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Cardiovascular medicine update 2007: Perioperative risk, carotid angioplasty, drug-eluting stents, stronger statins

■ ABSTRACT

Some recent clinical trials have concluded the following:

- Patients who need noncardiac surgery and who are at risk of major cardiac events should not undergo revascularization with the aim of achieving a better perioperative outcome. They should have an office evaluation only and be prescribed a beta-blocker, if indicated.
- Except for unusual, high-risk cases, patients at risk of stroke due to atherosclerotic carotid artery stenosis should undergo carotid endarterectomy rather than carotid stenting. Because the technology is still developing, however, carotid stenting may still be appropriate as part of a clinical trial.
- Although drug-eluting coronary stents reduce the risk of restenosis in the short term, they pose a small but significant risk of in-stent thrombosis. Clopidogrel (Plavix) should be prescribed for at least a year following drug-eluting stent placement, and perhaps indefinitely.
- Patients with known coronary heart disease have better outcomes if they receive aggressive statin therapy (eg, atorvastatin [Lipitor] 80 mg/day) to lower their serum levels of low-density lipoprotein cholesterol to less than 70 mg/dL.

SEVERAL STUDIES in recent years have made us rethink several questions that often arise in clinical practice:

- Should patients with coronary artery disease who need noncardiac surgery undergo angioplasty first to lessen their perioperative risk?
- Is percutaneous carotid angioplasty an acceptable alternative to carotid endarterectomy for patients with symptomatic carotid artery disease?
- Are drug-eluting stents safe in the long term?
- What is the best regimen and goal for managing lipid levels in patients with coronary artery disease?

■ MANAGING PERIOPERATIVE CARDIAC RISK

A 70-year-old man is seen for medical preoperative evaluation before a planned hip replacement. He has hypertension, type 2 diabetes mellitus, and a history of an anterior myocardial infarction. He takes aspirin, a statin, hydrochlorothiazide, ramipril (Altace), and insulin. Single-photon emission computed tomography (SPECT) with adenosine stress shows an anterior scar, peri-infarct ischemia, inferior ischemia, and an ejection fraction of 55%.

Should he be referred for coronary angiography before his hip replacement?

Risk of perioperative infarcts is high

Elderly patients are at especially high risk of cardiac events during or after noncardiac surgery. The elevated risk is primarily due to increased sympathetic tone during the first

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few days after surgery, making plaque rupture more likely from moderate shear stress on coronary artery walls. In addition, a hypercoagulable state develops, enhancing thrombus formation. The risk of death from a perioperative event is very high: some studies have found the mortality rate from a perioperative infarct to be as high as 50%.¹

Estimating perioperative risk

The Goldman index, developed in 1977, is often used to evaluate perioperative cardiac risk before surgery.² The index is a score derived from nine risk factors, eg, the patient's age, health status, type of procedure, electrocardiographic characteristics, and other clinical factors.

In 1999, Lee et al³ analyzed data from a large cohort of patients and developed a simplified index based on just six risk factors that can readily be determined:

- High-risk surgical procedure (ie, major intraabdominal, vascular, thoracic, and orthopedic procedures)
- History of ischemic heart disease
- History of congestive heart failure
- History of cerebrovascular disease
- Insulin therapy for diabetes
- Renal dysfunction (preoperative serum creatinine concentration > 2.0 mg/dL).

The more risk factors a patient has, the greater the risk. Lee et al reported that, in the cohort from which they derived their index, the risk of major cardiac complications was 0.5% with 0 risk factors, 1.3% with 1 risk factor, 4% with 2 risk factors, and 9% with 3 or more risk factors. In a separate cohort in which they validated their index, the numbers were 0.4%, 0.9%, 7%, and 11%, respectively.

The patient in our case study has three risk factors: orthopedic surgery, myocardial infarction, and insulin therapy. Lee et al also analyzed their data according to the specific type of high-risk surgery: a patient with three risk factors, one of which is orthopedic surgery, is estimated to have a risk of a major cardiac perioperative complication of about 3%. If he were instead undergoing a major vascular procedure, his risk would jump to 8%.³

Until now, patients deemed to be at high risk based on either the Goldman index or the Lee index have generally been referred for a

noninvasive test, such as single-photon emission computed tomography (SPECT) with pharmacologic stress, to determine whether severe coronary disease is present. If testing indicates severe disease, patients have been referred for coronary angiography and revascularization in hopes of lowering the perioperative risk.

Preoperative revascularization does not change perioperative risk

The Coronary Artery Revascularization Prophylaxis (CARP) trial⁴ randomized 510 patients about to undergo vascular surgery who were deemed to be at high risk of a perioperative event to either undergo revascularization or receive medical management.

The groups were similar in their baseline characteristics. The mean age was in the mid-60s, about 40% of patients had a history of myocardial infarction, and about 40% had diabetes mellitus. In addition, about 85% of patients in both groups were taking beta-blockers, which may help prevent perioperative events.

At a median follow-up of 2.7 years, the death rates were the same in both groups: 22% in the revascularization group and 23% in the no-revascularization group. Even subsets of patients who were deemed to be at especially high risk by imaging results or by the Lee index had no differences in outcome between the two groups. The authors concluded that coronary artery revascularization before elective vascular surgery offers no benefit and should not be recommended.

'Clearing' patients for surgery: Recommendations

Patients who are about to undergo surgery should have a simple office evaluation to estimate their risk. The Lee index can be used for this purpose.

Patients deemed at high risk (ie, those with any of the six risk factors from the Lee index) should be considered for beta-blocker therapy.⁵ No noninvasive tests (eg, SPECT) are necessary because revascularization is no longer indicated to minimize perioperative risk, based on the recent findings.^{6,7} The only reason for which noninvasive tests may be justified is to determine if a patient is at high risk

Risk of major perioperative complications with no risk factors: 0.5%
1 factor: 1.3%
2 factors: 4%
≥ 3 factors: 9%

of premature death because of cardiac disease, and if so, the upcoming surgery would be canceled or modified because of that knowledge.

When I am asked to “clear” a patient for surgery (a term that internists and cardiologists dislike), I have two primary concerns: whether the patient is taking a beta-blocker and whether he or she has a cardiac problem that has not been properly addressed. However, I do not order tests specifically because a patient is scheduled to undergo surgery. Revascularization should be recommended only if it would be indicated regardless of any upcoming noncardiac surgery.

■ CAROTID STENTS VS CAROTID SURGERY

A 75-year-old woman had a recent cerebral transient ischemic attack. She has hypertension and diabetes but no known history of coronary artery disease. Her medications are aspirin, hydrochlorothiazide and amlodipine (Norvasc) for hypertension, glyburide (Diabeta, Micronase) for diabetes, and a statin. She is now neurologically intact and completely functional (Modified Rankin Scale = 0, indicating no symptoms).

Carotid angiography reveals that her carotid artery on the same side as her former symptoms is narrowed by about 95%, ie, she has severe symptomatic but not occlusive carotid disease. The lesion is amenable to a surgical approach, and she has no features that would prohibit carotid endarterectomy, such as severe chronic obstructive pulmonary disease or prior neck irradiation. On the other hand, she says that she would prefer a nonsurgical treatment option.

Should carotid stenting or carotid endarterectomy be recommended?

Stenting is not equivalent to endarterectomy

Two recent trials were designed to find out whether carotid stenting—a less-invasive and nonsurgical procedure—is as safe and effective as carotid endarterectomy.

EVA-3S. The Endarterectomy Versus Angioplasty in Patients With Severe Symptomatic Carotid Stenosis (EVA-3S) trial⁸ randomized 520 patients to undergo either carotid stenting or endarterectomy.

The procedures were performed at multiple centers by experienced surgeons with low complication rates.

All the patients had had a recent cerebral or retinal transient ischemic attack, had carotid stenosis of 60% to 99%, and had a Rankin score of less than 3 (indicating no more than mild neurologic disability). The groups were similar in age (a mean of about 70 years) and in numbers of patients with a history of stroke (about half) and cerebral and ocular transient ischemic attacks. Few patients had a history of myocardial infarction (13% in the endarterectomy group and 11% in the stenting group).

No single type of stent was used throughout the trial: more than half of the patients in the stenting group received a Carotid Wallstent Monorail (Boston Scientific Corp.), and 29% received an Acculink (Abbott Vascular).

Because atherosclerotic debris can be dislodged during stenting, the procedure poses a risk of causing cerebral embolism. As the trial progressed, new recommendations were issued about using a protective capture device. Before the recommendations were issued, 78% of the patients in the angioplasty group received one of these devices, vs 98% after the recommendations. Overall, more than 90% of patients in the stenting group received one.

The trial was stopped early by the Data Safety and Monitoring Board for reasons of both safety and futility. The primary end point—death or stroke in 30 days—occurred in 3.9% of patients receiving endarterectomy vs 9.6% of patients receiving a stent (relative risk 2.5). Few patients died; the major difference between the two groups was stroke incidence (2.7% of patients receiving endarterectomy vs 8.8% of those receiving a stent, $P = .004$).

SPACE. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) study⁹ was similar but larger, involving 1,200 patients who were randomized to receive either carotid stenting or endarterectomy.

Patients all had symptomatic carotid artery stenosis and recent transient ischemic attack or moderate stroke. The median age was 68 years in both treatment groups, about

Carotid stenting should be done only if surgery is not feasible

44% of the patients had a history of stroke, and there was a nearly equal mix of cerebral and ocular transient ischemic attacks. Known coronary artery disease was present in 21% of the patients in the endarterectomy group and 25% of the stenting group.

The results were not as dramatic as in the EVA-3S trial, but again carotid artery stenting was not equivalent to carotid endarterectomy. The risk of death was about the same in the two groups, but the stenting group had a higher rate of stroke (7% vs 5%). The authors concluded that stenting should not be considered an acceptable routine alternative to carotid endarterectomy.

Both trials evaluated only short-term end points. It will be interesting to see the long-term outcomes when they become available.

The earlier **Stenting and Angioplasty With Protection in patients at High Risk for Endarterectomy (SAPPHIRE) trial**,¹⁰ which included 1-year end points, found that stenting was superior to endarterectomy, but the trial had a more complicated composite end point than simply stroke or death, so is not readily comparable.

Furlan,¹¹ in a recent editorial, concluded that the only group of patients who should undergo carotid artery stenting should be those who have cerebral ischemic symptoms, high-grade stenosis (> 70%), and high surgical risk (eg, due to severe chronic obstructive pulmonary disease, prior neck irradiation or dissection, or a lesion that is not amenable to surgical repair) or those enrolled in clinical trials.

■ DRUG-ELUTING CORONARY STENTS

A 70-year-old man is seen 12 months after receiving a coronary artery drug-eluting stent. One year ago, he presented with severe angina and underwent SPECT, which revealed extensive ischemia. Subsequently, angiography revealed a lesion in the proximal left anterior descending artery and an ejection fraction of 50%. A drug-eluting stent was inserted without complications.

He currently takes aspirin, clopidogrel (Plavix), a statin, an angiotensin-converting enzyme inhibitor, and a beta-blocker. He is doing well and feels fine, but he asks, "Do I really need all these medications?"

Should the clopidogrel be discontinued at this time?

Drug-eluting stents:

A breakthrough in preventing restenosis

When angioplasty was first developed in the 1970s, symptoms frequently recurred within 6 months of the procedure, indicating restenosis. Endovascular atherectomy was tried as an alternative procedure but proved unsuccessful. Stents began to be commonly used in the late 1990s, and although they reduced the rate of restenosis, they did not eliminate the problem. Local irradiation also lowered restenosis rates somewhat, but the problem remained.

Stents impregnated with either paclitaxel (the Taxus stent) or sirolimus (the Cypher stent) prevent the process of neointimal proliferation that leads to restenosis and have dramatically reduced its development to the point that restenosis is now uncommon.

However, reports of late stent thrombosis have emerged, in which patients develop a thrombus many months after stent placement at the site of the stent, often leading to a large, fatal infarct.

Dual antiplatelet therapy needed

After stent placement, patients require antiplatelet therapy for some time to prevent thrombosis at the site of the stent, typically aspirin plus clopidogrel.

This therapy was originally recommended for 30 days, but this changed with the Clopidogrel for Reduction of Events During Observation (CREDO) trial,¹² which found that 1 year of dual therapy significantly reduced the risk of adverse ischemic events. Many physicians now prescribe clopidogrel for an extended time, but the optimal duration is still unknown. The CREDO trial was published in 2002, before drug-eluting stents were widely used, so whether the findings are relevant to patients with drug-eluting stents is unclear.

In a recent observational study, Eisenstein et al¹³ also evaluated the role of dual antiplatelet therapy. The researchers divided 4,666 consecutive patients at Duke Heart Center who received stents into four groups

I recommend that patients with drug-eluting stents stay on clopidogrel at least 1 year—and perhaps indefinitely

according to whether they had a bare metal or drug-eluting stent and whether they took clopidogrel for less than or more than 6 months. The patients were similar in all groups in terms of age (median about 61 years) and sex (about 64% men), but had some important differences: patients who received drug-eluting stents were less likely to have had a myocardial infarction and tended to have higher incomes.

Patients who were event-free (no death, myocardial infarction, or revascularization) at 6 or 12 months after the procedure were further followed for the subsequent year or more. Many of the deaths or myocardial infarctions during the follow-up period were assumed to be due to stent thrombosis, although it cannot be proven short of seeing the thrombus by angiography or autopsy.

Among patients with a drug-eluting stent, those taking clopidogrel had significantly lower event rates than those not taking it. Among patients with a bare metal stent, no difference in event rates was evident with or without clopidogrel.

Are drug-eluting stents safe in the long term?

A lot of attention has recently focused on the safety of drug-eluting stents, and important questions remain about the decision by the US Food and Drug Administration (FDA) to approve them. Was it wise to base approval on studies in which the primary end point for determining efficacy was avoiding restenosis rather than avoiding death or myocardial infarction? And should approval have waited for a longer evaluation period and evidence from larger studies?

The FDA maintains that drug-eluting stents are safe and effective in patients who are similar to the patients in the clinical trials that led to the approval of these stents. It acknowledges that the mechanisms, risks, and incidence of thrombosis are not yet known.¹⁴

The FDA also recognizes that the optimal duration of clopidogrel therapy is not yet known.¹⁴ In my own practice, I recommend that patients with drug-eluting stents remain on clopidogrel for at least a year and then indefinitely if no contraindications exist.

■ ARE HIGH-DOSE STATINS BETTER THAN LOW-DOSE STATINS?

A 62-year-old man with diabetes and a history of a myocardial infarction and a coronary artery bypass graft comes in for a checkup. He is now doing well. He is taking simvastatin (Zocor) 20 mg/day and metoprolol (Toprol). His serum low-density lipoprotein cholesterol (LDL-C) concentration is 95 mg/dL, high-density lipoprotein cholesterol 47 mg/dL, and triglycerides 136 mg/dL.

Should this patient be placed on a more aggressive statin regimen?

Statin therapy saves lives

The Scandinavian Simvastatin Survival Study (4S),¹⁵ published in 1994, demonstrated that cholesterol-lowering therapy is beneficial in patients with coronary artery disease. The study randomized 4,444 patients with angina pectoris or previous myocardial infarction and serum total cholesterol levels of 213 to 310 mg/dL to receive either simvastatin 20 mg/day or placebo. Patients treated with simvastatin had a lower rate of death, myocardial infarction, stroke, and revascularization procedures.

Guidelines from the National Cholesterol Education Program's Adult Treatment Panel III (ATP III)¹⁶ state that in patients with established coronary disease, the target serum LDL-C level should be less than 100 mg/dL. Our patient has met this goal.

Now that more powerful statins have become available, the next question is, do they provide an advantage over standard statin therapy? Three similar trials that were run simultaneously were designed to answer this question.

PROVE IT-TIMI 22 (the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 study)¹⁷ randomized more than 4,000 patients who had recently been hospitalized for an acute coronary syndrome to receive either standard therapy—pravastatin (Pravachol) 40 mg/day—or intensive therapy—atorvastatin (Lipitor) 80 mg/day. The primary end point was a composite of death from any cause, myocardial infarction, unstable angina requiring rehospitalization, revascularization, and stroke.

I recommend that patients with coronary disease bring their LDL-C down to < 70 mg/dL, if possible

TNT (the Treating to New Targets study)¹⁸ randomized more than 10,000 patients with clinically evident coronary heart disease and serum LDL-C levels of less than 130 mg/dL to receive either atorvastatin 10 mg/day or atorvastatin 80 mg/day and followed them for a median of nearly 5 years. The primary end point was the occurrence of a first major cardiovascular event, defined as death from coronary heart disease, myocardial infarction, resuscitation after cardiac arrest, or stroke.

IDEAL (the Incremental Decrease in End Points Through Aggressive Lipid Lowering study)¹⁹ randomized 8,888 patients with a history of acute myocardial infarction to receive either standard lipid-lowering therapy (simvastatin 20 mg/day) or aggressive therapy (atorvastatin 80 mg/day). The primary end point was a 5-year composite of death, nonfatal myocardial infarction, or cardiac arrest with resuscitation.

In both treatment groups of the IDEAL trial, patients were an average of 62 years old, 81% were male, 17% had had more than one myocardial infarction at baseline, 80% were taking aspirin, and about three fourths were taking a beta-blocker.

Both groups started with an average serum LDL-C level of 120 mg/dL, which is well above the ATP III target. During treatment, patients randomized to simvastatin had a mean LDL-C level of 104 mg/dL vs 81 mg/dL in the atorvastatin group. A major coronary event (defined as death from coronary disease, nonfatal myocardial infarction, or cardiac arrest with resuscitation) occurred in 10.4% of patients taking simvastatin vs 9.3% of patients taking atorvastatin ($P = .07$). When stroke

was also included in the composite end point, the rate of events was significantly lower in the intensive treatment group ($P = .02$). Differences between the two groups did not emerge until patients were treated for 6 months, which is a trend consistent with other statin trials.

Although the trials were not completely comparable because of different end points, all three of them showed that therapy with atorvastatin 80 mg/day achieved lower event rates than did standard statin therapy.

In light of recent studies, the National Heart, Lung, and Blood Institute, the American College of Cardiology Foundation, and the American Heart Association²⁰ called for modifying the ATP III guidelines as follows:

- Patients with established coronary disease or who are thought to be at high risk of coronary events should have a goal serum LDL-C concentration of less than 100 mg/dL. A stricter goal of less than 70 mg/dL (as might be achieved with high-dose atorvastatin therapy) can be considered for patients at very high risk but is not mandatory.
- For patients at very high risk who have a baseline LDL-C concentration of less than 100 mg/dL, a goal of less than 70 mg/dL is also reasonable.

In my practice, I recommend that patients with coronary artery disease bring their LDL-C levels to below 70 mg/dL if possible. The simplest regimen is atorvastatin 80 mg/day. This regimen is far less likely to cause rhabdomyolysis than simvastatin in high doses, ie, more than 40 mg/day. ■

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