

STATE-OF-THE-ART PAPER

Pre-Operative Risk Assessment and Risk Reduction Before Surgery

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Perioperative myocardial infarctions are the predominant cause of morbidity and mortality in patients undergoing noncardiac surgery. The pathophysiology of perioperative myocardial infarction is complex. Prolonged myocardial ischemia due to the stress of surgery in the presence of a hemodynamically significant coronary lesion, leading to subendocardial ischemia, and acute coronary artery occlusion after plaque rupture and thrombus formation contribute equally to these devastating events. Perioperative management aims at optimizing the patient's condition by identification and modification of underlying cardiac risk factors and diseases. During recent decades there has been a shift from the assessment and treatment of the underlying culprit coronary lesion toward a systemic medical therapy aiming at prevention of myocardial oxygen supply demand mismatch and coronary plaque stabilization. Beta-blockers, statins, and aspirin are widely used in this setting. The role of prophylactic coronary revascularization has been restricted to the same indications as the nonoperative setting. Therefore pre-operative cardiac testing is recommended only if test results will change perioperative management. In addition to the limited perioperative period, physicians should benefit from this opportunity to initiate lifestyle changes and medical therapy to lessen the impact of cardiac risk factors, as patients should live long enough after the operation to enjoy the benefits of surgery. (J Am Coll Cardiol 2008;51:1913-24) © 2008 by the American College of Cardiology Foundation

Patients undergoing major noncardiac surgery are at significant risk of cardiovascular morbidity and mortality. It is estimated that in Europe 40 million surgical procedures are performed annually with a post-operative myocardial infarction (MI) rate of 1% (400,000), and a cardiovascular mortality rate of 0.3% (133,000). Although the perioperative event rate has declined over the past 30 years as a consequence of recent developments in anesthesiologic and surgical techniques (e.g., regional anesthesia and endovascular treatment modalities), perioperative cardiac complications remain a significant problem. A pooled analysis of several large studies found a 30-day incidence of cardiac events (perioperative myocardial infarction [PMI] or cardiac death) of 2.5% in unselected patients over the age of 40 years (1). These complications were higher in vascular surgery patients, who had an incidence of 6.2% for cardiac events (2). The risk of perioperative cardiac complications is the summation of the individual patient's risk and cardiac stress related to the surgical procedure. In addition, the incidence is also related to the post-operative surveillance screening adopted, as the great majority of cardiac events are asymptomatic (Fig. 1). Studies that routinely assessed post-

operative cardiac isoenzymes (i.e., troponin T or I measurements) detected an incidence of PMI up to 25% in high-risk patients (3,4).

According to the World Health Organization, the global epidemic of cardiovascular disease will not only increase, but will also shift from developed to developing nations. It is further estimated that in the second half of the 21st century, more than 1 in 4 individuals will be 65 years of age or older. In the past, major surgery was rarely performed on patients in their '80s or '90s. Nowadays, many major surgical interventions are performed in this very elderly population. A recent study of 1,351 patients undergoing noncardiac surgery showed that the rate of cardiac events increased with advanced age, independent of other clinical variables, in those patients with myocardial perfusion abnormalities during stress scintigraphy (5). With the growing elderly population, an increased incidence of underlying cardiovascular disease, and the availability of advanced surgical techniques, these noncardiac surgery patients continue to demand our attention.

Pathophysiology of PMI

Although the pathophysiology of PMI is not entirely clear, it is now well accepted that coronary plaque rupture, leading to thrombus formation and subsequent vessel occlusion, is an important cause of acute perioperative coronary syndromes. This is similar to the nonoperative setting. The

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Abbreviations and Acronyms

- ACC** = American College of Cardiology
- AHA** = American Heart Association
- ASA** = acetylsalicylic acid
- CAD** = coronary artery disease
- MI** = myocardial infarction
- MPS** = myocardial perfusion scintigraphy
- PMI** = perioperative myocardial infarction

perioperative surgical stress response includes a catecholamine surge with associated hemodynamic stress, vasospasm, reduced fibrinolytic activity, platelet activation, and consequent hypercoagulability (6). In patients with significant coronary artery disease (CAD), PMI may also be caused by a sustained myocardial supply/demand imbalance due to tachycardia and increased myocardial contractility (6).

Episodes of perioperative ST-segment depression, indicating subendocardial myocardial ischemia,

have been described in up to 41% of vascular surgery patients, mostly occurring within the first 2 days after surgery (7). The association of PMI with myocardial ischemia and nontransmural or circumferential subendocardial infarction supports this mechanism. Landesberg et al. (8) demonstrated that 85% of postoperative cardiac complications were preceded by prolonged ST-segment depression. Fleisher et al. (9) found that 78% of patients with cardiac complications had at least 1 episode of prolonged myocardial ischemia (i.e., >30 min), either before or at the same time as the cardiac event. In the majority of cases, it presents without Q waves. The hypothesis that ST-segment depression can lead to PMI is further supported by increased troponin T levels during or shortly after prolonged ST-segment depression ischemia (10).

ST-segment elevation-type ischemia is considered to be relatively uncommon, confirmed by the incidence (12%) of intraoperative ST-segment elevation in a study by London et al. (11). Few data exist on this topic. As demonstrated in the autopsy study by Dawood et al. (12), 55% of the fatal

PMIs have direct evidence of plaque disruption defined as fissure or rupture of plaque and hemorrhage into the plaque cavity. Similar autopsy results were found in the study by Cohen and Aretz (13); a plaque rupture was found in 46% of patient with post-operative MI. Time-to-death interval in patients with plaque rupture was significantly longer than in patients without plaque rupture.

In a submitted study of Feringa and colleagues (personal communication, February 2008) 401 vascular surgery patients were evaluated by continuous 12-lead electrocardiographic monitoring during surgery and studied for the presence and location of ischemia. The relationship with the pre-operatively assessed culprit coronary artery lesion using noninvasive cardiac imaging was studied. In patients with perioperative ST-segment depression, the location corresponded with the pre-operatively assessed coronary lesion in 89%, and only in 53% of those with ST-segment elevation ($p < 0.001$). This study showed one of the limitations of pre-operative cardiac risk assessment focusing on the identification of the culprit coronary artery lesion. Using cardiac testing, one can identify the patient at risk; however, the location of the PMI is difficult to foresee, owing to the unpredictable progression of (asymptomatic) coronary artery lesions toward unstable plaques owing to the stress of surgery.

Perioperative Management

Risk stratification. The first step in pre-operative care is an adequate identification of patients at risk for perioperative cardiac events. In the past decades, several risk indexes have been developed in this context to stratify surgical patients. Goldman et al. (14) in 1977 developed the first multifactorial risk index specifically for cardiac complications. The risk index was developed in a large surgical population and included 9 independent risk factors correlated with serious or fatal cardiac complications (14). Subsequently, this index was modified by Detsky et al. (15) in 1986, who used a Bayesian approach using pre-test probabilities and presented the modified cardiac risk index in a simple nomogram. The Revised Cardiac Risk Index, developed in 1999 by Lee et al. (16), is nowadays the most widely used model of risk assessment in noncardiac surgery. This index identifies 6 predictors of major cardiac complications: high-risk surgery, ischemic heart disease, congestive heart failure, cerebrovascular disease, insulin-dependent diabetes mellitus, and renal failure. Based on the presence of none, 1, 2, or ≥ 3 predictors, the rate of major cardiac complications in the validation cohort ($n = 1,422$) was estimated to be 0.4%, 0.9%, 7%, and 11%, respectively. Recently, it was demonstrated in 108,593 patients undergoing all types of noncardiac surgery that this Revised Cardiac Risk Index was indeed predictive of cardiovascular mortality but could be substantially improved by adding age and a more detailed classification of type of surgical procedure (C-statistic improved from 0.63 to 0.85) (17).

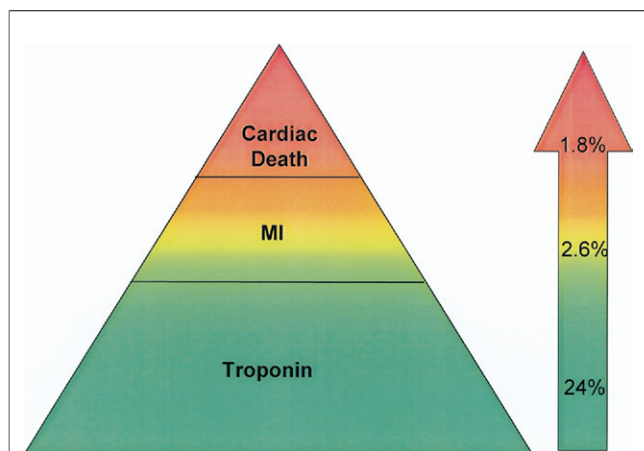


Figure 1. Perioperative Cardiac Events

The incidence of perioperative cardiac events in major noncardiac surgery. Data from Poldermans et al. (19). MI = myocardial infarction.

Noninvasive testing. Once the pre-operative risk assessment indicates an increased cardiac peri- or post-operative risk, further cardiac testing is warranted. The predominant theme of testing is the impact of test results on perioperative management; if test results will not influence management, testing is not recommended (18). According to the 2007 guidelines of the American College of Cardiology (ACC) and American Heart Association (AHA), patients with active cardiac conditions (i.e., unstable coronary syndromes, decompensated heart failure, significant arrhythmias, or severe valvular disease) have to be evaluated and treated before surgery (18). Pre-operative cardiac testing for elective surgery is reasonable for patients with ≥ 3 clinical risk factors and poor functional capacity who require vascular surgery (Class IIa) (Table 1, Fig. 2). Pre-operative testing may be considered in patients with at least 1 to 2 clinical risk factors and poor functional capacity who require intermediate-risk noncardiac surgery and in patients with at least 1 to 2 clinical risk factors and good functional capacity who are undergoing vascular surgery (Class IIb). Noninvasive testing is not recommended for patients without clinical risk factors undergoing intermediate- or low-risk noncardiac surgery (Class III).

Although pre-operative testing may be considered for patients with 1 or 2 risk factors scheduled for vascular surgery, the results of the randomized, multicenter DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo)-II study showed differently. If patients received beta-blockers with tight heart rate control, the perioperative cardiac event rate was already so reduced that test results and subsequent alteration in perioperative management were redundant (19). No differences in cardiac death and MI at 30 days were observed between 770 patients assigned to no testing versus cardiac stress testing (1.8% vs. 2.3%; odds ratio [OR] 0.78, 95% confidence interval [CI] 0.28 to 2.1). Importantly, pre-operative testing delayed surgery for more than 3 weeks.

Several noninvasive and exercise stress tests are available for perioperative risk assessment. The most commonly used stress test for detecting myocardial ischemia is the treadmill or cycle ergometer test. These tests provide an estimate of the functional capacity and hemodynamic response and detect myocardial ischemia by ST-segment changes. The accuracy varies widely among studies (20). However, an important limitation in patients undergoing noncardiac

surgery is the frequently limited exercise capacity in the elderly and the presence of claudication, arthrosis, or chronic obstructive pulmonary disease. Consequently, non-physiologic stress tests, such as dobutamine stress echocardiography or dipyridamol myocardial perfusion scintigraphy (MPS), are recommended in patients with limited exercise capacity.

During dobutamine stress echocardiography, incremental doses of dobutamine mimic physical exercise by increasing myocardial contractility and heart rate, leading to enhanced oxygen demand. In a region supplied by a hemodynamically significant coronary artery lesion, myocardial ischemia is induced, leading to contractile dysfunction that can be assessed by echocardiography as new wall motion abnormalities. Dobutamine stress echocardiography is an established test to predict perioperative events in patients undergoing surgery, with a high negative predictive value and a moderate positive predictive value (18,20–25).

Myocardial perfusion scintigraphy is a widely used imaging technique for pre-operative evaluation. This technique involves intravenous administration of a small quantity of a radioactive tracer such as a technetium^{99m}-labeled radiopharmaceutical. Images are obtained at rest and during vasodilator stress. Detection of CAD is based on a difference in blood flow distribution during vasodilator stress, induced by insufficient coronary blood flow increment attributed to coronary stenosis. A positive MPS is associated with increased risk of peri- and post-operative cardiac complications. Studies indicate that MPS is highly sensitive for prediction of cardiac complications, but the specificity has been reported as less satisfactory (20,21,26,27).

Although no head-to-head comparisons of large numbers of patients have been performed, 2 large meta-analyses have compared these techniques with respect to sensitivity and specificity. The studies by Kertai *et al.* (20) and Beattie *et al.* (21) concluded that stress echocardiography was slightly favorable to predict post-operative events owing to the better negative predictive characteristics. However, the literature gives no definite answer in selecting the most accurate test. The choice of the test should therefore be based on the center's experience and short-term availability as highlighted in the ACC/AHA guidelines (18).

Prophylactic revascularization. Prophylactic pre-operative coronary revascularization of the culprit lesion may prevent perioperative complications in patients with significant

Table 1 ACC/AHA Classification of Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa	Weight of evidence/opinion is in favor of usefulness/efficacy.
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.
Class III	Conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective, and in some cases may be harmful.

Type of Surgery	Functional Capacity	Number of Clinical Risk Factors				
		0	1	2	3	≥4
Vascular Surgery	Good	[Green bar from 0 to 1, Orange bar from 1 to 4]				
	Poor	[Green bar from 0 to 1, Orange bar from 1 to 3, Red bar from 3 to 4]				
Intermediate Risk Surgery	Good	[Green bar from 0 to 4]				
	Poor	[Green bar from 0 to 1, Orange bar from 1 to 4]				
Low Risk Surgery	Good	[Green bar from 0 to 4]				
	Poor	[Green bar from 0 to 4]				

Figure 2 Recommendations for Noninvasive Stress Testing According to the ACC/AHA Guidelines (2007)

Green bars indicate no recommendation of noninvasive stress testing and that patients can go directly to surgery; orange bars indicate patients for whom testing may be considered if it will change management (class IIb); and the red bar indicates a class IIa recommendation for noninvasive stress testing. ACC/AHA = American College of Cardiology/American Heart Association. Data from Fleisher et al. (18).

CAD scheduled for surgery. However, the value of prophylactic revascularization is controversial (28–30). Whereas former evidence was based on small observational studies and expert opinions, 2 recent randomized controlled trials have clarified this issue. The CARP (Coronary Artery Revascularization Prophylaxis) trial conducted by McFalls et al. (31) was the first randomized trial that investigated the benefit of coronary revascularization before elective major vascular surgery. In that study, 510 patients with significant artery stenosis were randomized to either revascularization or no revascularization before surgery. Within 30 days, no reduction in the number of MIs or deaths or in lengths of hospital stay was observed. Furthermore, as illustrated in Figure 3, long-term outcome in patients who underwent pre-operative coronary revascularization was similar to pa-

tients who received optimized medical therapy (22% vs. 23% mortality; relative risk [RR] 0.98, 95% CI 0.70 to 1.37). Because the majority of patients in the CARP trial had only 1- or 2-vessel disease with a preserved left ventricular function, the optimal pre-operative management for patients with left main disease, severe left ventricular dysfunction, unstable angina pectoris, and aortic stenosis was not determined. In a recent study evaluating vascular surgery patients with predominantly 3-vessel disease, similar findings were obtained (32). The incidence of the composite end point of all-cause mortality and MI at 30 days was 43% versus 33% (OR 1.4, 95% CI 0.7 to 2.8) and at 1 year was 49% versus 44% (OR 1.2, 95% CI 0.7 to 2.3). Both studies suggest that prophylactic coronary revascularization of cardiac-stable patients provides no benefit for immediate post-operative outcome, although the studies were not significantly powered to detect differences in outcome. In accordance with this evidence, the new ACC/AHA guidelines indicate that routine prophylactic coronary revascularization is not recommended in patients with stable CAD before noncardiac surgery (18).

Another important clinical situation is the management of patients with previous coronary stenting undergoing noncardiac surgery (33). The risk of perioperative stent thrombosis in these patients is increased by the noncardiac surgical procedure, especially when surgery is performed early after stent implantation and particularly if dual antiplatelet therapy is discontinued. When possible, it is advised to delay surgery until after the time window that requires dual antiplatelet therapy. The new ACC/AHA guidelines recommend, based on expert opinion, 30 to 45 days for bare-metal stents and 1 year for drug-eluting stents (18).

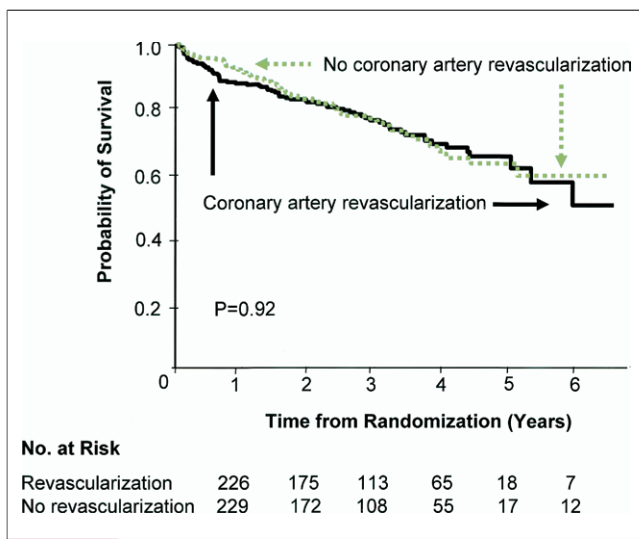


Figure 3 Prophylactic Coronary Revascularization

Results of the CARP (Coronary Artery Revascularization Prophylaxis) study: long-term survival among patients assigned to undergo coronary artery revascularization or no revascularization. Reprinted with permission from McFalls et al. (31).

Perioperative Management—New Insights

The beneficial effect of a pre-operative localized treatment of a coronary stenosis is hampered because of the unpredictable progression of a nonsignificant coronary lesion

toward plaque rupture, thrombus formation, and subsequent coronary artery occlusion. Plaque instability is driven by the stress of surgery. Systemic therapy with medical treatment aiming at plaque stabilization therefore seems promising for perioperative as well as long-term risk reduction. Perioperative beta-blockers, statins, and aspirin have all shown a significant benefit in decreasing cardiac mortality and morbidity (34–38). These effects can be divided into acute and chronic effects.

Beta-blocker therapy. Beta-adrenergic receptor antagonists (beta-blockers) are divided into β_1 -selective and non-selective (β_1 and β_2) adrenoreceptor blockers. Atenolol, metoprolol, and bisoprolol, all β_1 -selective blockers, are commonly used for perioperative care. The classic idea of the benefit of beta-blocking agents is its effect on restoring the oxygen supply/demand mismatch. However, the complexity of the interactions among the heart, the sympathetic nervous system, and inflammation also contributes to the benefit of beta-blockade (39). This latter effect is supposed to evolve only after some time.

Although nowadays widely prescribed, there is still considerable debate about the protective effect of beta-blockers, especially after the results of the POISE (Perioperative Ischemic Evaluation) trial became available (40). Some studies showed a clear evidence in favor of beta-blocker use in the perioperative period (35,37), although other studies failed to demonstrate a cardioprotective effect (41–43). A recent large meta-analysis by Schouten et al. (44) included 15 studies (1,077 patients) and showed a significant beneficial effect of beta-blockers in noncardiac surgery patients (Fig. 4). The recently presented POISE study showed a benefit of high-dose metoprolol controlled-release therapy on the risk of MI but, importantly, at the cost of an increased risk of stroke and overall mortality (40,45). Different explanations exist regarding the conflicting evidence for perioperative beta-blocker use. In particular, the initiation time and dose of beta-blocker therapy, the type of beta-blocker, dose adjustments for heart rate control, and

the patients' underlying cardiac risk are important factors that may relate to the effectiveness of therapy.

INITIATION TIME. It is unclear whether the effect on coronary plaque stabilization, in contrast to heart rate control, can be achieved instantly after beta-blocker start. The onset of beta-blocker therapy before surgery in studies evaluating the cardioprotective effect differs considerably, from months to just hours before operation. Mangano et al. (35) conducted the first randomized controlled trial investigating the effect of beta-blockers in patients undergoing noncardiac surgery. In that trial, 200 patients with known or suspected CAD were randomized for atenolol or placebo just before the induction of anesthesia. No difference in perioperative cardiac events was observed, although the incidence of electrocardiographically assessed ischemia was reduced. The MAVS (Metoprolol After Vascular Surgery) trial randomized 496 patients to metoprolol or placebo starting 2 h before surgery until hospital discharge or a maximum of 5 days after surgery (43). No significant differences in outcome were observed at 30 days after surgery or after 6 months. In the POBBLE (Perioperative Beta-Blockade) trial, 103 patients undergoing vascular surgery who were randomized to metoprolol or placebo, starting less than 24 h before surgery until 7 days after, also showed no beneficial effect on 30-day cardiovascular outcome (41). Within 30 days, cardiovascular events occurred in 32% and 34% patients in the metoprolol and placebo groups, respectively (adjusted RR 0.87, 95% CI 0.48 to 1.55). The DIPOM (Diabetic Postoperative Mortality and Morbidity) trial, which started therapy at the earliest in the evening before major noncardiac surgery, again showed no improved 30-day outcome (42). The POISE trial randomized patients to receive either controlled-release metoprolol or placebo starting 2 to 4 h before surgery and continued for 30 days. In contrast to these studies, the DECREASE-I trial started bisoprolol at an average of 37 (range 7 to 89) days before surgery in 112 high-risk patients. In this period, careful

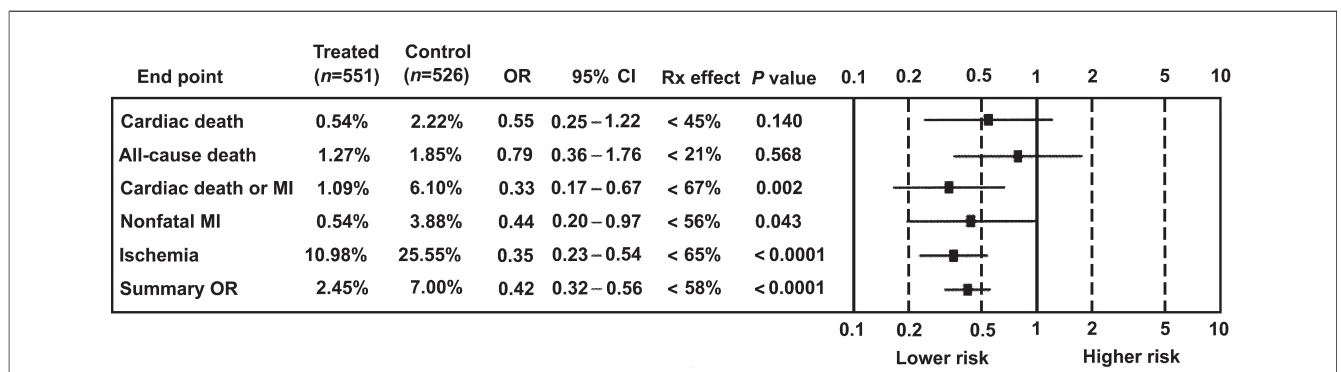


Figure 4 Perioperative Beta-Blocker Therapy

Comparison of patients treated with perioperative beta-blocker therapy versus no drug or placebo.

CI = confidence interval; MI = myocardial infarction; OR = odds ratio; Rx = treatment. Reprinted, with permission, from Schouten et al. (44).

titration of bisoprolol therapy was performed. That study showed a 10-fold reduction in incidence of perioperative cardiac death and MI versus placebo (3.4% vs. 34%; $p < 0.001$) (37).

The importance of the initiation time of beta-blocker therapy before surgery can be argued by the pathophysiology of PMI. The acute effects of beta-blockade include the reduction of myocardial oxygen demand by a decrease in heart rate, systolic pressure, and ventricular contractility. Otherwise, the suggested effect of beta-blockers on coronary plaque stabilization may be related to anti-inflammatory properties and possibly only be observed after prolonged use. Beta-blockade has been shown to decrease the level of inflammatory cytokines in both the myocardium and the systemic circulation (46–48). A study in patients with acute MI demonstrated that beta-blocker treatment reduced inflammatory responses only after 48 h of treatment (49).

Although the study of Mangano *et al.* (35) did not demonstrate a perioperative effect, atenolol use was associated with significantly lower mortality rates at 6 months after discharge (0% vs. 8%; $p = 0.001$), over the first year (3% vs. 14%; $p = 0.005$), and over 2 years (10% vs. 21%; $p = 0.019$). Another randomized trial also showed benefit of beta-blocker use on the long term, even up to 30 months (37). These findings support the hypothesis that not all effects of beta-blockers are achieved immediately after initiation of therapy. The long-term beneficial effects of beta-blockers were recently confirmed by a study which demonstrated a decreased progression of coronary atherosclerosis in patients receiving beta-blockers. Sipahi *et al.* (50) performed a pooled analysis of individual patient data from 4 intravascular ultrasonography trials to investigate the relationship between concomitant beta-blocker treatment and the progression of coronary atherosclerosis. The use of beta-blockers was significantly associated with a decrease of the atheroma volume at follow-up, whereas this was not changed in patients without beta-blockers. In addition, it seems to be crucial to continue beta-blockers in the perioperative period. It has been shown that perioperative withdrawal of beta-blocker therapy was associated with a 2.7-fold increased risk of 1-year mortality compared with patients not using beta-blockers (51).

TYPE. The predominant perioperative cardioprotective effect is regulated by β_1 -adrenoreceptor blockade. The perioperative period is associated with high adrenaline and noradrenalin levels (52,53), creating a potentially dangerous situation in the presence of vulnerable plaques. The danger has 2 aspects: a hemodynamic effect and a stimulation of the inflammatory process. The hemodynamic risk is associated with increased heart rates and blood pressure associated with high sympathetic nerve activity (7). The beta-blocker benefit could thus clearly be operating via its ability to lower heart rate. Blood pressure and velocity of blood flow rise under the influence of high catecholamine activity, and so beta-blocker normalizes turbulent flow and vessel wall shear

forces. However, blocking both β_1 - and β_2 -receptors in the presence of raised adrenaline levels during surgery will lead to uncontrolled alpha stimulation and a subsequent adverse rise in blood pressure (54). Metoprolol and atenolol, which are only moderately β_1 -selective, may increase myocardial oxygen demand and might therefore be less recommended than the highly β_1 -selective bisoprolol. In the same vein, the inflammatory process is exacerbated by high noradrenalin levels (55), undoubtedly acting through β_1 -receptor overactivity, which increases inflammation, necrosis, apoptosis, and matrix metalloproteinase activity (56). Interestingly β_2 -receptor overactivity inhibits the inflammatory necrotic/apoptotic process (57), thus making β_2 -blockade unwelcome.

The different beta-blockers have various plasma half-lives and peak ratios. Bisoprolol and atenolol are long-acting agents with half-lives of 10 to 11 h and 6 to 7 h, respectively, whereas metoprolol has a short duration of action of about 3.5 h. A study by Redelmeier *et al.* (58) in elderly patients undergoing elective surgery reported that long-acting beta-blockers are associated with higher cardioprotective benefits than short-acting beta-blockers in the perioperative period. In patients with CAD/unstable plaques, beta-blockers with short half-lives will increase the risk of a cardiovascular event on sudden withdrawal (51,59). In the acute absence of β_2 -blockade, the up-regulated β_1 -receptors plus high catecholamine levels would be a dangerous mix. Therefore, long-acting beta-blockers, such as bisoprolol, will be safer than agents with short half-lives (21).

DOSING AND TIGHT HEART RATE CONTROL. In addition to the initiation time before surgery and type of beta-blocker, dose adjustment for heart rate control is important. Raby *et al.* (60) were the first to show positive results on strict heart rate control in 26 patients undergoing major noncardiac surgery. A recent study demonstrated in 272 patients that higher doses of beta-blockers and tight heart rate control were associated with reduced perioperative myocardial ischemia, troponin T release, and improved long-term outcome (Fig. 5) (61). Accordingly, the new ACC/AHA guidelines on perioperative care strongly recommend achieving and maintaining a heart rate of 60 to 65 beats/min (18). Tight heart rate control will increase the likelihood that a patient will receive the benefit of beta-blockade.

The POISE trial initiated randomized treatment of controlled-release metoprolol just before surgery, and the maximum recommended therapeutic dose of metoprolol (400 mg) was already achieved within the first day of surgery (45). Medication was continued at 200 mg daily afterwards. This is in contrast to the DECREASE studies, where a low dose of bisoprolol at an average 12.5% of maximum recommended therapeutic dose was carefully up-titrated during a mean period of 30 days. The primary findings of the POISE trial were a reduction of perioperative MI by high-dose metoprolol controlled-release therapy, but an excess of overall mortality (40). They observed an incidence of stroke of 1% in the group randomized to metoprolol

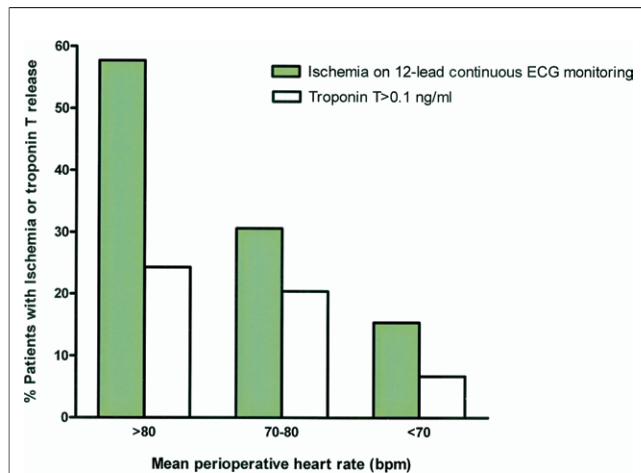


Figure 5 Heart Rate Control

Mean heart rate in relation to myocardial ischemia assessed by continuous electrocardiography and troponin T release. Data from Feringa *et al.* (61). ECG = electrocardiogram.

compared with an incidence of 0.4% in the DECREASE studies. Several issues have to be clarified in the POISE study to interpret their findings properly. The increased incidence of ischemic stroke in the POISE study in combination with intraoperative bradycardia and hypotension suggests an overtreatment effect. The lesson from the POISE study might be that beta-blockers should be carefully titrated and that the stopping rule of a systolic blood pressure of 100 mm Hg for metoprolol controlled-release therapy might be hazardous in elderly patients with a history of stroke.

CARDIAC RISK. Another important issue is the identification of surgical patients who may benefit from beta-blocker therapy. The evidence of the beneficial effect of beta-blockers is strongest in high-risk patients. Lindenauer *et al.* (62) performed a retrospective cohort study of 782,969 patients who underwent major noncardiac surgery to investigate the association of beta-blockers with perioperative outcome. They observed a relationship between cardiac risk and the effect of perioperative beta-blocker use. Beta-blocker use showed no benefit or possible harm in low-risk patients but had a significant beneficial effect in high-risk patients. Important to note is that in the MAVS trial, most patients were at low risk for complications, as almost 60% had a Revised Cardiac Risk Index score of only 1 (43). The negative DIPOM trial also included many low-risk patients (42). Additionally, in contrast to the ACC/AHA guidelines (18), in the Juul *et al.* study (42), major noncardiac surgery was defined as surgery with an expected duration of >1 h.

GUIDELINES. Recently, the ACC and AHA introduced a guideline update on perioperative beta-blocker therapy (63). These recommendations are summarized in Table 2. The

class I recommendations of these guidelines are to continue beta-blocker therapy in patients already receiving beta-blockers and to start patients with a positive stress test on beta-blockers. Furthermore, beta-blocker therapy is probably recommended for patients undergoing vascular surgery in which pre-operative assessment identifies coronary heart disease or high cardiac risk as defined by the presence of multiple clinical risk factors (Class IIa). The same class of recommendation holds for patients in whom pre-operative assessment identifies coronary heart disease or high cardiac risk and who are undergoing intermediate- or high-risk procedures. Class IIb recommendations include patients with intermediate cardiac risk who are undergoing intermediate- or high-risk procedures and patients with low cardiac risk who are scheduled for vascular surgery and are currently not on beta-blockers.

Further large randomized trials are definitely needed to give more conclusive recommendations regarding beta-blocker therapy for patients undergoing noncardiac surgery in different risk groups. The ongoing DECREASE-IV study may give more insight into the optimal pharmaceutical prevention with beta-blockers and statins of perioperative cardiovascular complications (64).

Statins. Statins are widely prescribed in patients with or at risk for CAD, because of their well-established lipid-lowering capacity. Statins have other important beneficial effects on atherosclerotic vascular disease, which are known as its pleiotropic effects (65). These effects include atherosclerotic plaque stabilization, oxidative stress reduction, and a decrease of vascular inflammation. In human carotid plaques, statins have been demonstrated to decrease lipids, lipid oxidation, inflammation, matrix metalloproteinases, and cell death and to increase tissue inhibitors of metalloproteinases and collagen (66). These properties of statins may stabilize coronary artery plaques, thereby preventing plaque rupture and subsequent MI in the perioperative period.

Different large clinical trials in patients with CAD have shown a beneficial effect of statins. The 4S (Scandinavian Simvastatin Survival Study) demonstrated that simvastatin in CAD patients was safe and improved long-term outcome (67). Importantly, that same research group showed that the beneficial effect of simvastatin is not restricted to coronary atherosclerosis, as statin use was also associated with a reduction of new or worsening intermittent claudication and other noncoronary ischemic symptoms and signs (68). These positive observations of statin therapy are also observed during vascular surgery (Fig. 6). A retrospective case-control study among 2,816 patients who underwent major noncardiac vascular surgery was the first study to show a benefit of statins in the perioperative period. That study demonstrated a 4-fold significant reduction in all-cause mortality (adjusted OR 0.22, 95% CI 0.10 to 0.47) (36). A year later, the first prospective, placebo-controlled, blinded, randomized clinical trial evaluating the effects of statin therapy on perioperative cardiovascular complications was reported by Durazzo *et al.* (34). They randomized 100

Table 2 Recommendations for Perioperative Beta-Blocker Therapy According to the ACC/AHA Guidelines

Surgery	No Clinical Risk Factors	≥1 Clinical Risk Factors	CHD or High Cardiac Risk	Patients Currently Taking Beta-Blockers
Vascular	Class IIb, Level of Evidence: B	Class IIa, Level of Evidence: B	Class I*/Class IIa†, Level of Evidence: B	Class I, Level of Evidence: B
Intermediate risk	—	Class IIb, Level of Evidence: C	—	Class I, Level of Evidence: C
Low risk	—	—	—	Class I, Level of Evidence: C

Adapted from Fleisher et al. (18). Level of evidence according to the ACC/AHA: A = data derived from multiple, randomized, clinical trials; B = data derived from a single randomized trial or nonrandomized studies; C = only consensus opinion of experts, case studies, or standard-of-care. *Applies to patients found to have coronary ischemia on pre-operative testing. †Applies to patients found to have coronary heart disease.

CHD = coronary heart disease; other abbreviations as in Table 1.

patients to either 20 mg atorvastatin or placebo for 45 days. The combined cardiovascular end point in the trial was defined as cardiac death, nonfatal MI, stroke, or unstable angina pectoris. After 6 months of follow-up, the incidence of cardiovascular events was more than 3-fold higher with placebo than with atorvastatin (26% vs. 8%; $p = 0.031$).

Different retrospective trials have also evaluated the effects of statin therapy on perioperative complications in patients undergoing noncardiac surgery (69–71). Lindenauer et al. (70) performed a large retrospective cohort study of 780,591 patients undergoing major noncardiac surgery at 329 hospitals. After correction for numerous baseline differences, the 70,159 statin users had a 1.4-fold reduced risk of in-hospital mortality (adjusted OR 0.62, 95% CI 0.58 to 0.67). The STARRS (Statins for Risk Reduction in Surgery) study assessing the effect of statins on cardiac complications in patients undergoing noncardiac vascular surgery also supported the use of perioperative statin therapy (71). In that retrospective study cohort of 1,163 patients, statin users had a significantly lower perioperative complication rate than patients without statin therapy (adjusted OR 0.52, 95% CI 0.35 to 0.77). The protective effect of statin use was similar across the different risk group categories and persisted after adjusting for the propensity of statin use. Several systematic review articles have demonstrated supportive evidence of statin therapy (72–74).

In addition, the long-term benefit of statins was reported in patients undergoing successful abdominal aortic aneurysm surgery. Kertai et al. (75) followed 510 patients who survived aortic aneurysm surgery for a median of 4.7 years.

SAFETY OF PERIOPERATIVE STATIN USE. A major concern of statin therapy is the potential side effects, such as statin-induced myopathy and rhabdomyolysis. Perioperatively, patients might be unaware of these symptoms, owing to sedation, or they are erroneously associated with post-operative surgery complaints. In a retrospective study, Schouten et al. (76) studied 981 consecutive patients undergoing major vascular surgery without PMI to assess the potential risk of myopathy associated with statin therapy. Statin therapy was initiated before surgery in a total of 44 patients with elevated cholesterol levels and continued in 182 patients already taking statin therapy. Blood samples were taken and patients were monitored for muscle complaints at days 1, 3, and 7 after surgery and at discharge. Myopathy was defined as creatine kinase elevations with or without observed muscle complaints. After correcting for cardiac risk factors and clinical risk factors for myopathy, length of surgery remained the only factor independently associated with creatine kinase elevations. Rhabdomyolysis, defined as creatine kinase levels above 10 times the upper limit of normal, was not observed. Considering that the risk

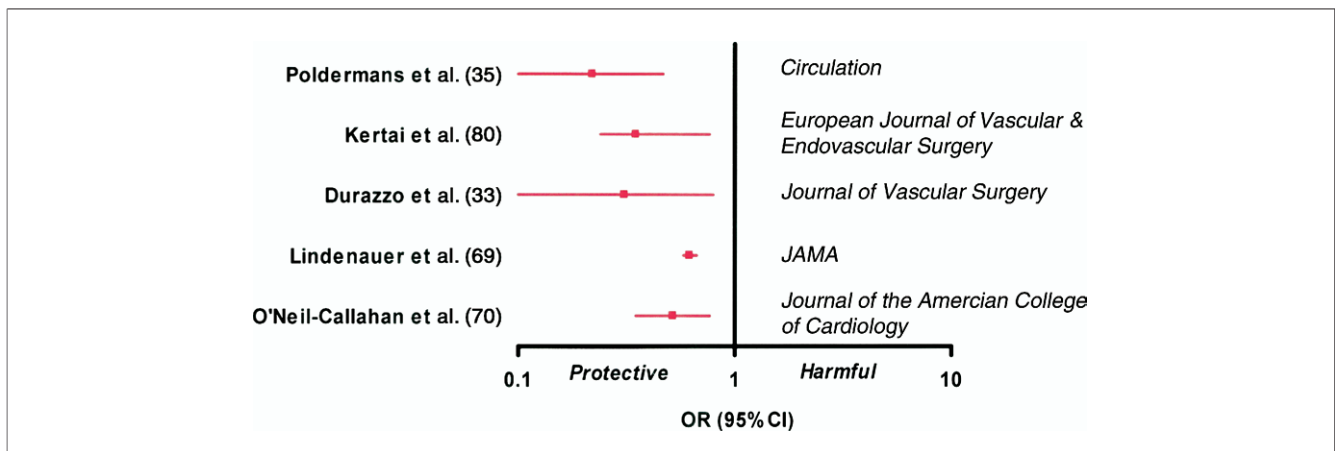


Figure 6 Perioperative Statin Therapy

Results of the effect of perioperative statin therapy in different studies. CI = confidence interval; OR = odds ratio.

of perioperative cardiovascular complications is far greater than the risk of statin-induced myopathy and rhabdomyolysis, the potential benefits of perioperative statin use appear to outweigh the potential hazards. It has to be noticed that these observations need confirmation in large randomized trials.

DOSAGE AND TIMING. The optimal dosing and timing of statins for the prevention of perioperative events has still to be elucidated. An important concern is the continuation of statins in the perioperative period. Unintended interruption in the immediate post-operative period is a well-known phenomenon because of the unavailability of an intravenous formula of statins. From patients with CAD, it is known that sudden withdrawal of statin therapy can be harmful (77,78). Recently, it has been demonstrated in vascular surgery patients that statin discontinuation was associated with an increased risk for post-operative troponin release (hazard ratio [HR] 4.6, 95% CI 2.2 to 9.6) and the combination of MI and cardiovascular death (HR 7.5, 95% CI 2.8 to 0.1) (79). Furthermore, they observed that the extended release of fluvastatin appeared to have beneficial effects over other statins when discontinued. The increased post-operative risk associated with the withdrawal of statins was also observed by Le Manach *et al.* (80). These findings indicate that statins with a prolonged half-life time or with an extended release formula should be preferred.

Following the available evidence of both beta-blockers and statins in the perioperative period, the question arises whether these medications should be used as a combination therapy. Some retrospective studies have already reported a beneficial effect of using both beta-blockers and statins on perioperative outcome (81). The previously mentioned DECREASE-IV trial could give more insights in this topic as it aims to assess the clinical efficacy of beta-blocker, statin, and combination therapy in patients undergoing major noncardiac surgery (64).

Acetylsalicylic acid. Acetylsalicylic acid (ASA) is one of the cornerstones in the primary and secondary prevention of cardiovascular diseases. Furthermore, the combination of ASA and clopidogrel is commonly used for the prevention of stent thrombosis. The evidence of ASA in the perioperative period in patients undergoing noncardiac surgery is less clear. In a randomized trial of patients undergoing carotid endarterectomy, ASA was shown to be effective in preventing intraoperative and post-operative stroke but with no effect on death or MI (82). In another trial comparing low-dose and high-dose ASA in carotid surgery, results indicated reduced mortality, MI, and stroke in the low-dose group (83). A meta-analysis by Robless *et al.* (84) in 2001 demonstrated a reduction of serious vascular events and vascular death in patients with peripheral vascular disease. That study included 10 trials of antiplatelet treatment in lower limb bypass surgery, of which 6 involved ASA treatment. However, the benefit of antiplatelet therapy did not reach statistical significance for the combined end point of vascular events (OR 0.76, 95% CI 0.54 to 1.05) in that

vascular surgery population. Concerns of promoting perioperative hemorrhagic complications often withheld continuation of ASA in the perioperative period. No randomized controlled trials exist, however, on pre-operative discontinuation of ASA. A meta-analysis by Burger *et al.* (85) concluded that ASA should be discontinued only if low-dose ASA may cause bleeding risks with increased mortality or if sequels are similar to the observed cardiovascular risks after ASA withdrawal. In 41 studies they observed that ASA increased the risk of bleeding complications 1.5-fold but did not lead to higher severity levels of bleeding complications. A systematic review in subjects at risk for or with CAD demonstrated that ASA nonadherence/withdrawal was associated with a 3-fold higher risk of major adverse cardiac events (OR 3.14, 95% CI 1.75 to 5.61; $p = 0.0001$) (86).

Conclusions

In the growing elderly population with an increased cardiovascular comorbidity, underlying ischemic heart disease in surgical patients is becoming a key problem. Myocardial infarctions are the major cause of perioperative morbidity and mortality. The pathophysiology of PMI is related to the stress of surgery, inducing an oxygen supply/demand imbalance in the presence of a coronary artery stenosis or a sudden coronary plaque rupture with thrombosis and vessel occlusion. In the latter condition, inflammation plays a major role. To prevent these devastating conditions from multiplying, systemic strategies are required. Beta-blockers correct the imbalance between myocardial oxygen supply and demand, and statins and aspirin focus on plaque stabilization by a reduction of the inflammatory response. Moreover, current data clearly reveal a shift from pre-operative coronary revascularization toward intensified medical treatment. Current recommendations of prophylactic coronary revascularization have been restricted to the same indications as in the nonoperative setting. In cardiac-stable patients, noninvasive cardiac stress testing is therefore indicated only if it will change management. In high-risk patients, prophylactic coronary revascularization might be switched to later post-operative revascularization, preventing the delay of surgery. The optimal timing of beta-blocker therapy before surgery has not been resolved yet. Beta-blockers have both a hemodynamic and an anti-inflammatory effect. To obtain maximum benefits of beta-blockade, therapy should be initiated at least some days before surgery in combination with dose adjustments for tight heart rate control. Furthermore, it is strongly advised to continue the beta-blocker therapy throughout the perioperative period. The pleiotropic effects of statins have also been shown to be beneficial in patients undergoing noncardiac surgery. The pre-operative risk assessment is an ideal opportunity to initiate lifestyle changes and medical therapy to lessen the impact of cardiac risk factors to improve both perioperative and long-term outcome.

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REFERENCES

- Mangano DT. Adverse outcomes after surgery in the year 2001—a continuing odyssey. *Anesthesiology* 1998;88:561–4.
- Mangano DT, Goldman L. Preoperative assessment of patients with known or suspected coronary disease. *N Engl J Med* 1995;333:1750–6.
- Abraham N, Lemech L, Sandroussi C, Sullivan D, May J. A prospective study of subclinical myocardial damage in endovascular versus open repair of infrarenal abdominal aortic aneurysms. *J Vasc Surg* 2005;41:377–80.
- Le Manach Y, Godet G, Coriat P, et al. The impact of postoperative discontinuation or continuation of chronic statin therapy on cardiac outcome after major vascular surgery. *Anesth Analg* 2007;104:1326–33.
- Bai J, Hashimoto J, Nakahara T, Suzuki T, Kubo A. Influence of ageing on perioperative cardiac risk in noncardiac surgery. *Age Ageing* 2007;36:68–72.
- Mangano DT. Perioperative cardiac morbidity. *Anesthesiology* 1990;72:153–84.
- Mangano DT, Browner WS, Hollenberg M, London MJ, Tubau JF, Tateo IM, Study of Perioperative Ischemia Research Group. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. *N Engl J Med* 1990;323:1781–8.
- Landesberg G, Luria MH, Cotev S, et al. Importance of long-duration postoperative ST-segment depression in cardiac morbidity after vascular surgery. *Lancet* 1993;341:715–9.
- Fleisher LA, Nelson AH, Rosenbaum SH. Postoperative myocardial ischemia: etiology of cardiac morbidity or manifestation of underlying disease? *J Clin Anesth* 1995;7:97–102.
- Landesberg G, Mosseri M, Shatz V, et al. Cardiac troponin after major vascular surgery: the role of perioperative ischemia, preoperative thallium scanning, and coronary revascularization. *J Am Coll Cardiol* 2004;44:569–75.
- London MJ, Hollenberg M, Wong MG, et al. Intraoperative myocardial ischemia: localization by continuous 12-lead electrocardiography. *Anesthesiology* 1988;69:232–41.
- Dawood MM, Gupta DK, Southern J, Walia A, Atkinson JB, Eagle KA. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. *Int J Cardiol* 1996;57:37–44.
- Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. *Cardiovasc Pathol* 1999;8:133–9.
- Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977;297:845–50.
- Detsky AS, Abrams HB, Forbath N, Scott JG, Hilliard JR. Cardiac assessment for patients undergoing noncardiac surgery. A multifactorial clinical risk index. *Arch Intern Med* 1986;146:2131–4.
- Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation* 1999;100:1043–9.
- Boersma E, Kertai MD, Schouten O, et al. Perioperative cardiovascular mortality in noncardiac surgery: validation of the Lee Cardiac Risk Index. *Am J Med* 2005;118:1134–41.
- Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol* 2007;50:e159–241.
- Poldermans D, Bax JJ, Schouten O, et al. Should major vascular surgery be delayed because of preoperative cardiac testing in intermediate-risk patients receiving beta-blocker therapy with tight heart rate control? *J Am Coll Cardiol* 2006;48:964–69.
- Kertai MD, Boersma E, Bax JJ, et al. A meta-analysis comparing the prognostic accuracy of six diagnostic tests for predicting perioperative cardiac risk in patients undergoing major vascular surgery. *Heart* 2003;89:1327–34.
- Beattie WS, Abdelnaem E, Wijeyesundera DN, Buckley DN. A meta-analytic comparison of preoperative stress echocardiography and nuclear scintigraphy imaging. *Anesth Analg* 2006;102:8–16.
- Poldermans D, Arnesi M, Fioretti PM, et al. Improved cardiac risk stratification in major vascular surgery with dobutamine-atropine stress echocardiography. *J Am Coll Cardiol* 1995;26:648–653.
- Sicari R, Ripoli A, Picano E, et al., EPIC (Echo Persantine International Cooperative) Study Group. Perioperative prognostic value of dipyridamole echocardiography in vascular surgery: a large-scale multicenter study in 509 patients. *Circulation* 1999;100:II26974.
- Eichelberger JP, Schwarz KQ, Black ER, Green RM, Ouriel K. Predictive value of dobutamine echocardiography just before noncardiac vascular surgery. *Am J Cardiol* 1993;72:602–7.
- Shaw LJ, Eagle KA, Gersh BJ, Douglas Miller D. Meta-analysis of intravenous dipyridamole-thallium-201 imaging (1985 to 1994) and dobutamine echocardiography (1991 to 1994) for risk stratification before vascular surgery. *J Am Coll Cardiol* 1996;27:787–98.
- Boucher CA, Brewster DC, Darling RC, Okada RD, Strauss HW, Pohost GM. Determination of cardiac risk by dipyridamole-thallium imaging before peripheral vascular surgery. *N Engl J Med* 1985;312:389–94.
- Etchells E, Meade M, Tomlinson G, Cook D. Semiquantitative dipyridamole myocardial stress perfusion imaging for cardiac risk assessment before noncardiac vascular surgery: a meta-analysis. *J Vasc Surg* 2002;36:534–40.
- Eagle KA, Rihal CS, Mickel MC, Holmes DR, Foster ED, Gersh BJ, CASS Investigators, University of Michigan Heart Care Program. Cardiac risk of noncardiac surgery: influence of coronary disease and type of surgery in 3368 operations. *Coronary Artery Surgery Study. Circulation* 1997;96:1882–7.
- Hassan SA, Hlatky MA, Boothroyd DB, et al. Outcomes of noncardiac surgery after coronary bypass surgery or coronary angioplasty in the Bypass Angioplasty Revascularization Investigation (BARI). *Am J Med* 2001;110:260–6.
- Landesberg G, Mosseri M, Wolf YG, et al. Preoperative thallium scanning, selective coronary revascularization, and long-term survival after major vascular surgery. *Circulation* 2003;108:177–83.
- McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med* 2004;351:2795–804.
- Poldermans D, Schouten O, Vidakovic R, et al. A clinical randomized trial to evaluate the safety of a noninvasive approach in high-risk patients undergoing major vascular surgery: the DECREASE-V pilot study. *J Am Coll Cardiol* 2007;49:1763–9.
- Brilakis ES, Banerjee S, Berger PB. Perioperative management of patients with coronary stents. *J Am Coll Cardiol* 2007;49:2145–50.
- Durazzo AE, Machado FS, Ikeoka DT, et al. Reduction in cardiovascular events after vascular surgery with atorvastatin: a randomized trial. *J Vasc Surg* 2004;39:967–75; discussion 975–6.
- Mangano DT, Layug EL, Wallace A, Tateo I, Multicenter Study of Perioperative Ischemia Research Group. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. *N Engl J Med* 1996;335:1713–20.
- Poldermans D, Bax JJ, Kertai MD, et al. Statins are associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery. *Circulation* 2003;107:1848–51.
- Poldermans D, Boersma E, Bax JJ, et al., Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. The effect of bisoprolol on perioperative mortality and myocardial infarction in high-risk patients undergoing vascular surgery. *N Engl J Med* 1999;341:1789–94.
- Schouten O, Bax JJ, Dunkelgrun M, Feringa HH, van Urk H, Poldermans D. Statins for the prevention of perioperative cardiovascular complications in vascular surgery. *J Vasc Surg* 2006;44:419–24.
- Yeager MP, Fillingim MP, Hettelman BD, Hartman GS. Perioperative beta-blockade and late cardiac outcomes: a complementary hypothesis. *J Cardiothorac Vasc Anesth* 2005;19:237–41.

40. Devereaux PJ. Perioperative Ischemic Evaluation (POISE) trial. Presented at AHA Scientific Sessions 2007; November 7, 2007; Orlando, FL.
41. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. *J Vasc Surg* 2005;41:602-9.
42. Juul AB, Wetterslev J, Glud C, et al. Effect of perioperative beta blockade in patients with diabetes undergoing major noncardiac surgery: randomised placebo controlled, blinded multicentre trial. *BMJ* 2006;332:1482.
43. Yang H, Raymer K, Butler R, Parlow J, Roberts R. The effects of perioperative beta-blockade: results of the Metoprolol After Vascular Surgery (MAVS) study, a randomized controlled trial. *Am Heart J* 2006;152:983-90.
44. Schouten O, Shaw LJ, Boersma E, et al. A meta-analysis of safety and effectiveness of perioperative beta-blocker use for the prevention of cardiac events in different types of noncardiac surgery. *Coron Artery Dis* 2006;17:173-9.
45. Devereaux PJ, Yang H, Guyatt GH, et al. Rationale, design, and organization of the Perioperative Ischemic Evaluation (POISE) trial: a randomized controlled trial of metoprolol versus placebo in patients undergoing noncardiac surgery. *Am Heart J* 2006;152:223-30.
46. Jenkins NP, Keevil BG, Hutchinson IV, Brooks NH. Beta-blockers are associated with lower C-reactive protein concentrations in patients with coronary artery disease. *Am J Med* 2002;112:269-74.
47. Ohtsuka T, Hamada M, Hiasa G, et al. Effect of beta-blockers on circulating levels of inflammatory and antiinflammatory cytokines in patients with dilated cardiomyopathy. *J Am Coll Cardiol* 2001;37:412-7.
48. Prabhu SD, Chandrasekar B, Murray DR, Freeman GL. Beta-adrenergic blockade in developing heart failure: effects on myocardial inflammatory cytokines, nitric oxide, and remodeling. *Circulation* 2000;101:2103-9.
49. Anzai T, Yoshikawa T, Takahashi T, et al. Early use of beta-blockers is associated with attenuation of serum C-reactive protein elevation and favorable short-term prognosis after acute myocardial infarction. *Cardiology* 2003;99:47-53.
50. Sipahi I, Tuzcu EM, Wolksi KE, et al. β -blockers and progression of coronary atherosclerosis: pooled analysis of 4 intravascular ultrasonography trials. *Ann Intern Med* 2007;147:10-8.
51. Hoeks SE, Scholte Op Reimer WJ, van Urk H, et al. Increase of 1-year mortality after perioperative beta-blocker withdrawal in endovascular and vascular surgery patients. *Eur J Vasc Endovasc Surg* 2007;33:13-9.
52. Nishiyama T, Yamashita K, Yokoyama T. Stress hormone changes in general anesthesia of long duration: isoflurane-nitrous oxide vs. sevoflurane-nitrous oxide anesthesia. *J Clin Anesth* 2005;17:586-91.
53. Roth-Isigkeit A, Brechmann J, Dibbelt L, Sievers HH, Raasch W, Schmucker P. Persistent endocrine stress response in patients undergoing cardiac surgery. *J Endocrinol Invest* 1998;21:12-9.
54. Cruickshank JM. Are we misunderstanding beta-blockers? *Int J Cardiol* 2007;120:10-27.
55. Banfi C, Cavalca V, Veglia F, et al. Neurohormonal activation is associated with increased levels of plasma matrix metalloproteinase-2 in human heart failure. *Eur Heart J* 2005;26:481-8.
56. Seeland U, Selejan S, Engelhardt S, Muller P, Lohse MJ, Bohm M. Interstitial remodeling in beta1-adrenergic receptor transgenic mice. *Basic Res Cardiol* 2007;102:183-93.
57. Communal C, Singh K, Sawyer DB, Colucci WS. Opposing effects of beta(1)- and beta(2)-adrenergic receptors on cardiac myocyte apoptosis: role of a pertussis toxin-sensitive G protein. *Circulation* 1999;100:2210-2.
58. Redelmeier D, Scales D, Kopp A. Beta blockers for elective surgery in elderly patients: population based, retrospective cohort study. *BMJ* 2005;331:932.
59. Shammash JB, Trost JC, Gold JM, Berlin JA, Golden MA, Kimmel SE. Perioperative beta-blocker withdrawal and mortality in vascular surgical patients. *Am Heart J* 2001;141:148-53.
60. Raby KE, Brull SJ, Timimi F, et al. The effect of heart rate control on myocardial ischemia among high-risk patients after vascular surgery. *Anesth Analg* 1999;88:477-82.
61. Feringa HHH, Bax JJ, Boersma E, et al. High-dose β -blockers and tight heart rate control reduce myocardial ischemia and troponin T release in vascular surgery patients. *Circulation* 2006;114:I-344-39.
62. Lindenauer PK, Pekow P, Wang K, Mamidi DK, Gutierrez B, Benjamin EM. Perioperative beta-blocker therapy and mortality after major noncardiac surgery. *N Engl J Med* 2005;353:349-61.
63. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2006 guideline update on perioperative cardiovascular evaluation for noncardiac surgery: focused update on perioperative beta-blocker therapy: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol* 2006;47:2343-55.
64. Schouten O, Poldermans D, Visser L, et al. Fluvastatin and bisoprolol for the reduction of perioperative cardiac mortality and morbidity in high-risk patients undergoing noncardiac surgery: rationale and design of the DECREASE-IV study. *Am Heart J* 2004;148:1047-52.
65. Davignon J. Beneficial cardiovascular pleiotropic effects of statins. *Circulation* 2004;109:III-39-43.
66. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. *Circulation* 2001;103:926-33.
67. Pedersen TR, Kjekshus J, Berg K, et al. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). 1994. *Atheroscler Suppl* 2004;5:81-7.
68. Pedersen TR, Kjekshus J, Pyorala K, et al. Effect of simvastatin on ischemic signs and symptoms in the Scandinavian Simvastatin Survival Study (4S). *Am J Cardiol* 1998;81:333-5.
69. Kennedy J, Quan H, Buchan AM, Ghali WA, Feasby TE. Statins are associated with better outcomes after carotid endarterectomy in symptomatic patients. *Stroke* 2005;36:2072-6.
70. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA* 2004;291:2092-9.
71. O'Neil-Callahan K, Katsimaglis G, Tepper MR, et al. Statins decrease perioperative cardiac complications in patients undergoing noncardiac vascular surgery: the Statins for Risk Reduction in Surgery (STARRS) study. *J Am Coll Cardiol* 2005;45:336-42.
72. Paraskevas KI, Liapis CD, Hamilton G, Mikhailidis DP. Can statins reduce perioperative morbidity and mortality in patients undergoing noncardiac vascular surgery? *Eur J Vasc Endovasc Surg* 2006;32:286-93.
73. Kapoor AS, Kanji H, Buckingham J, Devereaux PJ, McAlister FA. Strength of evidence for perioperative use of statins to reduce cardiovascular risk: systematic review of controlled studies. *BMJ* 2006;333:1149.
74. Hindler K, Shaw AD, Samuels J, Fulton S, Collard CD, Riedel B. Improved postoperative outcomes associated with preoperative statin therapy. *Anesthesiology* 2006;105:1260-72.
75. Kertai MD, Boersma E, Westerhout CM, et al. Association between long-term statin use and mortality after successful abdominal aortic aneurysm surgery. *Am J Med* 2004;116:96-103.
76. Schouten O, Kertai MD, Bax JJ, et al. Safety of perioperative statin use in high-risk patients undergoing major vascular surgery. *Am J Cardiol* 2005;95:658-60.
77. Heesch C, Hamm CW, Laufs U, Bohm M, Snapinn S, White HD. Withdrawal of statins in patients with acute coronary syndromes. *Circulation* 2003;107:e27.
78. Spencer FA, Fonarow GC, Frederick PD, et al. Early withdrawal of statin therapy in patients with non-ST-segment elevation myocardial infarction: national registry of myocardial infarction. *Arch Intern Med* 2004;164:2162-8.
79. Schouten O, Hoeks SE, Welten GM, et al. Effect of statin withdrawal on frequency of cardiac events after vascular surgery. *Am J Cardiol* 2007;100:316-20.
80. Le Manach Y, Godet G, Coriat P, et al. The impact of postoperative discontinuation or continuation of chronic statin therapy on cardiac outcome after major vascular surgery. *Anesth Analg* 2007;104:1326-33.

81. Kertai MD, Boersma E, Westerhout CM, et al. A combination of statins and beta-blockers is independently associated with a reduction in the incidence of perioperative mortality and nonfatal myocardial infarction in patients undergoing abdominal aortic aneurysm surgery. *Eur J Vasc Endovasc Surg* 2004;28:343-52.
82. Lindblad B, Persson NH, Takolander R, Bergqvist D. Does low-dose acetylsalicylic acid prevent stroke after carotid surgery? A double-blind, placebo-controlled randomized trial. *Stroke* 1993;24:1125-8.
83. Taylor DW, Barnett HJ, Haynes RB, et al., ASA and Carotid Endarterectomy (ACE) Trial Collaborators. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. *Lancet* 1999;353:2179-84.
84. Robless P, Mikhailidis DP, Stansby G. Systematic review of antiplatelet therapy for the prevention of myocardial infarction, stroke or vascular death in patients with peripheral vascular disease. *Br J Surg* 2001;88:787-800.
85. Burger W, Chemnitz JM, Kneissl GD, Rucker G. Low-dose aspirin for secondary cardiovascular prevention—cardiovascular risks after its perioperative withdrawal versus bleeding risks with its continuation—review and meta-analysis. *J Intern Med* 2005;257:399-414.
86. Biondi-Zoccai GG, Lotrionte M, Agostoni P, et al. A systematic review and meta-analysis on the hazards of discontinuing or not adhering to aspirin among 50,279 patients at risk for coronary artery disease. *Eur Heart J* 2006;27:2667-74.