely too low in VS patients.
Furthermore, the initiation time and the half-life of the
β-blocker are important.

Table III. Summary of pivotal studies assessing the role of β-blocker therapy vs placebo in treating patients with risk factors for coronary artery disease in the perioperative and postoperative period undergoing noncardiac surgery

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>β-Blocker</th>
<th>Dose</th>
<th>Conclusion</th>
</tr>
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<tbody>
<tr>
<td>Mangan (1996)⁶</td>
<td>Atenolol</td>
<td>100 mg/d PO or 10 mg/d IV. Initial dose at induction of anesthesia, then immediately post-VS, and continued for 7 days</td>
<td>↓ Mortality and cardiac complications</td>
</tr>
<tr>
<td>DECREASE I (1999)⁵⁸</td>
<td>Bisoprolol</td>
<td>5 mg/d initiated 7 days pre-op, ↑ to 10 mg/d after 1 week if pulse &gt;60 bpm; continued for 30 days post-op</td>
<td>↓ Perioperative cardiac death and nonfatal MI in high-risk VS patients</td>
</tr>
<tr>
<td>POBBLE (2005)⁵⁹</td>
<td>Metoprolol</td>
<td>50 mg twice daily for 7 days</td>
<td>No difference in 30-day cardiovascular events in patients undergoing infrarenal VS</td>
</tr>
<tr>
<td>MaVS (2006)⁴⁰</td>
<td>Metoprolol</td>
<td>Weight-based: Initial dose at anesthesia induction then immediately post-op and continued for 7 days. Stopped at hospital discharge</td>
<td>No difference in 30-day or 6-month cardiac event rates; prophylaxis use of β-blockers in all VS patients is not indicated</td>
</tr>
<tr>
<td>POISE (2008)⁴¹</td>
<td>CR metoprolol</td>
<td>100 mg pre-op; 1 dose post-op. At 2nd post-op dose, ↑ 200 mg/d for 30 days</td>
<td>↓ MI, AF, coronary revascularization ≤30 days; ↑ stroke, death, hypotension, bradycardia</td>
</tr>
</tbody>
</table>

AF, Atrial fibrillation; CR, continuous release; DECREASE, Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; IV, intravenous; PO, by mouth; POBBLE, Perioperative β-Blockade; MaVS, Metoprolol After Vascular Surgery; POISE, PeriOperative Ischemic Evaluation; VS, vascular surgery.

Early prospective, randomized trials (1999) demonstrated the beneficial effects of perioperative β-blockers in patients undergoing major VS (Table III). Patients who took bisoprolol at least 1 week before VS and continued for 30 days demonstrated a significantly lower rate of death from cardiac causes and nonfatal MI compared with placebo, 3.4% and 34%, respectively.⁵⁸ On this basis, prior to 2007, the ACC/AHA guidelines recommended the routine use of β-blockers in patients undergoing VS.⁴²

However, recent evidence from prospective randomized trials has questioned the need for routine β-blocker therapy in VS patients. In the MaVS (Metoprolol after Vascular Surgery) study, 496 patients were randomized to receive placebo vs metoprolol on the day of surgery and continued for the hospital stay. The results demonstrated no significant difference in the incidence of cardiac complications at 30 days and 6 months. Intraoperative bradycardia and hypotension requiring treatment was more frequent in the metoprolol group. This study concluded that routine use of prophylactic β-blockers in all VS patients is not indicated.⁴⁰

In addition, the Perioperative Ischemic Evaluation (POISE) trial called into question the safety and efficacy of perioperative β-blockade.⁴¹ POISE was a prospective, randomized, controlled trial that assigned 8351 patients undergoing noncardiac surgery to receive a placebo or 100 mg of oral extended-release metoprolol 2 to 4 hours before the procedure and continued at a dose of 200 mg daily for 30 days. Patients were maintained on this regimen unless their systolic blood pressure (SBP) went <100 mm Hg or the heart rate went to <50 beats/minute.

The results demonstrated that although perioperative metoprolol reduced the risk of MI, coronary revascularization, and atrial fibrillation ≤30 days of the procedure compared with placebo, the metoprolol group also had a significant increase in death, stroke, and clinically significant hypotension and bradycardia. The POISE trial investigators believe the increase risk of nonfatal stroke was due to the hypotension and bradycardia in the metoprolol group. Also in this group, the clinically significant hypotension and bradycardia could have accounted for the increase in deaths; however, the most common cause of death in the metoprolol group was sepsis. The authors concluded that the β-blockers may have been a contributing factor to this by preventing tachycardia causing a delay in the recognition of infection and the initiation of antibiotics and preventing the normal hemodynamic response required to sustain organ perfusion and deliver the antibiotics to tissue.⁴¹

The POISE study raises questions about the safety, appropriate dosage, timing of the medication, and the type of β-blocker used. The safety is likely related to the dosage, because these patients were maintained on metoprolol at 200 mg/d, with dose adjustment only being made at a SBP ≤100 mm Hg or heart rate ≤50 beats/min. The threshold of 100 mm Hg for SBP is likely too low in VS patients. Furthermore, the initiation time and the half-life of the β-blocker are important.

The DECREASE I trial initiated the longer-acting, β-1 selective, bisoprolol, at an average of 37 days before the procedure, and the results demonstrated a 10-fold reduction in the incidence of perioperative cardiac death and MI vs placebo.⁴³ This may be explained by the pharmacology of β-blockers. The immediate action includes the reduction in ionotropic and chronotropic effects with the ensuing decrease in oxygen demand. However, the chronic effects seen with long-term β-blocker therapy may be related to the anti-inflammatory effects that are due to the β-1 blockade and the duration of treatment. Long term β-1 blockade decreases inflammatory cytokines and reduces atheroma
volume, as demonstrated on intravascular ultrasound imaging of the coronary arteries.\textsuperscript{7,8,11}

The current ACC/AHA guidelines for β-blocker therapy are: A class I recommendation is to continue the β-blocker if the patient is already taking the medication and initiate a β-blocker if a stress test is positive. The evidence also favors initiating them in high-risk patients, and this is currently class IIa recommendation. The evidence does not support β-blockers in intermediate- or low-risk patients (class IIb recommendation).

The ACC/AHA does not give recommendations on the start time or the type of β-blocker therapy. However, recent data indicate that initiation of treatment should begin at the first patient encounter in high-risk patients and selected intermediate-risk patients. The use of β-1 selective agents with a longer half-life may be the most appropriate drug. Currently, it is reasonable that one 2.5- to 5-mg bisoprolol dose should be give. A fixed dose is likely appropriate to achieve the long-term effects in intermediate-risk patients (discussed previously), whereas upward dosage titration to achieve a desired heart rate is likely indicated in patients at high-risk for myocardial ischemia. Bisoprolol should be started 30 days before VS and a higher SBP threshold of 120 mm Hg is appropriate to lower the dose or stop upward titration when trying to achieve a therapeutic heart rate of <70 beats/min.

**Status of statin therapy.** Evidence is increasing that optimal medical therapy should include the routine use of statins in the prevention of perioperative MI. Statins are 3-hydroxy-3-methylglutaryl coenzyme-reductase inhibitors that decrease lipid levels, stabilize atherosclerotic plaques, and decrease vascular inflammation. The effects of 3 months of statins on the composition of carotid plaques in humans after CEAs were examined. Statins decreased matrix metalloproteases, lipid oxidation, inflammation, and other factors that destabilize atherosclerotic plaques and increased the levels of collagen and inhibitors of matrix metalloproteases that lead to plaque stabilization.\textsuperscript{5,15} Statins have been shown to increase endothelial nitric oxide synthase (eNOS) messenger RNA in endothelial cells, augment eNOS function, and attenuate endothelial cell apoptosis, which is an important event in atherogenesis.\textsuperscript{44}

The important anti-inflammatory effects of statins were demonstrated in the Pravastatin Inflammation/CRP Evaluation (PRINCE) study. This was a prospective, randomized, double-blinded trial of 1702 patients to determine if pravastatin reduced the important inflammatory mediator C-reactive protein (CRP), which is known to enhance atherogenesis. In patients who were randomized to receive pravastatin or placebo, CRP levels at 24 weeks decreased 16.9% in the pravastatin arm vs no decrease in the placebo arm.\textsuperscript{45} Furthermore, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS-TexCAPS) demonstrated that elevated baseline CRP levels increased the risk of coronary events and that lovastatin decreased CRP levels by 14.8% at 12 months, an effect independent of the lipid profile effects.\textsuperscript{46}

Atorvastatin was also shown to decrease the inflammatory response associated with ACS and halt the progression of coronary plaque growth.\textsuperscript{5,47,48} Recently, leptin has been discovered to increase plasma CRP levels and enhance the mechanisms that lead to atherogenesis, and statins also decrease plasma leptin levels.\textsuperscript{49}

Clinical trials have also demonstrated the significance of the effects of statins on clinical outcomes in patients with CAD. Specifically, the randomized Scandinavian Simvastatin Survival Study (4S) demonstrated that statins improve prognosis in patients with CAD compared with placebo.\textsuperscript{50} A subgroup analysis demonstrated that statins were also associated with improvement in vascular disease other than in the coronary bed, including a reduction in the incidence of carotid bruits, cerebrovascular events, and claudication.\textsuperscript{51}

The protective effects of statins have also been examined specifically in patients with CAD undergoing VS. A retrospective study demonstrated a fourfold reduction in death in this patient population.\textsuperscript{52} A randomized, double-blinded trial compared atorvastatin with placebo to assess the reduction of cardiovascular events ≤6 months after VS. Patients were randomized to receive 20 mg of atorvastatin or placebo an average of 30 days before the proposed vascular operation. Patients were treated for 45 days with atorvastatin or placebo irrespective of their serum lipid profiles. For 6 months, patients were monitored for cardiovascular death, nonfatal MI, unstable angina, and stroke. The risk of a cardiac event was three times higher in the placebo group. The authors of this study concluded that short-term treatment with atorvastatin significantly reduces the incidence of cardiovascular events after VS.\textsuperscript{5,46}

The retrospective Statins for Risk Reduction in Surgery (StaRRS) study also demonstrated the cardioprotective effects of statins in patients undergoing VS.\textsuperscript{54} Multiple studies demonstrate the protective effects of statins in preventing MI, stroke, and death in VS patients (Table IV). Because there is no intravenous formulation for statins, statins are often withheld in the perioperative period. Sudden withdrawal of statin therapy in the surgical population can increase the risk of cardiovascular complications.\textsuperscript{55} A retrospective study concluded that abrupt statin withdrawal before VS was associated with an increase risk of troponin release, MI, and cardiovascular death.\textsuperscript{56} Furthermore, the use of statins with extended-release formulations, such as fluvastatin, appeared to have more beneficial effects compared with other statins when discontinued.\textsuperscript{57}

Therefore, the recommendation is that VS patients should be treated with statins as early as possible before their procedure, preferably 30 days before. In addition, they should be maintained on statins throughout the perioperative period and should resume taking them in the postoperative period once oral intake is resumed. To accomplish these aims, patients undergoing VS should be treated with extended-release fluvastatin at a dose of 80 mg/d. The extended-release formulation is particularly beneficial for patients who can be given nothing by mouth in the postoperative period.
Status of antiplatelet therapy. Antiplatelet therapy has been shown to reduce the risk of cardiovascular events in patients with CAD. Low-dose aspirin (81 mg) therapy is just as effective as high-dose aspirin (325 mg) therapy in decreasing the combined end point of vascular death, MI, and stroke.56,87 However, new antiplatelet agents used alone or as dual antiplatelet therapy have shown improved benefit vs aspirin alone.58 Clopidogrel has demonstrated superior efficacy to aspirin with a lower risk of bleeding in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial.58 The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial demonstrated that treatment with aspirin and clopidogrel resulted in a statistically significant reduction in ischemic events in patients with symptomatic atherosclerosis.58 These results must be interpreted carefully, however, because this trial demonstrated that for every adverse vascular event avoided by dual antiplatelet therapy with clopidogrel, one adverse bleeding event occurred.

Judgment is essential in determining which patients should receive dual antiplatelet therapy, and the extent of the surgical dissection should be taken into account. Some procedures, such as an open aneurysm repair, carry a significant bleeding risk and antiplatelet therapy must be stopped. Maintenance of single or dual antiplatelet therapy is advisable during some VS procedures, however, including patients being prepared to undergo carotid artery stenting, who should be started on aspirin and clopidogrel 1 week before the intervention with continuation during the perioperative period.59 In addition, the American College of Chest Physicians recommend single antiplatelet therapy with aspirin be started before and continued after CEA, and recent reports suggest a 10-fold lower risk of cerebral emboli is achieved intraoperatively during CEA when aspirin and clopidogrel are started preoperatively.59,60

Lower extremity revascularization procedures can also be performed safely on antiplatelet therapy, and we recommend that it be considered for use in the perioperative period. The American College of Chest Physicians also recommends that low-dose aspirin be started preoperatively before infragenial bypasses.61 Endovascular lower extremity revascularization procedures induce a prothrombotic state and platelets tend to aggregate at the site of the damaged arterial plaque and can cause thrombotic occlusion.61 Aspirin is therefore recommended before and after peripheral angioplasty procedures.

Cardiac risk stratification is a fundamental consideration in VS. Furthermore, the vascular surgeon may be the first to identify such patients and has the obligation to begin
Suggested Algorithm For The Preoperative Identification and The Perioperative Management of Patients With Coronary Artery Disease Undergoing Vascular Surgery

<table>
<thead>
<tr>
<th>Presence of Active Cardiac Conditions</th>
<th>Stress Test +/- Revascularization</th>
<th>Risk Stratify with Lee Index</th>
<th>Proceed to Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>2.5 to 5 mg/d (Low Fixed Dose)</td>
<td>Low</td>
<td>Proceed to Surgery</td>
</tr>
<tr>
<td>No</td>
<td>Bisoprolol 5 mg/d (titrate)</td>
<td>Intermediate</td>
<td>Proceed to Surgery</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg/d</td>
<td>High</td>
<td>Proceed to Surgery</td>
</tr>
<tr>
<td></td>
<td>Consider Stress Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consider Bisoprolol</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wait 30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Risk/Benefit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig 2. Algorithm for the perioperative identification and perioperative management of patients with coronary artery disease (CAD) undergoing vascular surgery. Of note, medical management should be optimized in high-risk patients identified by the Lee index. The role of stress testing in these patients is currently unclear. The judgment by the vascular surgeon and the cardiologist must be applied and the indication for stress testing depends on the need for the vascular procedure and the severity of the CAD. We recommend a 30-day period to achieve the greatest benefit from medical management in high-risk patients with a positive stress test.

appropriate medical treatment according to the following algorithm (Fig 2):

First, apply the Lee index and risk-stratify the patient. Patients with active cardiac conditions should undergo noninvasive stress testing. For high-risk patients, a stress test should presently be considered to identify those patients at risk for myocardial ischemia, provided the patient has a high-risk patient with a positive stress test should then consider delaying the VS until the medical therapy dosage is optimized and also allowing enough time (30 days) to attain the maximum pleiotropic effects, such as plaque stability. The vascular surgeon can proceed with the indicated vascular operation without a noninvasive stress test in low-risk and moderate-risk patients after medical therapy is optimized. A high-risk patient with a positive stress test warrants a risk/benefit analysis, and the vascular surgeon may need to consider a less-invasive surgical intervention, such as an endovascular option, even though the expected result may be inferior to more invasive VS. All circumstances are not fully covered by the current literature and judgment by the vascular surgeon and the cardiologist must be applied in some cases depending on the indications for the vascular surgical procedure and the severity of the CAD.

Second, high-risk VS patients should be prescribed β-blocker therapy at the initial patient encounter. We suggest bisoprolol, 2.5 to 5 mg/d. The β-blocker should be titrated to a heart rate <70 beats/min, and the SBP threshold for stopping titration or lowering the dose should be a SBP ≥120 mm Hg. Patients with a known positive stress test should be prescribed β-blockers if they are not already taking them. If any patient is currently taking a β-blocker, continue the medication. For intermediate-risk patients, β-blockers should be continued or started depending on the risk factors; for example, a patient with a prior MI undergoing VS should be taking a β-blocker. Judgment should be exercised in the use and dosage of β-blocker therapy in intermediate-risk patients. In these patients, a fixed dose with minimal or no heart rate titration should be used in light of the studies demonstrating the deleterious effects of high-dose β-blocker therapy. The goal here is to achieve the pleiotropic effects of β-blocker therapy. Low risk patients do not require β-blocker therapy.

Third, statin therapy should be initiated as soon as VS is considered in patients with known or suspected atherosclerosis. We recommend the long-acting formulation of fluvastatin at 80 mg/d with continuation through the perioperative period. Beyond the perioperative period, other statins may be substituted at appropriate dosage levels as determined by the patient’s tolerance and lipid levels.

Fourth, the status of antiplatelet agents in VS patients should be directed toward minimizing the risk of coronary stent thrombosis. This is achieved by continuing these agents through the perioperative period, but if too risky, then delaying the procedure if possible.

AUTHOR CONTRIBUTIONS

Conception and design: SB, FV
Analysis and interpretation: SB, NC, FV
Data collection: SB
Writing the article: SB, NC, FV
Critical revision of the article: SB, FV
Final approval of the article: SB, NC, FV
Statistical analysis: SB
Obtained funding: FV, NC
Overall responsibility: SB

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