

Prevention of Acute Coronary Events in Noncardiac Surgery: Beta-blocker Therapy and Coronary Revascularization

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Authors and Disclosures

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Abstract

During major vascular surgery, patients are at high risk for developing myocardial infarction and myocardial ischemia, and two risk-reduction strategies can be considered prior to surgery: pharmacological treatment and prophylactic coronary revascularization. β -blockers are established therapeutic agents for patients with hypertension, heart failure and coronary artery disease. There is still considerable debate concerning the protective effect of β -blocker therapy towards perioperative coronary events, which will be outlined in this article. Two randomized, controlled trials suggest that coronary revascularization of cardiac-stable patients provides no benefits in the postoperative outcomes. In the current American College of Cardiology/American Heart Association guidelines for 'Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery', routine prophylactic coronary revascularization is not recommended in patients with stable coronary artery disease. However, a recent retrospective, observational study suggests that intermediate-risk patients may benefit from preoperative coronary revascularization. The present article provides an extended overview of leading observational studies, randomized, controlled trials, meta-analyses and guidelines assessing perioperative β -blocker therapy and prophylactic coronary revascularization.

Introduction

Among the 30 million patients undergoing noncardiac surgery in the USA annually, cardiac complications are the leading cause of perioperative morbidity and mortality.^[1] A pooled analysis of several large studies found an incidence of 2.5% for perioperative cardiac events in patients over the age of 40 years (range: 2.0-3.7%).^[2] These cardiac events were more common among vascular surgery patients, with an incidence of 6.2% (range: 2.2-19.0%).^[3] Symptoms of perioperative cardiac events are uncommon and it is suspected that 95% of the episodes are asymptomatic.^[1,4-8] The high frequency of perioperative cardiac complications reflects the high prevalence of underlying coronary artery disease (CAD).^[9] According to the American College of Cardiology (ACC)/American Heart Association (AHA) guidelines on Perioperative Care, patients with active cardiac conditions need to be evaluated and treated prior to surgery.^[10] Two risk-reduction strategies can be performed to reduce the incidence of cardiac complications: pharmacological treatment and prophylactic coronary revascularization. The present article provides an extended and detailed overview of leading observational studies, randomized, controlled trials and guidelines assessing perioperative β -blocker therapy and prophylactic revascularization. The randomized trials are summarized, allowing readers to place their strengths and weaknesses into perspective. Based on the current literature and our own experience, treatment recommendations in patients scheduled for noncardiac surgery are also provided.

Current Concepts in Perioperative β -blocker Therapy

β -blockers are established therapeutic agents for patients with hypertension,^[11] heart failure^[12] and CAD.^[13] In the nonsurgical setting, β -blockers are widely used for the prevention and treatment of ischemic heart disease and heart failure, which are major determinants of the occurrence of perioperative cardiovascular complications. Pharmacological risk reduction plays an important role in the reduction of perioperative cardiovascular complications, and multiple studies have been performed to assess the risk-reduction value of β -blockers. β -blockers are known to exert anti-arrhythmic, anti-inflammatory and anti-renin-angiotensin effects, as well as shifting energy metabolism.^[14-16] During surgery, high catecholamine production is responsible for vasoconstriction and hemodynamic stress, leading to an increased oxygen demand,^[1] which (in combination with perioperative tachycardia and increased myocardial contractility) can result in an oxygen supply-demand mismatch, causing myocardial infarction (MI) or ischemia.^[17,18] β -blockers have been demonstrated to reduce heart rate and contractile force and, therefore, tend to reduce the myocardial oxygen demand.

Several observational studies have demonstrated the beneficial effects of perioperative β -blocker treatment in reducing perioperative cardiovascular complications. Wallace *et al.* showed that treatment with the long-acting β -blocker atenolol resulted in a reduced incidence of postoperative ischemia by 30-50%.^[19] A retrospective study performed by Redelmeier *et al.* evaluated 37,151 elderly surgery patients treated with atenolol, using the database of the Canadian Institutes for

Health Information. They demonstrated that atenolol treatment was associated with greater cardioprotective benefits perioperatively, compared with treatment with short-acting β -blockers, such as metoprolol tartrate.^[20] Lindenauer *et al.* conducted a retrospective cohort study of 782,969 patients, using the Premier's Perspective database for 'small-to-midsized nonteaching hospitals' in the USA and concluded that preoperative β -blocker therapy was associated with a reduced risk of inhospital death in high-risk (but not in low-risk) patients undergoing vascular surgery. However, patients with moderate risk for CAD did not derive any benefits from β -blocker treatment and may experience worse outcomes compared with controls.^[21] An observational study conducted by Feringa *et al.* showed that bisoprolol treatment was associated with a reduced incidence of perioperative myocardial ischemia, detected with Holter monitoring (hazard ratio [HR]: 2.49; 95% CI: 1.79-3.48), and troponin T release (HR: 1.53; 95% CI: 1.16-2.03). They concluded that high-dose bisoprolol and concomitant tight heart-rate control may lead to reduced perioperative myocardial ischemia and troponin T release, thereby improving the long-term outcome.^[22] Several randomized, controlled trials have demonstrated beneficial effects of perioperative β -blocker treatment on the postoperative outcomes of surgery patients, of which the most important trials will be discussed in the following sections.

Mangano et al.

In 1996, Mangano *et al.* randomized 200 patients with either known or suspected CAD who were undergoing high-risk, noncardiac surgery to receive atenolol 50 or 100 mg, or placebo.^[23] They hypothesized that intensive perioperative β -blockade and strict heart rate control may limit the development of ischemia. Treatment was initiated prior to the induction of anesthesia, administered immediately following surgery and continued once-daily throughout the patients' hospital stay for up to 7 days after surgery ([Table 1](#)).^[23] In most patients, atenolol treatment was continued for up to 2 years following surgery. Although the study only demonstrated a perioperative effect towards ischemia (detected using Holter monitoring), atenolol use was associated with significantly lower mortality rates at 6 months after discharge (0 vs 8%; $p = 0.005$) and after 2 years (10 vs 21%; $p = 0.019$).

Table 1. Randomized, Controlled Trials Demonstrating a Beneficial Effect of Perioperative β -blockade Towards Cardiovascular Complications

Medscape						
Trial	Patients (n)	Trial protocol			Main findings	Ref.
		Inclusion criteria	Main exclusion criteria	Treatment		
Mangano <i>et al.</i> (1996)	200	Noncardiac surgery Presence of CAD ^a or at least two CAD risk factors ^b		Atenolol: treatment continued up to 7 days after surgery 5–10 mg intravenously 30 min before and after surgery 50–100 mg orally once a day, from day 1 to 7 following surgery	Atenolol treatment can reduce mortality and the incidence of cardiovascular complications for as long as 2 years after surgery	[23]
Raby <i>et al.</i> (1999)	26	Vascular surgery	Left-bundle branch block Left ventricular hypertrophy ST-T changes precluding accurate Holter interpretation	Esmolol: initiation immediately after surgery, 100–300 µg/kg/min intravenously for 48 h	Esmolol can reduce perioperative myocardial ischemia	[24]
DECREASE-I (1999)	112	Vascular surgery Patients with at least one cardiac risk factor ^b and ischemia during cardiac stress testing Strong evidence during stress testing of left main or severe three-vessel disease	Current β-blocker use or history of intolerance Extensive wall-motion abnormalities (WMI > 1.7 at rest)	Bisoprolol: initiation at least 1 week before surgery Treatment continued 30 days after surgery 5–10 mg orally once-daily for 30 days	Bisoprolol reduces the perioperative incidence of cardiovascular mortality and nonfatal MI	[25]
POISE (2008)	8351	Noncardiac surgery Expected hospital stay > 24 h Age ≥ 45 years At least one of the following criteria: history of CAD, PAD, stroke or hospitalization for CHF in previous 3 years, undergoing major vascular surgery or any three of seven risk criteria ^d	Current β-blocker use or history of intolerance Bradycardia Second- or third-degree AV block Low-risk surgical procedure	Metoprolol: initiation 2–4 h before surgery Treatment continued for 30 days after surgery 100 mg 2–4 h prior to surgery 100 mg up to 6 h after surgery and 200 mg 12 h later 200 mg orally once-daily for 30 days	Metoprolol prevents nonfatal MI but increases the risk of nonfatal stroke	[26]

^aPrevious MI, typical angina pectoris or atypical angina pectoris with a positive stress test.
^bAge > 65 years, hypertension, current smoking, hypercholesterolemia or diabetes mellitus.
^cAge > 70 years, angina, previous MI (on basis of history, pathologic Q-waves on ECG), CHF (history or compensated), current treatment for ventricular arrhythmias, current treatment for DM, limited exercise capacity.
^dUndergoing intra-thoracic or intra-peritoneal surgery, history of CHF, transient ischemic attack, diabetes mellitus, serum creatinine > 175 µmol/L, age > 70 years or undergoing emergency or urgent surgery.
 AV: Atrioventricular; CAD: Coronary artery disease; CHF: Chronic heart failure; DECREASE: Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DM: Diabetes mellitus; MI: Myocardial Infarction; PAD: Peripheral arterial disease; POISE: Perioperative Ischemic Evaluation; WMI: Wall-motion Index.

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Raby *et al.*

In 1999, Raby *et al.* were the first to demonstrate the beneficial effect of strict heart-rate control immediately after surgery.^[24] They included 26 major vascular surgery (MVS) patients with preoperative ischemia that was detected by Holter monitoring. These patients were randomized to receive β-blockade with esmolol or placebo immediately following MVS (Table 1).^[24] This study demonstrated that a reduction of postoperative heart rate to 20% below the ischemic threshold markedly reduced postoperative ischemia.

DECREASE-I Trial

Poldermans *et al.* performed a randomized, controlled Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography (DECREASE)-I trial to assess the effect of perioperative bisoprolol treatment on the incidence of death from cardiac causes and nonfatal MI within 30 days following MVS (Table 1).^[25] With the use of preoperative dobutamine stress-echocardiography, 112 patients with evidence of myocardial ischemia were included in the study and defined as high risk for cardiac events. A total of 59 patients were randomly assigned to receive bisoprolol, and 53 to receive standard care. Bisoprolol treatment was started an average of 37 days prior to MVS (Table 2), and careful titration was performed to prevent adverse side effects, such as hypotension and bradycardia. Compared with placebo, a reduction in the

incidence of perioperative cardiovascular death and MI from 34 to 3.4% ($p < 0.001$) was demonstrated in patients treated with bisoprolol.^[25]

POISE Trial

In 2008, the randomized, controlled Perioperative Ischemic Evaluation (POISE) trial was published and prompted discussion regarding β -blocker use in perioperative care. A total of 8351 patients were randomized to receive either metoprolol succinate or placebo ([Table 1](#)). Metoprolol succinate was administered at high dosages using the following treatment protocol: 100 mg was given 2-4 h prior to surgery, another 100 mg within 6 h, and followed by another 200 mg 12-18 h post-surgery if permitted by heart rate and blood pressure. Therefore, the maximum recommended daily dose of 400 mg was administered on the day of surgery and treatment was continued with 200-mg daily doses for 30 days post-surgery. The primary end point of cardiac death, MI or cardiac arrest was reduced in the metoprolol group compared with placebo (5.8 vs 6.9%, respectively; HR: 0.83; 95% CI: 0.70-0.99; $p = 0.04$). However, the 30% decrease in nonfatal MI (3.6 vs 5.1%; $p = 0.0008$) was accompanied by a 33% increase in total mortality (3.1 vs 2.3%; $p = 0.03$) and a twofold increased risk in stroke (1.0 vs 0.5%; $p = 0.0005$).^[26] Metoprolol succinate did lower the incidence of MI by more than 25% (from 5.7 to 4.2%); however, this benefit was outweighed by the previously mentioned increased incidence of stroke and death.^[26] Stroke was associated with perioperative bradycardia, hypotension and bleeding complications. *Post hoc* analysis also showed that hypotension had the largest population-attributable risk for death and stroke. Importantly, hypotension can be related to the use of a high dose of metoprolol without dose titration.

There is still considerable debate concerning the protective effect of β -blocker therapy towards perioperative coronary events, and several randomized, controlled trials have demonstrated negative results. We will discuss the most important trials to have questioned the use of perioperative β -blockade in the following sections.

POBBLE Trial

The randomized, placebo-controlled Perioperative β -blockade (POBBLE) trial included low-risk patients (history of ischemic heart disease was an exclusion criteria) scheduled for MVS.^[27] In total, 103 patients were randomized to receive either metoprolol 25 or 50 mg, or placebo ([Table 2](#)). Treatment began 1 day prior to surgery and continued until 7 days postoperatively. Although the POBBLE trial was designed to evaluate the effect of perioperative β -blockade in low-risk patients, they found a remarkable number of perioperative events (i.e., MI, unstable angina pectoris, ventricular tachycardia or stroke) in more than 30% of all patients who were supposed to have a low prevalence of pre-existing heart disease. Furthermore, this trial did not show a difference in the incidence of perioperative cardiovascular events between the two small,

randomized groups (placebo: 34%, metoprolol 32%; relative risk: 0.87; 95% CI: 0.48-1.55). However, the duration of hospitalization was shorter for those patients receiving metoprolol versus placebo (10 vs 12 days). It should be mentioned that the POBBLE trial only included 103 patients over a period of nearly 3 years and was discontinued because of poor recruitment and lack of funding.

Table 2. Randomized, Controlled Trials Demonstrating no Beneficial Effect of Perioperative β -blockade Towards Cardiovascular Complications

Medscape						
Trial	Patients (n)	Trial protocol			Main findings	Ref.
		Inclusion criteria	Main exclusion criteria	Treatment		
POBBLE (2005)	103	Vascular surgery patients	Current β -blocker use or history of intolerance MI, unstable AP or AP with a positive cardiac stress test	Metoprolol: initiation 1 day before surgery Treatment continued 7 days after surgery 2–4 mg intravenous 5–10 min before intubation 25–50 mg orally twice a day from day 1 to 7	Metoprolol did not seem to reduce 30-day cardiovascular events In patients receiving metoprolol treatment Time from surgery to discharge was decreased	[27]
MAVS (2006)	496	Vascular surgery patients ASA \leq 3	Current β -blocker use or history of intolerance History of CHF or AV block	Metoprolol: initiation day of surgery Treatment continued 5 days after surgery 25–100 mg orally 2 h before and after surgery 25–100 mg orally twice a day from day 1 to 5	Metoprolol was not effective in reducing the 30-day and 6-month postoperative cardiac event rates	[28]
DIPOM (2006)	921	Noncardiac surgery patients with diabetes mellitus Age \geq 40 years	Current β -blocker use or history of intolerance CHF New York Heart Association Class IV	Metoprolol: initiation 30 min before surgery Treatment continued up to 6 days after surgery 50 mg orally evening before surgery 100 mg orally 2 h prior to surgery 100 mg orally once a day from day 1 to 6	Metoprolol did not significantly affect mortality and cardiac morbidity	[29]
BBSA (2007)	224	Surgery with spinal block, in-hospital stay > 24 h Presence of CAD or at least two CAD risk factors*	Current β -blocker use or history of intolerance History of CHF, high-degree heart block or LBBB	Bisoprolol: initiation at least 3 h before surgery Treatment continued up to 10 days after surgery 5–10 mg orally 3 h before and 6 h after surgery 2–10 mg orally once a day from day 1 to 10	Bisoprolol did not affect cardiovascular outcome	[30]

*Age > 65 years, hypertension, current smoking, hypercholesterolemia or diabetes mellitus.
 AP: Angina pectoris; ASA: American Society of Anaesthesiologists; AV: Atrioventricular; BBSA: β -Blocker in Spinal Anesthesia; CAD: Coronary artery disease; CHF: Chronic heart failure; DIPOM: Diabetic Postoperative Mortality and Morbidity; LBBB: Left-bundle branch block; MAVS: Metoprolol After Vascular Surgery; MI: Myocardial infarction. POBBLE: Perioperative β -Blockade.

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MAVS Trial

The Metoprolol After Vascular Surgery (MAVS) trial randomized 496 patients to receive metoprolol or placebo. Medical treatment started 2 h prior to surgery and continued until hospital discharge or 5 days after surgery ([Table 2](#)).^[28] In the MAVS trial, there was no difference between the metoprolol- and placebo-treated groups for the occurrence of cardiovascular death, MI, heart failure, arrhythmias or stroke 30 days postoperatively (10.2 and 12%, respectively; $p = 0.057$).

DIPOM Trial

The randomized, controlled Diabetic Postoperative Mortality and Morbidity (DIPOM) trial also did not show a difference in 30-day morbidity and mortality between metoprolol- and placebo-treated groups (21 vs 20%; $p = 0.66$). This trial included 921 diabetic patients, randomized to receive metoprolol 100 mg or placebo. Treatment was started the evening before major noncardiac surgery ([Table 2](#)). The DIPOM trial concluded that perioperative metoprolol did not significantly affect mortality and cardiac morbidity in patients with diabetes.^[29]

BBSA Trial

The double-blinded, placebo-controlled, Swiss β -blocker in Spinal Anesthesia (BBSA) trial noted that bisoprolol therapy did not affect cardiovascular outcomes in elderly patients undergoing surgery with neuraxial blockade ([Table 2](#)).^[30] The lack of benefit of β -blocker treatment could be explained by the varying cardiac risk profiles of the patients included and the fact that it was an underpowered study. Interestingly, the authors suggest that polymorphisms in β_1 -adrenergic receptor genotypes could be associated with different responses to β -blocker therapy and may be of use to optimize therapy by maximizing efficacy and limiting toxicity.^[30]

A meta-analysis performed by Bangalore *et al.* was published in the *Lancet* in 2008 and included 33 randomized trials, with a total of 12,306 patients, evaluating perioperative β -blocker therapy. They concluded that β -blocker treatment resulted in 16 fewer nonfatal MIs per 1000 patients, but at the expense of three nonfatal, disabling strokes and possibly three fatal cardiac or noncardiac complications.^[31] Based on these results, the main conclusion was that evidence does not support the use of perioperative β -blocker therapy in surgery patients. However, the authors acknowledged that results derived from the POISE trial had the greatest influence on their results.

A comment from Boersma and Poldermans was published in the same edition of the *Lancet*, in which they concluded that the general mechanism underlying the excess cerebral complications is unknown and additional hemodynamic data are needed. They stated that these data will be crucial to future updates of treatment guidelines.^[32]

Discussion: Perioperative β -blockade

There are different explanations regarding the conflicting evidence for perioperative β -blocker use. Important factors that may relate to the effectiveness of β -blocker therapy are the patients' underlying cardiac risk and variations of treatment protocols in initiation time, β -blocker type, starting dose, dose adjustments for heart-rate control and duration of treatment.

Patients' Cardiac Risk Profiles

Boersma *et al.* have suggested that the absolute risk reduction associated with β -blocker treatment is most pronounced in patients who are at high risk for coronary events.^[33] The MAVS trial and DIPOM trial both included many patients at low risk for cardiovascular complications. In the MAVS trial, almost 60% of the patients had a Lee Risk Index of only one. This is in contrast to the DECREASE-1 trial, which randomized vascular surgery patients with a positive dobutamine echocardiography, so that only 112 patients from an initial population of 1351 patients met the entrance criteria of inducible myocardial ischemia. The high incidence of perioperative cardiovascular events could be explained by the selection of high-risk cardiac patients, in which bisoprolol treatment was highly effective in reducing perioperative cardiovascular mortality and nonfatal MI.

Treatment Protocols

The initiation time of β -blocker treatment may be related to the effectiveness of β -blocker therapy. In the DECREASE-I trial, the mean time between initiation of β -blocker treatment and surgery was 37 days and the largest effect of perioperative β -blocker treatment was demonstrated.^[25] By contrast, the POBBLE, MAVS, DIPOM and BBSA trials began treatment either 1 day prior to or on the day of surgery.

The type of β -blocker used may influence the effectiveness of β -blocker therapy. Negative inotropic and chronotropic effects derived from selective β_1 -blockade are thought to exert the most beneficial perioperative effects towards cardiovascular outcome. This may be the reason why treatment with the highly β_1 -selective β -blocker bisoprolol was associated with better results compared with metoprolol or atenolol, which are moderately β_1 -selective.

Aside from the initiation time, the administered dosage of β -blocker was also different among the randomized studies we assessed. In the POISE trial, metoprolol succinate could have been administered on the first day of surgery at a dose of up to 400 mg, which is 100% of the maximum daily therapeutic dose. In the nonsurgical setting, much lower starting doses are recommended; for instance, in patients with New York Heart Association Class II heart failure, starting doses of 12.5-25 mg daily are administered for 2 weeks, and for hypertension, the initial dose is between 25 and 100 mg, and usually increased at weekly intervals. In the editorial to the

publication of the POISE trial, Fleisher and Poldermans compared the POISE trial results with results from the DECREASE-I trial, in which patients undergoing MVS were treated with low-dose bisoprolol (between 5 and 10 mg once-daily).^[34] The incidence of stroke in the DECREASE-I trials was 0.4%, which is comparable with placebo, while maintaining a significant reduction in cardiac death and nonfatal MI from 34% in the standard-care group to 3.4% in the bisoprolol-treated group in the first DECREASE-I trial.^[25,34] The DECREASE-I trial has demonstrated that low-dose bisoprolol treatment is associated with overall benefits compared with risks.

To maximize the benefit a patient will receive from β -blocker treatment, tight heart-rate control is paramount, without overtreating the patient. Analyzing the safety and tolerability of β -blockers is as important as assessing the beneficial effects of β -blockers regarding efficacy. The most important side effects to be expected with β -blocker treatment are bradycardia and hypotension, which usually occur dose-dependently. The use of a fixed versus an individualized dose titrated to the patients heart rate may also be of importance. As recommended by the guidelines for treatment of congestive heart failure and shown in β -blocker studies for treatment of heart failure, such as the Cardiac Insufficiency Bisoprolol Study (CIBIS) studies, β -blocker treatment should begin with a very low dose and then be uptitrated to the maximum tolerated dose.^[12,35] Titration according to tolerance is of utmost importance to obtain tight heart-rate control and prevent adverse side effects such as hypotension. The value of adequate heart-rate control in improving cardiovascular outcome is not only confirmed in a recent large meta-analysis,^[36] the latest 2007 ACC/AHA guidelines on perioperative care also strongly recommend achieving a heart rate of 65-70 bpm.^[10]

A factor that could also influence the effect of β -blockers in surgical patients is the duration of β -blocker treatment. Withdrawal of β -blocker therapy shortly before surgery or in the immediate postoperative period may contribute to adverse myocardial effects resulting from a 'rebound' effect, thereby inducing increased arterial blood pressures, heart rates and plasma noradrenalin concentrations.^[37] Discontinuation of β -blocker therapy immediately after MVS could increase the risk of postoperative cardiovascular mortality,^[38] and early withdrawal of β -blockers after surgery is associated with a higher 1-year mortality compared with continuous β -blocker therapy, which highlights the importance of continuing β -blocker therapy in the perioperative period.^[39] Recently, it has been suggested that the long-term beneficial effects of β -blocker therapy may be explained by a decrease in the progress of coronary atherosclerosis.^[40] In contrast to the instant effect on heart-rate control, the effect of β -blockers on plaque stabilization may, therefore, only be achieved after prolonged treatment. As demonstrated by Mangano *et al.*, treatment with atenolol during hospitalization can reduce mortality and the incidence of cardiovascular complications for as long as 2 years following noncardiac surgery.^[23] In most patients, atenolol treatment was indeed continued for up to 2 years after surgery.

Guidelines

Current recommendations concerning perioperative β -blocker use, as provided in the ACC/AHA 2006 Guideline Update on 'Perioperative Cardiovascular Evaluation for Noncardiac Surgery: Focused Update on Perioperative β -blocker Therapy', are illustrated in [Box 1](#).^[41] Although these guidelines advocate perioperative β -blocker use, data from observational studies and registries observe a poor compliance with guidelines in pharmacological treatment. Several studies have demonstrated that there is still an underuse of β -blockers in patients undergoing MVS, even when patients are considered to be at high risk for cardiovascular events and despite a worldwide increase in β -blocker prescription.^[39,42]

Box 1. American College of Cardiology/American Heart Association recommendations, Focused on Perioperative β -blocker Therapy



Medscape

Class I

- β -blockers should be continued in patients undergoing surgery who are receiving β -blockers to treat angina, symptomatic arrhythmias, heart failure, hypertension or other Class I guideline indications (Level of Evidence: C)
- β -blockers should be given to patients undergoing vascular surgery at high cardiac risk owing to the finding of ischemia on preoperative testing (Level of Evidence: B)

Class IIa

- β -blockers are probably recommended for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk, as defined by the presence of multiple clinical risk factors* (Level of Evidence: B)
- β -blockers are probably recommended for patients in whom preoperative assessment for vascular surgery identifies high cardiac risk as defined by the presence of multiple clinical risk factors* (Level of Evidence: B)
- β -blockers are probably recommended for patients in whom preoperative assessment identifies coronary artery disease or high cardiac risk as defined by the presence of multiple clinical risk factors* and who are undergoing intermediate- or high-risk procedures (Level of Evidence: B)

Class IIb

- β -blockers may be considered for patients who are undergoing intermediate- or high-risk procedures, including vascular surgery, in whom preoperative assessment identifies intermediate cardiac risk as defined by the presence of a single clinical risk factor* (Level of Evidence: C)
- β -blockers may be considered for patients undergoing vascular surgery with low cardiac risk who are not currently taking β -blockers (Level of Evidence: C)

Class III

- β -blockers should not be given to patients undergoing surgery who have absolute contraindications to β -blockade (Level of Evidence: C)

*Clinical predictors of increased perioperative risk: major – unstable coronary syndromes, decompensated heart failure, significant arrhythmias and severe valvular disease; intermediate – mild angina pectoris, previous myocardial infarction, compensated or prior heart failure, diabetes mellitus and renal dysfunction; minor – advanced age, abnormal ECG, rhythm other than sinus, low functional capacity, history of stroke and uncontrolled systemic hypertension.
Data from [41].

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Current Concepts in Prophylactic Revascularization

In patients undergoing MVS surgery, there is a high prevalence of significant CAD. A classification of 1000 coronary angiograms in peripheral arterial disease patients, performed by Hertzler *et al.*, demonstrated a prevalence of 18% for patients with severe three-vessel disease and 4% for patients with left main disease. In patients undergoing MVS, preoperative cardiac-risk evaluation by means of risk-factor assessment and noninvasive testing may often identify patients at increased cardiac risk. These patients may either have documented symptomatic involvement or be fully asymptomatic. Therefore, in patients requiring MVS within a matter of weeks or a few months, the need for diagnostic evaluation and subsequent revascularization will need to be questioned. When the presence of CAD is confirmed by angiography or cardiac computed tomography, coronary revascularization via percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) can be considered as prophylactic therapy prior to noncardiac surgery in these patients.^[9] However, the cumulative risk of prophylactic coronary revascularization and MVS needs to be weighed up against the risk of the surgical procedure performed without preoperative interventions. Several observational studies have evaluated the value of prophylactic revascularization to prevent adverse cardiovascular events after noncardiac surgery.^[43-48] In 1997, Eagle *et al.* evaluated 24,959 participants with suspected CAD in the Coronary Artery Surgery Study database. They demonstrated that, among the 1961 patients undergoing higher-risk surgery, prior CABG was associated with fewer postoperative deaths compared with medically managed coronary disease.^[48] The value of PCI prior to MVS was retrospectively evaluated by Gottlieb *et al.*, who found a low rate of perioperative cardiovascular events.^[45] Fleisher *et al.* retrospectively included 6895 patients, a random sample of the Medicare population, and demonstrated a reduced long-term mortality among patients who had previously undergone revascularization (i.e., PCI or CABG) and underlined the need for a randomized trial to determine the value of preoperative revascularization.^[46] Back *et al.* concluded that previous coronary revascularization, defined as CABG fewer than 5 years or PCI fewer than 2 years prior to surgery, may only have a modest beneficial effect in preventing adverse cardiovascular events, and stated that further evaluation by randomized trials was needed.^[47] Two prospective, randomized trials have provided new insights concerning preoperative interventions: the Coronary Artery Revascularization Prophylaxis (CARP) trial and the DECREASE-V trial.

CARP Trial

The CARP trial, conducted by McFalls and colleagues, screened 5859 patients at 18 Veterans Affairs US hospitals and was the first prospectively randomized study to investigate the benefit of coronary revascularization before elective MVS.^[49] In total, 510 patients with significant coronary artery stenosis were randomized to either revascularization or no revascularization prior to MVS ([Table 3](#)). The main finding of the CARP trial was that there was no difference in the primary

outcome of long-term mortality (median follow-up: 2.7 years) in patients who underwent preoperative coronary revascularization, compared with patients who received optimized medical therapy (22 vs 23%, relative risk: 0.98; 95% CI: 0.70-1.37). No reduction in the number of MIs, deaths or length of hospital stay was observed within 30 days. Although the study was not powered to test the short-term benefit of prophylactic revascularization, results point to the suggestion that prophylactic revascularization may not provide additional benefits in reducing the incidence of perioperative and long-term cardiac morbidity and mortality in cardiac-stable MVS patients. As the majority of patients in the CARP trial only had one- or two-vessel disease with a preserved left ventricular function, the optimal preoperative management for patients with left main disease, severe left ventricular dysfunction, unstable angina pectoris and aortic stenosis was not determined yet. As already noted, the CARP trial included 5859 patients from which 1048 patients underwent coronary angiography prior to vascular surgery. These patients were used by the CARP investigators in a subanalysis to determine the impact of prophylactic coronary revascularization on long-term survival in patients with multivessel CAD.^[50] They demonstrated that 382 (36.5%) of the 1048 patients presented with multivessel CAD without previous CABG. No long-term survival benefit was observed in patients with two- and three-vessel disease. However, in a cohort of 48 patients (4.6%) with left main coronary artery stenosis, preoperative revascularization did seem to have an improved 2.5-year survival (84 vs 52%; $p < 0.01$). A secondary analysis of the CARP trial that solely evaluated patients with significant CAD and either critical limb ischemia or intermittent claudication indicated that mortality and morbidity were not improved by coronary artery revascularization prior to vascular surgery.^[51] Another subgroup analysis of the CARP trial, performed by Ward *et al.*, demonstrated that rates of perioperative and long-term MIs were lower in patients who had undergone CABG prior to vascular surgery, compared with patients with preoperative PCI. In the CABG group, the length of hospital stay was also decreased, and the authors concluded that this observation may be related to more complete revascularization in the CABG group.^[52]

Table 3. Randomized, Controlled Trials Evaluating the Use of Prophylactic Revascularization Prior to Vascular Surgery

Medscape					
Trial	Patients (n)	Patient population		Main findings	Ref.
		Inclusion criteria	Main exclusion criteria		
CARP (2004)	510	Elective vascular surgery patients CAG: stenosis of at least 70% in one or more major coronary arteries suitable for revascularization	Prior revascularization without evidence of recurrent ischemia CAG: stenosis of left main coronary artery of at least 50% LVEF < 20% or severe aortic stenosis	In patients with stable CAD, coronary-artery revascularization does not improve long-term survival	[49]
DECREASE-V (2007)	101	Elective vascular surgery patients ≥ three cardiac risk factors* Extensive stress-induced ischemia during cardiac stress testing	Emergency surgery patients	Preoperative coronary revascularization was not associated with an improved outcome	[53]

*Age > 65 years, hypertension, current smoking, hypercholesterolemia or diabetes mellitus.
CAD: Coronary artery disease; CAG: Coronary angiography; CARP: Coronary Artery Revascularization Prophylaxis; DECREASE: Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; LVEF: Left ventricular ejection fraction.

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DECREASE-V Trial

In the prospectively randomized DECREASE-V trial, comparable results to the CARP trial were obtained; however, this trial mainly included patients with three-vessel disease.^[53] Cardiac-stable, elective MVS patients were screened for the following risk factors: age of more than 70 years, history of MI, presence of angina pectoris, congestive heart failure, diabetes mellitus or renal dysfunction, and history of cerebrovascular events (Table 3). In total, 430 patients with three or more clinical risk factors underwent cardiac-stress testing, from which 101 (23%) patients showed extensive stress-induced ischemia. The patients with extensive stress-induced ischemia were randomly assigned to receive either no revascularization (n = 52) or revascularization (n = 49). Of the 49 patients assigned for revascularization, 12 (24%) had two-vessel disease, 33 (67%) had three-vessel disease and four (8%) had left main disease. Although the study population in the DECREASE-V trial reflects MVS patients at highest cardiac risk, revascularization did not improve cardiovascular outcomes. The incidence of the composite end point of 30-day cardiovascular mortality and MI was 43 versus 33% (odds ratio: 1.4; 95% CI: 0.7-2.8). Furthermore, no benefit was observed during 1-year follow-up after coronary revascularization: 49 versus 44% (odds ratio: 1.2; 95% CI: 0.7-2.3; p = 0.48). Comparable with the DECREASE-I trial, a high incidence of perioperative cardiovascular events was observed.^[25] This could be explained by the selection of high-risk cardiac patients with extensive ischemia during cardiac stress testing.

In 2007, Landesberg *et al.* included 502 patients in a retrospective observational study, in which thallium scanning was performed prior to MVS. They demonstrated improved long-term survival in patients with moderate-to-severe ischemia who were undergoing preoperative revascularization.^[54] Furthermore, Landesberg *et al.* constructed a long-term survival score (LTSS) for the prediction of cardiac risk in patients undergoing MVS. On the basis of the following

risk factors, MVS patients were stratified to be at low, intermediate or high cardiac risk: age of more than 65 years, presence of diabetes mellitus or congestive heart failure, history of previous MI, chronic renal dysfunction, cerebrovascular disease and ST-segment depression on ECG. Intermediate-risk patients (two or three LTSS risk factors) were most likely to benefit from preoperative coronary revascularization (3-year mortality, odds ratio: 0.45; 95% CI: 0.21-0.97, and long-term mortality; HR: 0.48; 95% CI: 0.31-0.75; p = 0.001). Patients with a low-risk LTSS score (0 or 1) had good long-term survival that was not affected by revascularization. High-risk patients (LTSS > 4) had poor long-term survival, which was also unaffected by revascularization.^[55,56]

Discussion: Prophylactic Revascularization

The main difference between the CARP trial and the retrospective study conducted by Landesberg *et al.* was the criteria for patients inclusion. In the CARP trial, patients with left main disease were excluded and 33% of the enrolled patients had three-vessel disease. By comparison, in the study conducted by Landesberg *et al.*, 73% of the enrolled patients had left main or three-vessel disease.^[54] In the DECREASE-V trial, preoperative dobutamine stress echocardiography, stress nuclear imaging and cardiac-risk scores were used to identify cardiac high-risk patients. Therefore, the DECREASE-V trial mainly included patients with three-vessel disease, the group most likely to benefit from prophylactic revascularization. The majority of patients in the CARP trial had one- or two-vessel disease.^[53] In an editorial paper by Garcia and McFalls, it was reported that patients with major risk factors (i.e., unstable coronary syndromes, decompensated congestive heart failure, severe valvular abnormalities and life-threatening arrhythmias) were not included in the major randomized trials because the unstable cardiac status would probably influence the postoperative cardiovascular outcome.^[50] No trials exist investigating the role of prophylactic revascularization in patients with unstable angina pectoris requiring MVS. However, if MVS can be postponed safely, diagnosis and treatment for these patients should be in line with the recent guidelines on unstable angina management.^[13]

Guidelines

In the current ACC/AHA guidelines for 'Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery', it is stated that coronary revascularization before noncardiac surgery is useful in patients with acute ST-elevation MI, non-ST-elevation MI, high-risk unstable angina or stable angina in combination with significant left main coronary artery stenosis, three- or two-vessel disease with significant proximal left anterior descending stenosis and either an ejection fraction of less than 50% or ischemia during noninvasive testing.^[10] Furthermore, it is stated that the usefulness of preoperative coronary revascularization is not well established for high-risk ischemic patients (with an abnormal dobutamine stress echocardiogram with wall motion

abnormalities in at least five segments) or low-risk ischemic patients (wall motion abnormalities in up to four segments).^[10] In patients with stable CAD, routine prophylactic coronary revascularization is not recommended prior to noncardiac surgery.^[10] In patients who undergo coronary angiography without stent placement, noncardiac surgery should be postponed for at least 2 weeks.^[57] Regarding the management of patients with previous coronary stenting undergoing noncardiac surgery, a time window to surgery of at least 6 weeks for bare-metal stents and 1 year for drug-eluting stents is recommended.^[58] For CABG, noncardiac surgery should be postponed for at least 1 month.^[57]

Expert Commentary & Five-year View

The value of perioperative β -blocker therapy and preoperative prophylactic coronary revascularization has been widely debated over the years. Garcia and McFalls state in their editorial paper that it is time for clinicians to shift the emphasis from extensive preoperative testing to evidence-based medical therapies, including β -blocker treatment.^[59]

We agree with this statement and propose that all patients undergoing high-risk surgical procedures, such as open vascular surgery, should be treated with low-dose β -blockade, preferably the β_1 -selective β -blocker bisoprolol. Treatment should be initiated at least 30 days prior to surgery, and to maximize the beneficial effects, titration according to tolerance and heart-rate control to between 65 and 70 bpm is of utmost importance. Furthermore, we promote the idea of prolonged treatment after surgery. Next to β -blockers, patients should also receive statins and aspirin, to optimize medical treatment. In all patients with unstable angina and coronary artery stenosis, prophylactic revascularization should be performed, preferably prior to surgery if surgery can be safely postponed. Asymptomatic patients or patients with one- or two-vessel coronary disease (not including left main disease) should receive optimal medical treatment without the need for coronary revascularization. Asymptomatic patients with left main, two- or three-vessel disease with significant proximal left anterior descending stenosis and either an ejection fraction of less than 50% or ischemia during noninvasive testing should receive coronary revascularization, next to optimal medical therapy. If noncardiac surgery can be postponed, coronary revascularization should be performed prior to surgery. However, if noncardiac surgery cannot be postponed, coronary revascularization should still be performed after surgery.

Future randomized trials are needed to further evaluate the value of β -blocker therapy and prophylactic revascularization. Withdrawal of β -blocker therapy shortly before surgery, or in the immediate postoperative period, may contribute to adverse myocardial effects resulting from a rebound effect, leading to increases in arterial blood pressure, heart rate and plasma noradrenalin concentrations. Intraoperative infusion with esmolol may be effective in preventing intraoperative tachycardia and reduce intraoperative left ventricular contractile force. The short-

acting character of esmolol and continuous hemodynamic monitoring during surgery limit potential adverse side effects, such as hypotension or bradycardia. The beneficial effect of intraoperative esmolol treatment next to pre- and post-operative treatment with low-dose bisoprolol may further improve postoperative outcome, which should be evaluated in randomized, controlled trials. Prophylactic treatment of high-risk patients with CABG or PCI apparently provides insufficient extra protection on top of β -blocker treatment as demonstrated in the CARP and DECREASE-V trials. Retrospective data indicate that prophylactic revascularization may be the most effective option in intermediate-risk cardiac patients. To assess the additional value of prophylactic revascularization next to optimal medical therapy, future randomized trials are needed, focusing on coronary revascularization and low-dose β -blocker treatment in low-, intermediate- and high-risk patient groups.

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