Vascular and Endovascular Surgery

Preoperative Cardiac Evaluation of the Vascular Surgery Patient—An Anesthesia Perspective

Hesham R. Omar, Devanand Mangar and Enrico M. Camporesi

The online version of this article can be found at:

Published by:

$SAGE

Additional services and information for *Vascular and Endovascular Surgery* can be found at:

Email Alerts: http://ves.sagepub.com/cgi/alerts

Subscriptions: http://ves.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

Citations: http://ves.sagepub.com/content/46/3/201.refs.html

>> Version of Record - May 7, 2012

OnlineFirst Version of Record - Mar 9, 2012

What is This?

Preoperative Cardiac Evaluation of the Vascular Surgery Patient—An Anesthesia Perspective

Hesham R. Omar, MD[1], Devanand Mangar, MD[2], and
Enrico M. Camporesi, MD[2,3]

Abstract

The morbidity and mortality associated with vascular surgery procedures are largely the results of cardiac events. National guidelines have been regularly proposed and updated by the American College of Cardiology (ACC)/American Heart Association (AHA) to ensure optimal perioperative management and risk stratification. Controversy remains between experts and other cardiology societies regarding several patient care issues including revascularization before surgery, timing of β-blocker therapy, and the administration of antiplatelet therapy. Several landmark articles recently published have helped to modify the guidelines in the hope of improving vascular patient outcomes. In this review, we searched all recent available literature pertaining to perioperative cardiac evaluation before major vascular surgery. We propose an algorithm for preoperative cardiac evaluation, which is a modification to the AHA recommendations. Incorporated in this algorithm are recent published pivotal articles that can help in guiding physicians caring for the vascular patient requiring major operative or endovascular interventions.

Introduction

The leading cause of mortality and morbidity following major vascular surgery procedures is cardiac events such as myocardial infarction (MI), arrhythmia, and heart failure. Approximately 230 million patients undergo major surgery annually with a perioperative MI incidence[1] of approximately 1%. The incidence is higher in patients undergoing major vascular surgery procedures because they are older and have both increased cardiovascular risk factors and, in approximately one third, known coronary artery occlusive disease. Standard of care dictates that a thoughtful evaluation of the cardiac risk should be performed prior to elective surgery in all vascular patients. In this review, we discuss the relevant issues regarding preoperative cardiac assessment, perioperative risk factor management, and the expected benefit to the vascular patient requiring major "open" or endovascular arterial interventions. Our intent was to develop a clinically useful, evidence-based algorithm for preoperative cardiac assessment.

Perioperative Cardiac Risk

The vascular patients requiring abdominal aortic aneurysm (AAA) repair or lower limb revascularization should be considered "high risk" for ischemic cardiac event. The occurrence of MI can be caused by coronary artery plaque rupture and subsequent vessel thrombosis or supply–demand mismatch exacerbated by tachycardia and hypertension.[2] Surgery is associated with increased production of catecholamine leading to vasoconstriction and hemodynamic stress[3] and subsequent increased oxygen demand to the myocardium. When the increased oxygen demand is not met by a proportional increase in the oxygen supply, myocardial ischemia can occur. The propensity of the surgical stress to induce plaque rupture was demonstrated by Dawood et al[4] and Cohen and Aretz[5] in 55% and 46% of patients, respectively, who developed fatal perioperative MI. This mechanism is likely presented in the vascular surgery patients with a known higher prevalence of coronary artery disease (CAD) in addition to other cardiovascular risk factors such as hypertension, hyperlipidemia, and diabetes present in more than one half of patients.

[1] Internal Medicine Department, Mercy Hospital and Medical Center, Chicago, IL, USA
[2] CEO, Florida Gulf to Bay Anesthesiology (FGTBA) Tampa, FL, USA
[3] University of South Florida, Tampa, FL, USA

Corresponding Author:
Enrico M. Camporesi, University of South Florida College of Medicine, Tampa General Circle, Suite A327, Tampa, FL 33606, USA
Email: ecampore@health.usf.edu

Procedural and postoperative fluid shifts caused by blood loss and hypotension are another contributing factors increasing the cardiac risk associated with major arterial repairs. Precise fluid administration can restore the preload and afterload of the left ventricle[6] and attenuate the resulting tachycardia caused by volume loss. In these patients, increased myocardial oxygen demands can lead to the episodes of myocardial ischemia.[7] It is well established that patients who experience a perioperative acute MI have angiographic evidence of extensive CAD.[8]

The likelihood of adverse cardiac events is highest with major "open" arterial repairs of the aorta, visceral arteries, and with lower limb revascularization for critical limb ischemia. Endovascular AAA repair, carotid endarterectomy, and extremity percutaneous transluminal angioplasty are considered intermediate cardiac risk procedures because of their associated lower blood loss, reduced myocardial stress, and less fluid shifts.[9,10] Dialysis access procedures, surgery for varicose veins, and minor extremity amputation involving the foot or digits are low-risk surgeries. All emergent or urgent peripheral arterial interventions, that is, embolectomy, graft thrombectomy, and arterial repair should be considered "high risk" for cardiac events. The value of this procedure-dependent classification is to develop appropriate cardiac evaluation to decrease cardiac event rates and perioperative myocardial ischemia.

It is well known that more than 80% of the perioperative MI are asymptomatic and 60% to 100% are of the non-Q-wave type; therefore, many cardiac events are not recognized or treated, which may contribute to an increase in long-term cardiovascular mortality.[11-15] In vascular surgery patients, asymptomatic troponin elevation has been associated with an increased risk of more than 4- to 6-fold of cardiac events during a 6-month follow-up.[16] Early mortality after perioperative MI ranges between 3.5% and 25% and is proportionate to the level of troponin elevation, especially persistant abnormal levels of tropoin.[17]

Preoperative Assessment

There are many factors that determine the outcomes of the vascular surgery, the most important of which are cardiac factors, especially CAD. According to American Heart Association (AHA) guidelines, vascular surgery is a high cardiac-risk surgery with a cardiac morbidity of greater than 5%. Several scoring systems have been adapted to stratify patient's risk prior to noncardiac surgery. In 1996, American College of Cardiology (ACC)/AHA guidelines developed guidelines for preoperative cardiac assessment that relied on the Eagle criteria for risk evaluation,[18] which included patients older than 70 years, diabetes mellitus (DM), angina, renal insufficiency, Q waves in electrocardiogram (EKG), ventricular arrythmias, and a history of congestive heart failure. The modifications to the Eagle criteria incorporated in the 1996 AHA guidelines were the inclusion of the functional capacity and using any previous

history of MI (a more sensitive indicator of coronary ischemia) rather than Q waves on EKG. These guidelines[19] were later updated in 2002.

Recent studies for preoperative cardiac assessment relied on the basis of the original Goldman index that was developed in 1977[20] and was later replaced in 1986 by the modified cardiac risk index. In 1999, Lee et al[21] identified, from a data set of 4315 patients undergoing noncardiac surgery, 6 independent predictors of complications and developed the Revised Cardiac Risk Index (RCRI). The 6 factors included in the RCRI are high-risk surgical procedures, history of ischemic heart disease, history of congestive heart failure, history of cerebrovascular disease, DM requiring insulin treatment, and preoperative serum creatinine of >2.0 mg/dL. Rates of major cardiac complications among 1422 patients with 0, 1, 2, or ≥3 of these factors were 0.4%, 0.9%, 7%, and 11%, respectively. Patients with 3 or more points are considered at high risk and those with 1 or 2 points are considered at intermediate risk.

In 2005, Boersma et al retrospectively evaluated the ability of the Lee index (RCRI) to predict cardiovascular death in 108 593 patients who underwent noncardiac surgery at the Erasmus Medical Center from 1991 to 2000. They concluded that if age and more detailed information regarding the type of surgery were included, the area under the curve for the prediction of cardiovascular mortality using the Lee index[22] increased from 0.63 to 0.85. The ACC/AHA committee chose to replace the intermediate risk category with 5 risk factors from the Lee score, with the exclusion of the type of surgery that is incorporated elsewhere in the management algorithm, which further emphasizes the importance of the RCRI index. We have developed an algorithm for preoperative cardiac assessment prior to high-risk vascular surgery taking into account the updated 2007[23] ACC/AHA guidelines and results from recent landmark articles (Figures 1 and 2).

Prophylactic Coronary Artery Revascularization

The prevalence of CAD in vascular surgery patients approaches 50%[24] reflecting the importance of perioperative cardiac assessment to rule out reversible ischemia. Initially, experts recommended that preoperative revascularization appears to be beneficial for patients with unstable symptoms or for whom coronary artery bypass grafting (CABG) offers a long-term survival benefit.[25,26] Also, retrospective studies indicated a better long-term outcome with revascularization.[27] However, other studies favored a more conservative approach after the retrospective data of patients undergoing vascular surgery revealed higher procedure-related complications leading to critical delays in surgery.[28] Other landmark articles have been published to demonstrate the outcome of patients undergoing coronary revascularization with either percutaneous coronary intervention (PCI) or CABG.
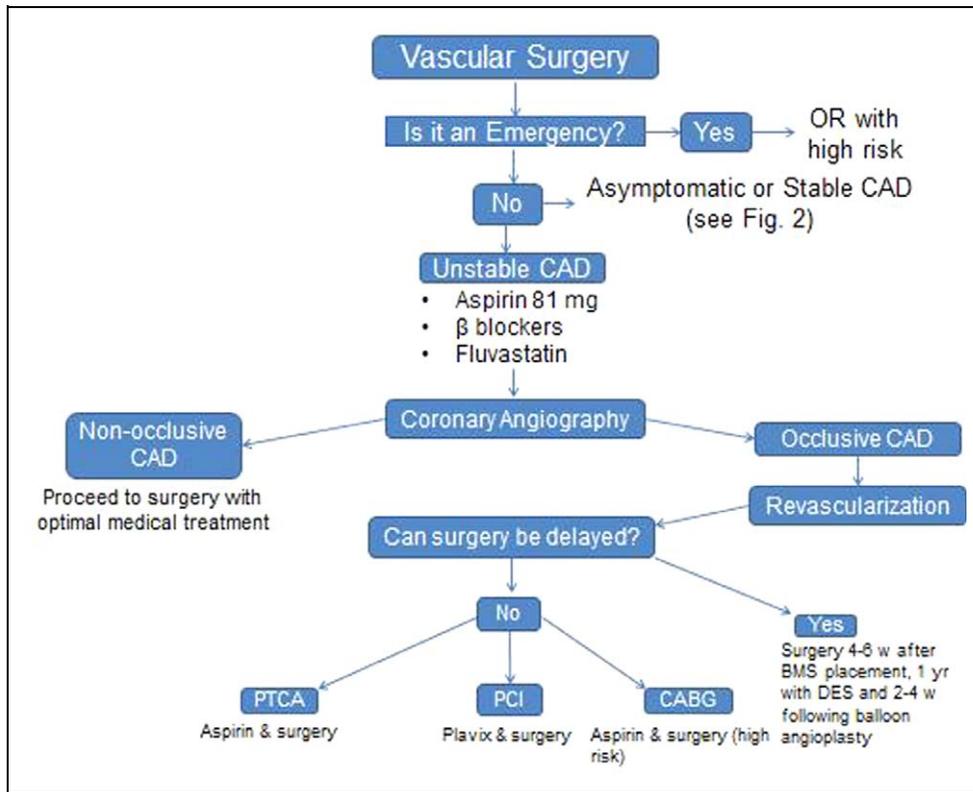
Figure 1. Algorithm for preoperative cardiac evaluation in patients with unstable coronary artery disease prior to major vascular surgery.
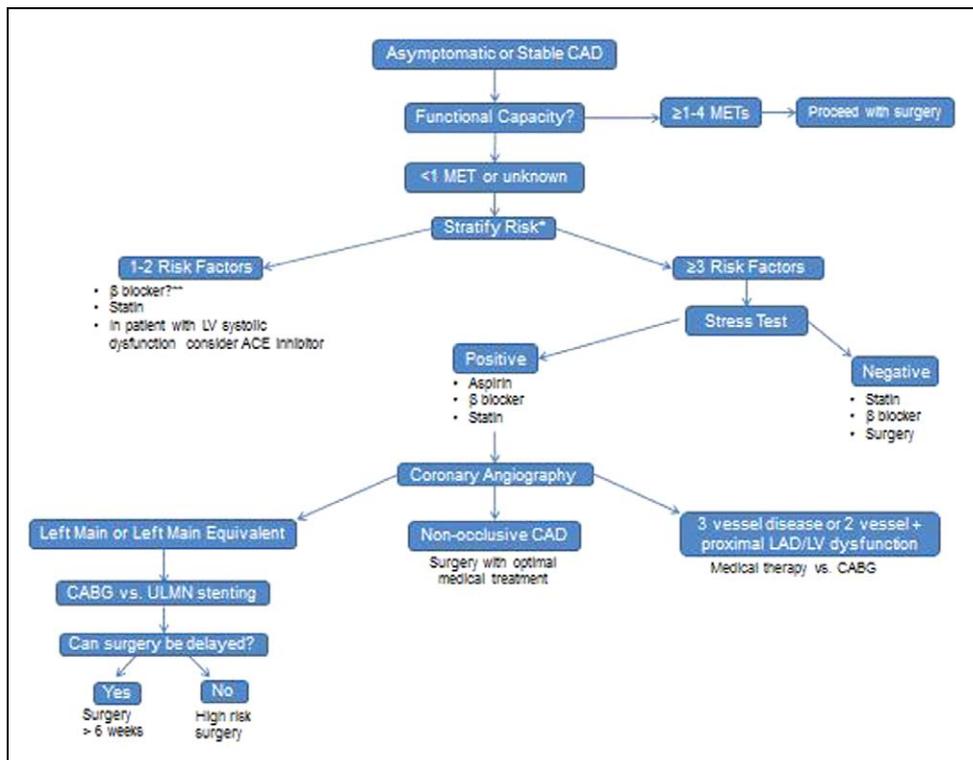
Figure 2. Algorithm for preoperative cardiac evaluation prior to major vascular surgery in asymptomatic patients or those with stable CAD. *The 5 risk factors include ischemic heart disease, compensated or prior heart failure, diabetes mellitus, renal insufficiency, and cerebrovascular disease. **Differing guideline recommendations, class I in ESC and class IIa in the ACC/AHA guidelines. ULMN indicates unprotected left main; ESC, European Society of Cardiology; ACC/AHA, American College of Cardiology/American Heart Association.

Percutaneous Coronary Intervention Before Surgery

In a retrospective study by Posner et al of patients who underwent noncardiac surgery, there were no significant outcome benefits in patients with recent percutaneous transluminal coronary angioplasty (PTCA; ≤90 days before surgery) when compared with matched controls with nonrevascularized CAD (odds ratio [OR]: 0.90; P = .396).[29] Patients revascularized by PTCA for >90 days before surgery had a lower risk of poor outcomes than nonrevascularized patients, although not as low as normal controls.[29] In 2003, Wilson et al[30] evaluated 207 patients undergoing noncardiac surgery within 2 months after successful PCI and described 8 patients (4%) who suffered major cardiac events. These 8 patients were among 168 patients who underwent surgery within 6 weeks of PCI. No major complication was observed in the 39 patients who had surgery 7 to 9 weeks after stent placement. He concluded that, when possible, noncardiac surgery should be delayed at least 6 weeks after a stent placement, by which time stents are generally endothelized, and a course of antiplatelet therapy to prevent stent thrombosis has been completed.

Therefore, we recommend that if there are no signs of active ischemia and if coronary angiography does not reveal significant stenosis of the left main, left main equivalent, severe 3 vessel disease or 2 vessel disease with a critical proximal LAD, then the patient can proceed with vascular surgery. Myocardial revascularization can be performed at a later time, preferably after 6 weeks.

Coronary Artery Bypass Grafting Before Surgery

The coronary artery revascularization prophylaxis (CARP) trial was conducted on 510 patients with stable CAD randomized to either coronary revascularization (PCI 59% and CABG 41%) or no revascularization to assess long-term benefits.[31] After 2.7 years of randomization, there was no significant mortality difference (22% and 23% in the revascularization and no-revascularization group, respectively, relative risk 0.98; 95% CI: 0.70-1.37; P = .92) or postoperative MI at 30 days (12% and 14% in the revascularization and no-revascularization group, respectively; P = .37). Reanalysis of the CARP results by the type of procedure (CABG vs PCI) revealed lower death and MI rates in the CABG group.[32] Further analysis revealed that only 1 subgroup benefited from preoperative revascularization, namely, patients with left main disease.[33] In a subsequent randomized trial by Poldermans et al, there was no advantage for preoperative coronary revascularization.[34] Revascularization prior to vascular surgery is therefore best advised for patients with unstable CAD or those with left main disease.

Timing of Vascular Surgery After Revascularization

The AHA guidelines for antiplatelet therapy after PCI recommends that clopidogrel (Plavix, Bristol-Myer Squibb/Sanofi,

Brisgewater) should be continued for at least 1 month after bare metal stent deployement and for 1 year after drug eluting stent deployement to decrease the incidence of stent thrombosis. The traditional management has been favoring bare metal stent placements for the patients who are expected to have surgery within 1 month for the expected need to stop clopidogrel therapy. Although it had long been advised that patients who will need surgery require discontinuation of clopidogrel, the pivotal article by Stone et al demonstrated that no difference in the incidence of transfusion among antiplatelet treatment groups in addition to no statistically significant difference regarding reoperation for bleeding.[35] This study is expected to change the abovementioned management strategy.

On the other hand, in a retrospective case-control study, higher mortality was demonstrated in patients who underwent high-risk vascular surgery within 1 month of CABG with a trend toward a higher incidence of MI than those undergoing surgery at a later date.[36] A previous study by Reul et al demonstrated a higher mortality in patient undergoing CABG and vascular surgery either simultaneously (10% of patient) or during the same hospitalization (10% of the patients) and a mortality of only 0.2% when the vascular surgery was performed during a different hospital admission.[37] Cruchley et al also demonstrated increased mortality in patients undergoing noncardiac surgery within 1 to 6 months of CABG when compared with surgery performed later than 6 months.[38]

Left Main Disease Prior to Major Vascular Surgery

The CABG has long been considered the standard treatment option for patients with left main disease (left main disease [LMND])[39] based on previous randomized and observational studies.[40] Over the past decade, stenting of the left main has been utilized in cases of LMND to avert the need for CABG in patients with significant comorbidities. The main risk with unprotected left main stenting is the expected occurrence of stent-related complications including dissection, thrombosis, and in-stent stenosis. However, recent advances in the PCI technology with the development of drug eluting stents in addition to the evolution of dual antiplatelet therapy have reshaped the utilization of PCI in left main disease.

The outcome of the SYNTAX trial, the major randomized controlled trial that compared the outcome of left main stenting and CABG, revealed comparable safety and efficacy outcomes between both the groups, but higher incidence of repeat revascularization in the PCI group.[41] There are no randomized control studies comparing the outcome of left main stenting versus CABG in patients with left main disease undergoing major vascular surgery. Reul et al demonstrated a higher mortality in patients undergoing CABG and vascular surgery simultaneously or during the same hospitalization.[37] Whether PCI is favorable over

Table 1. The 8 studies describing the outcome of peri-operative Beta blocker use

References	N	Drug	Onset	Surgery	Results
Mangano[44]	200	Atenolol, 50-100 mg	Before induction and 7 days postoperatively	Noncardiac surgery	Reduced mortality over 6 months (0% vs 8%, $P < .001$), over the first year (3% vs 14%, $P < .005$), and over 2 years (10% vs 21% $P < .019$).
DECREASE 1[45]	112	Bisoprolol, 5-10 mg	Started 1 week before surgery till 30 days postoperatively	Major vascular surgery	3.4% of patients in the bisoprolol group died of cardiac causes when compared with 17% in standard therapy group ($P = .02$). Nonfatal MI occurred in 0% in bisoprolol group in comparison with 17% ($P < .001$)
Lindenauer et al[46]	122 338	Undetermined	Hospital day 2	Major noncardiac surgery	RCRI score 0 or 1, no benefit and possible harm. RCRI score 2,3 or 4, or more, adjusted OR for in-hospital death is 0.88, 0.71, or 0.58, respectively
POBBLE[49]	103	Metoprolol, 50 mg BID	Day before surgery till 7 days	Infrarenal vascular surgery	No difference in 30 days cardiovascular events (34% and 32% in the placebo and metoprolol groups, respectively, 95% confidence interval, 0.53-1.66).
MAVS[48]	496	Metorpolol, 25-100 mg	2 Hours preoperatively and 5 days after surgery or discharge	Vascular surgery	No difference in 30 days or 6-month cardiac events (primary outcome at 30 days occurred in 10.2% vs 12.0%in metoprolol and placebo groups respectively; $P = .57$). At 6 months, no significant difference ($P = .81$).
DIPOM[50]	921	Metoprolol, 100 mg SR	1 Day preoperatively to 8 days postoperatively	Major noncardiac surgery	Primary outcome occurred in 21% and 20% in metoprolol and placebo, respectively (CI: 0.80-1.41), during a median follow-up of 18 months. All-cause mortality was 16% in both groups (CI: 0.74-1.42; $P = .88$).
BBSA[51]	224	Bisoprolol, 5 mg	3 Hours before surgery till discharge or 10 days.	Surgery with spinal block.	Primary outcome was 22.7% and 22.0% in bisoprolol and placebo group during the 1-year follow-up ($P = .90$).
POISE[47]	8351	Metoprolol ER, 200 mg.	2 to 4 hours before to 30 days postoperatively	Noncardiac surgery	Fewer MI ($P = 0.0017$) and more stroke ($P = .0053$) in metoprolol group.

Abbreviations: RCRI, Revised Cardiac Risk Index; MI, myocardial infarction; OR, odds ratio; BID, twice a day.

CABG in this group of patients undergoing major vascular surgery is yet to be studied.

Perioperative β-Blockers

Reduction of the perioperative adrenergic stress response is the key pathophysiological intervention that explains improved cardiac outcome with perioperative β-blocker therapy. β-Blockers decrease the heart rate with subsequent prolongation of the diastolic filling time, thus reducing the systolic blood pressure and force of ventricular contraction in addition to their well-known antiarrythmic properties. β-Blockers have also been shown to exert a coronary plaque stabilizing effect.[42,43] Several studies were conducted to evaluate the effect of β-blocker therapy on perioperative cardiac damage. Table 1 lists all these 8 studies and their outcomes. A special reference is given to the number of patients in

each study, type of β-blocker used, onset of start of the β-blockers prior to surgery, and the type of surgery, that is, whether noncardiac surgery or vascular surgery. While the initial studies by Mangano et al,[44] Poldermans et al,[45] and Lindenauer et al[46] concluded a statistically significant benefit for the β-blocker group over the placebo group, the POISE trial,[47] the MAVS study by Yang et al,[48] the POBBLE study,[49] the DIPOM study,[50] and the BBSA study[51] showed no statistically significant difference between both the groups.

In the DECREASE trial, bisoprolol was titrated to achieve a heart rate of 60 to 70 and was titrated 30 days prior to major vascular surgery and was continued for 30 days. The incidence of primary end points, a composite of death from cardiac cause or nonfatal MI was reduced from 34% in the standard therapy group to 3.4% in the bisoprolol group ($P < .001$). In the study by Lindenauer et al on 122 338 patients, β-blockers were started on the hospital day 2. Patients in whom β-blockers were started on the hospital day 3 or after were grouped with the control group. The study showed an improved in-hospital deaths in the β-blocker group with RCRI score 2, 3, 4, or more with an adjusted OR of 0.88 (95% confidence interval [CI]: 0.8-0.98), 0.71 (95% CI: 0.63-0.8), and 0.58 (95% CI: 0.5-0.67), respectively. The early utilization of β-blockers in these 2 studies might explain the superiority of the β-blocker group regarding the outcome. Therefore, one can hypothesize when analyzing this table that onset of starting β-blocker therapy played a pivotal role in the outcome. It is also important to realize that administering β-blockers is not sufficient to produce the beneficial effect, but titrating to target heart rate and blood pressure should be encouraged.

On the contrary, it is clear that in the study by Yang et al, β-blockers were started only 2 hours preoperatively and there was no statistically significant difference between both the groups. In the POBBLE trial, metoprolol was started the day before surgery and also there was no statistically significant difference in the outcome between the metoprolol and placebo group (34% and 32% in the placebo, 95% CI: 0.53-1.66). In the DIPOM study, 921 patients were randomized to either 100 mg of metoprolol or placebo and metoprolol was given the day before major noncardiac surgery. There was no statistically significant difference between both the groups during a median of 18-month follow-up (all-cause mortality was 16% in both groups, CI: 0.74-1.42; $P = .88$). In the BBSA study performed on 224 patients randomized to either bisoprolol given 3 hours prior to surgery or placebo, there was also no significant difference in primary outcome between both the groups 22.7% versus 22.0% in bisoprolol versus placebo group during the 1-year follow-up (hazard ratio, 0.97; 95% CI: 0.55-1.69; $P = .90$). Finally in 2008, the POISE trial was published, which randomized 8351 patients to either extended release metoprolol or placebo. Metoprolol was given without any titration 2 to 4 hours prior to surgery and the maximum recommended dose was prescribed during the first 24 hours (200 mg). Although there was a clear-cut reduction in primary end points, a composite of cardiovascular death, nonfatal MI, or nonfatal cardiac arrest (5.8% vs 6.9% with placebo $P = .399$), there was a

significant 33% increase in the total mortality and a 2-fold increased risk of stroke compared with the placebo group. Most of the mortalities with the metoprolol group was caused by strokes due to cerebral infarction and not hemorrhage (3 of 60).

One can conclude that in all the 4 studies that showed no significant benefit for perioperative β-blockers, the onset of starting the drug was either immediately before or the evening prior to the surgery. This might have affected the outcome of these studies because β-blockers were not given enough time in advance to allow for titration to target heart rate. In the DECREASE study, the 53 patients who were excluded from the bisoprolol group as they were already taking β-blockers underwent planned vascular surgery under continued but not specified β-blocker therapy. In this subpopulation, the 30-day perioperative cardiac mortality was 7.5%, which is twice as high as that reported in the randomized part of the trial suggesting that perioperative β-blocker therapy might be less effective when target heart rate and blood pressure are not achieved.

The design and results of the POISE trial were later critically questioned by Poldermans and others, who thought that the dose of the metoprolol was excessive and that the drug was only given 2 to 4 hours prior to surgery. Poldermans et al then studied β-blockers and stroke in a meta-analysis of the 7 major studies and concluded that there was a higher incidence of stroke in the β-blocker group. However, when used in a small dose and up-titrated in the perioperative period, the risk of stroke seems to be similar to that of those who do not receive β-blockers, while the cardioprotective effects are maintained. These studies and especially the POISE have contributed to several controversies between the AHA association and the European Society of Cardiology guidelines.

When Should We Start β-Blocker Therapy?

Perioperative cardioprotection was demonstrated when the β-blockers were initiated either weeks before the scheduled surgery[45] or as late as during induction of anesthesia.[44] However, it is well known that the desired effect of plaque stabilization is likely to take weeks of β-blocker therapy to develop. Also, the earlier the β-blocker therapy is started, the more time you have to titrate and achieve the target heart rate and blood pressure. In his study on 940 patients undergoing vascular surgery, Flu et al concluded that β-blocker treatment initiated more than 1 week before surgery is associated with lower preoperative heart rate and improved outcome when compared with treatment initiated <1 week preoperatively.[52] Treatment initiated >1 to 4 or >4 weeks before surgery was associated with a lower 30-day cardiac events (OR: 0.46, 95% CI: 0.27-0.76, OR: 0.48, 95% CI: 0.29-0.79) and long-term mortality (hazard ratio: 0.52, 95% CI: 0.21-0.67, hazard ratio: 0.50, 95% CI: 0.25 to 0.71) when compared with treatment initiated <1 week preoperatively. The improved outcome in the group that received β-blockers >1 week was attributed to better rate control. Therefore, one can explain the results of the POISE trial by the late onset of administration, just 2 to 4 hours

prior to the surgery. The European Society of Cardiology (ESC) guidelines recommend starting β-blockers optimally 30 days or at least 1 week before surgery and the AHA guidelines recommends starting days to weeks before surgery.

Which β-Blocker and What Target Should be Achieved

As clear from Table 1, in the 8 studies, comparing the outcome of β-blockers versus placebo, totally 3 β-blockers were used; atenolol, metoprolol, and bisoprolol. Atenolol was used in 1 study (did not reach significance), metoprolol in 4 studies (1 of 4 reached significance), and bisoprolol in 2 studies (1 of 2 reached significance). There was no head-to-head comparison between different classes of β-blockers regarding the outcomes and so far, there is no data to suggest superiority of 1 β-blocker over the other. Once the drug is titrated to achieve the therapeutic goal, outcome should improve. In the meta-analysis of Poldermans et al, who compared all 3 drugs and stroke outcome, while metoprolol was associated with a higher incidence of perioperative stroke, atenolol and bisoprol were not.[53] The increased stroke incidence with metoprolol was observed in 1 of the 4 studies that utilized this drug, which was the POISE. However, these results were later questioned. High-dose β-blocker (200-400 mg metoprolol) might block the heart rate response to hypotension (in cases of bleeding), which might explain the higher risk of stroke in the POISE study.

The target of β-blocker therapy is to slowly achieve the optimal heart rate and blood pressure control, which are the markers of the patient's sympathetic tone. In patients not on chronic β-blocker therapy, the drug should be started at a low dose and titrated slowly. In patients on chronic β-blocker therapy, it is better to continue the same β-blocker class and make sure it is also titrated to achieve target heart rate and blood pressure. The definition of target heart rate and blood pressure was determined by the ESC[54] and AHA[55] association guidelines with slight differences between the both. While the ESC guidelines recommended a target heart rate of 60 to 70 bpm, the AHA adapted a more flexible definition and recommended a target heart rate of 60 to 80 bpm. In the ESC guidelines, β-blocker therapy should be omitted if systolic blood pressure is not >100 mm Hg, while in the AHA, it should be omitted if there is hypotension (level not defined).

How Long Should it be Continued

In the 8 studies listed in Table 1, β-blockers were continued to 5 to 30 days postoperative. In the DECREASE study, of 101 survivors, 57 continued taking bisoprolol and 44 were on standard care and were followed up to 2 years with an end point of cardiac death and MI.[56] The incidence of cardiac events during follow-up in the bisoprolol group was 12% versus 32% in the standard care group ($P = ·025$). The study concluded that bisoprolol reduces long-term cardiac death and MI in high-risk patients after vascular surgery. However, in the study by

Mangano et al,[44] treatment was stopped after discharge, and at 2-year follow-up, patients previously treated with atenolol had a significantly lower overall death rate than those given placebo. Freedom from any cardiac event was also greater in patients given atenolol (82% vs 68%); concluding that there was no clear benefit of sustained β-blocker therapy. Therefore, the optimal duration for β-blockers in these patients is still controversial. Nonetheless, patients who were on β-blockers for any indication preoperatively should indefinitely continue taking it.

Guidelines Controversies Regarding Perioperative β-Blockers

The conflicting results of these 8 major trials and especially the most recent large POISE trial have led to several controversies between the AHA[55] and the ESC guidelines.[54] Both the guidelines agreed that the patients on chronic β-blocker treatment should be maintained on this medication throughout the perioperative period (class 1). A major difference between both the guidelines is in patients undergoing high risk or vascular surgery, which is considered a class 1 indication for β-blockers in the ESC guidelines but a class IIb in AHA guidelines (in patients with no other risk factors). Another major difference is that the patients with known ischemic heart disease or evidence of myocardial ischemia on preoperative testing are considered a class 1 indication in the ESC guidelines but a class IIa indication in the AHA guidelines. Both the guidelines recommended starting β-blockers ideally 30 days or at east 7 days prior to the surgery. The target heart rate is 60 to 70 bpm in the ESC and 60 to 80 bpm in the AHA guidelines. Therefore, administration of β-blockers needs to be decided according to a case by case basis.

Discontinuing β-Blockers

Discontinuation of long-term β-blockers is another important concern. This sometimes happens in surgical patients when oral β-blocker therapy is not changed to its equivalent intravenous dose in the perioperative period. At times, it is only changed to a PRN order to be given only when the patient's blood pressure is elevated. Discontinuation of β-blockers has been associated with an elevation in heart rate and blood pressure[57] and an increased risk of myocardial ischemia. Hypertensive patients have a transient 4-fold increase in the relative risk of coronary heart disease after stopping their β-blockers.[58] Withdrawal of β-blockers after cardiac surgery has also been associated with myocardial ischemia.[59] In a study of 140 patients on preoperative β-blockers undergoing vascular surgery, Shammash et al compared 2 groups of patients to be either continuing (132) or discontinuing their β-blockers (8).[60] All-cause mortality in the 8 patients, where β-blockers were discontinued postoperatively (50%) was significantly greater than in the 132 patients with continued β-blocker administration

(1.5%, OR: 65.0, $P < .001$) in addition to an increased cardiovascular mortality (0% vs 29%, $P = .005$) and postoperative MI (OR: 17.7, $P = .003$). The effects of withdrawal of other medications including calcium channel antagonists and angiotensin-converting enzyme inhibitors were also examined and were not associated with any statistically significant MI or mortality. In cases where there is a clear contraindication to β-blockers, it has been advised to discontinue therapy gradually after a period of 30 days postoperatively.[61]

Perioperative Statin Therapy

As discussed earlier regarding the pathophysiology of perioperative myocardial ischemia, type 1 MI due to plaque instability needs a multifactorial strategy to combat the ischemia with β-blockers, aspirin and the addition of statins to reduce coronary inflammation.[62] Ridker et al found that the patients with acute coronary syndrome who experience a decline in the level of high-sensitivity C-reactive protein after statin therapy have better outcomes regardless of their level of low-density lipoprotein.[63] The DECREASE III trial demonstrated the significant reductions in perioperative myocardial ischemia and cardiovascular death with extended-release (ER) fluvastatin 80 mg without any associated increase in liver dysfunction or myopathy.[64] Retrospective cohort data have also demonstrated reductions in perioperative cardiac complications with statin in vascular surgery.[65-67] The ER formulation is particularly beneficial for patients who can be given nothing by mouth in the postoperative period. Statins have also been found to be helpful in restoring kidney function after aortic cross-clamping during vascular surgery. Another important concern is that statin withdrawal prior to surgery because of absence of IV forms is associated with increased cardiac events.[68] In the most recent ESC guidelines, initiation of statins is indicated in patients undergoing high risk surgery (optimally between 30 days and 1 week prior to surgery).

Clopidogrel (Plavix R) and Other Antiplatelets

Antiplatelet therapy is another major debate prior to vascular surgery. Treatment with aspirin or clopidogrel is recommended in patients with CAD to prevent cardiovascular events. Low-dose aspirin of 81 mg is just as effective as high dose aspirin (325 mg) in decreasing the combined end points of vascular death, MI, and stroke. This is especially important in patient with concomitant CAD with recent stent deployment. The AHA guidelines recommend at least 1 month of clopidogrel therapy prior to vascular surgery in bare metal stent and 1 year of clopidogrel for drug eluting stent. This can represent a challenge for the patient requiring vascular surgery because of the expected increase in bleeding complications. The most recent ESC guidelines recommended continuation of aspirin in the perioperative

period for patients previously treated with aspirin and this is a class IIa indication. Stone et al have recently demonstrated in their study on 10 406 patient undergoing vascular surgery randomized to either aspirin alone, clopidogrel alone, aspirin and clopidogrel, or neither, that there was no difference in the incidence of transfusion utilization among antiplatelet treatment groups (none: 18%, acetylsalicylic acid [ASA]: 17%, clopidogrel: 0%, ASA/clopidogrel: 24%, $P = .1$).[35] Reoperation for bleeding was also not significantly different (none: 1.5%, ASA: 1.3%, clopidogrel: 0.9%, ASA/clopidogrel: 1.5%, $P = .74$). He concluded that clopidogrel can safely be continued preoperatively in patients with appropriate indications for its use, such as symptomatic carotid disease or recent drug-eluting coronary stents.[35]

Conclusions

After the release of the 2007 guidelines and its update in 2009, several landmark articles have been published that are expected to reshape the algorithm of cardiac assessment prior to major vascular surgery (Figures 1 and 2). These articles answered many questions that have been debatable, until recent times. We provided an algorithm for preoperative cardiac assessment, management, and risk stratification for patient undergoing major vascular surgery, illustrated in Figures 1 and 2. This algorithm is based on the most recent ACC/AHA guidelines in addition to other major articles that affect the recent evaluation process. There are several comments. First, the utilization of preoperative β-blockers is mandatory in patients previously on β-blockers (class I in both AHA and ESC) and in patients undergoing vascular surgery who are high cardiac risk (class I in ESC but class IIa in AHA guidelines). Second, the utilization of long-acting statins is supported, preferably fluvastatin, in patients undergoing vascular surgery for its favorable effects. Third, the decision regarding stopping clopidogrel prior to surgery in patients with recent PCI and bare metal stents <1 month or drug eluting stents [DES] <1 year undergoing vascular surgery should be revisited in the face of the recent trial by Stone et al,[35] which showed no increase in bleeding complications or need for transfusion. Duration of vascular surgery after revascularization should be delayed to more than 6 weeks if possible, to improve outcome. Patient with left main disease undergoing major vascular surgery, which carries high surgical risk can be offered left main DES placement instead of CABG. The purpose of this preoperative summary is not only to give medical clearance and assess the patient's cardiac risk prior to vascular surgery but rather to suggest recommendations for optimizing the patient's condition prior to surgery. No test should be performed unless we think it will change the management options and affect the patient's outcome. The anesthesiologist, the vascular surgeon, and the cardiologist must coordinate the best care in order to offer best outcomes to the patient. Table 2 presents a review of most frequent issues pertaining to perioperative cardiac evaluation in vascular surgery.

Table 2. Review of Most Frequent Issues Pertaining to Perioperative Cardiac Evaluation in Vascular Surgery

Preoperative revascularizaton	• Only patients with unstable CAD or left main disease seem to benefit for revascularization. • Routine prophylactic revascularization prior to surgery is not associated with better outcome. • After revascularization, delay surgery 2 to 4 weeks after balloon angioplasty, 4 to 6 weeks after BMS and 1 year after DES placement.
Perioperative B-blockers	• Perioperative beta blockade is beneficial in those previously on β-blockers and those with reversible ischemia on preoperative testing. • Start β-blockers at least 1 week or optimally 1 month prior to surgery. • Beta blockade should be started with low dose and titrated slowly to achieve target heart rate.
Aspirin	• Low dose aspirin of 81 mg is effective as high dose aspirin, 325 mg in decreasing combined end points of vascular death, MI, and stroke. • Continuation of aspirin in the perioperative period for patients previously treated with aspirin (class IIa indication).
Plavix	• In patients with recent PCI undergoing urgent or emergent vascular surgery, clopidogrel can be continued to avoid adverse outcomes.
Statins	• In patients on statins, long acting statins should be started perioperative and continued postoperatively.

Abbreviations: BMS, bare metal stent; CAD, coronary artery disease; DES, drug eluting stents; MI, myocardial infarction; PCI, percutaneous coronary intervention.

References

1. Weiser TG, Regenbogen SE, Thompson KD, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. *Lancet*. 2008;372(9633):139e44.
2. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50(22):2173e95.
3. Mangano DT. Perioperative medicine: NHLBI working group deliberations and recommendations. *J Cardiothorac Vasc Anesth*. 2004;18(1):1e6.
4. Dawood MM, Gutpa 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(1):37e44.
5. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. *Cardiovasc Pathol*. 1999;8(3):133e9.
6. Schrier RW, Ecder T. Gibbs memorial lecture. Unifying hypothesis of body fluid volume regulation: implications for cardiac failure and cirrhosis. *Mt Sinai J Med*. 2001;68(6):350e61.
7. Doesch AO, Celik S, Ehlermann P, et al. Heart rate reduction after heart transplantation with beta-blocker versus the selective If channel antagonist ivabradine. *Transplantation*. 2007;84(8):988e96.
8. Ellis SG, Hertzer NR, Young JR, Brener S. Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. *Am J Cardiol*. 1996;77(12):1126-1128
9. Elkouri S, Gloviczki P, McKusick MA, et al. Perioperative complications and early outcome after endovascular and open surgical repair of abdominal aortic aneurysms. *J Vasc Surg*. 2004;39(3):497-505.
10. Brown OW, Hollier LH, Pairolero PC, Kazmier FJ, McCready RA. Abdominal aortic aneurysm and coronary artery disease. *Arch Surg*. 1981;116(11):1484-1488.
11. Badner NH, Knill RL, Brown JE, et al. Myocardial infarction after noncardiac surgery. *Anesthesiology*. 1998;88(3):572-578.
12. Fleisher LA, Nelson AH, Rosenbaum SH. Postoperative myocardial ischemia: aetiology of cardiac morbidity or manifestation of underlying disease? *J Clin Anesth*. 1995;7(2):1-6.
13. Landesberg G, Mosseri M, Wolf Y, et al. Perioperative myocardial ischemia and infarction. Identification by continuous 12-lead electrocardiogram with online ST-segment monitoring. *Anesthesiology*. 2002;96(2):262-270.
14. Schouten O, Dunkelgrun M, Feringa HH, et al. Myocardial damage in high-risk patients undergoing elective endovascular or open infrarenal abdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg*. 2007;33(5):544-549.
15. McFalls EO, Ward HB, Moritz TE, et al. Predictors and outcomes of a perioperative myocardial infarction following elective vascular surgery in patients with documented coronary artery disease: results of the CARP trial. *Eur Heart J*. 2008;29(3):394-401.
16. Raby KE, Goldman L, Cook EF, et al. Long-term prognosis of myocardial ischemia detected by Holter monitoring in peripheral vascular disease. *Am J Cardiol*. 1990;66(19):1309-1313.
17. Kim LJ, Martinez EA, Faraday N, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. *Circulation*. 2002;106(18):2366-2371.
18. Eagle KA, Brundage BH, Chaitman BR, et al. Guidelines for perioperative cardiovascular evaluation for noncardiac surgery. Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol*. 1996;27(4):910-948.
19. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA Guideline Update for Perioperative Cardiovascular Evaluation for Noncardiac Surgery—Executive Summary. A report of the American College of Cardiology/American Heart Association Task Force

on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Anesth Analg*. 2002;94(5):1052-1064.

20. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med*. 1977;297(16):845-850.

21. 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(10): 1043-1049.

22. 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(10):1134-1141.

23. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: 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). *Anesth Analg*. 2008; 106(3):685-712.

24. Hertzer NR, Young JR, Kramer JR, et al. Routine coronary angiography prior to elective aortic reconstruction: results of selective myocardial revascularization in patients with peripheral vascular disease. *Arch Surg*. 1979;114(11):1336-1344.

25. American College of Physicians. Guidelines for assessing and managing the perioperative risk from coronary artery disease associated with major noncardiac surgery. *Ann Intern Med*. 1997;127(4):309-312.

26. Eagle KA, Berger PB, Calkins H, et al. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol*. 2002;39:542-553.

27. Hertzer NR, Young JR, Bevern EG, et al. Late results of coronary bypass in patients with peripheral vascular disease. II. Five-year survival according to sex, hypertension, and diabetes. *Cleve Clin J Med*. 1987;54(1):15-23.

28. Mesh CL, Cmolik BL, Van Heekeren DW, et al. Coronary bypass in vascular patients: a relatively high-risk procedure. *Ann Vasc Surg*. 1997;11(6):612-619.

29. Posner KL, Van Norman GA, Chan V. Adverse cardiac outcomes after noncardiac surgery in patients with prior percutaneous transluminal coronary angioplasty. *Anesth Analg*. 1999;89(3):553-560.

30. Wilson HS, Fasseas P, Orford JL, et al. Clinical outcome of patients undergoing non-cardiac surgery in the two months following coronary stenting. *J Am Coll Cardiol*. 2003;42(2): 234-240.

31. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med*. 2004;351(27):2795-2804.

32. Ward HB, Kelly RF, Thottapurathu L, et al. Coronary artery bypass grafting is superior to percutaneous coronary intervention in prevention of perioperative myocardial infarctions during

subsequent vascular surgery. *Ann Thorac Surg*. 2006;82(3): 795-800; discussion 800-801.

33. Garcia S, Moritz TE, Ward HB, et al. Usefulness of revascularization of patients with multivessel coronary artery disease before elective vascular surgery for abdominal aortic and peripheral occlusive disease. *Am J Cardiol*. 2008;102(7):809-813.

34. Poldermans D, Schouten O, Vidakovic R, et al; DECREASE Study Group. 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(17):1763-1769.

35. Stone DH, Goodney PP, Schanzer A, et al; Vascular Study Group of New England. Clopidogrel is not associated with major bleeding complications during peripheral arterial surgery. *J Vasc Surg*. 2011;54(3):779-784.

36. Breen P, Lee JW, Pomposelli F, Park KW. Timing of high-risk vascular surgery following coronary artery bypass surgery: a 10-year experience from an academic centre. *Anaesthesia*. 2004;59(5):422-427.

37. Reul GJ, Cooley DA, Duncan JM, et al. The effect of coronary bypass on the outcome on peripheral vascular operations in 1093 patients. *J Vasc Surg*. 1986;3(5):788-798.

38. Cruchley PM, Kaplan JA, Hug CC Jr, Nagle D, Sumpter R, Finucane D. Non-cardiac surgery in patients with prior myocardial revascularization. *Can Anaesth Soc J*. 1983;30(6):629-634.

39. Stone PH, Goldschlager N. Left main artery disease: review and appraisal. *Cardiovasc Med*. 1979;4:165-177.

40. DeMots H, Rösch J, McAnulty JH, Rahimtoola SH. Left main coronary artery disease. *Cardiovasc Clin*. 1977;8(2):201-211.

41. Morice MC, Serruys PW, Kappetein AP, et al. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation*. 2010;121(24):2645-2653.

42. Godet G, Dumerat M, Baillard C, et al. Cardiac troponin I is reliable with immediate but not medium-term cardiac complications after abdominal aortic repair. *Acta Anaesthesiol Scand*. 2000; 44(5):592e7.

43. Jamieson WR, Janusz MT, Miyagishima RT, Gerein AN. Influence of ischemic heart disease on early and late mortality after surgery for peripheral occlusive vascular disease. *Circulation*. 1982;66(2 pt 2):I92eI97.

44. Mangano DP, Layug EL, Wallace A, Tatco I. Effect of atenolol on mortality and cardiovascular morbidity after noncardiac surgery. Multicenter Study- of Perioperative Ischemia Research Group. *N Engl J Med*. 1996;335(23):1713-1720.

45. Poldermans D, Boersma E, Bax JJ. The effect of bisoprolol on periopera tive mortality and myocardial infarction in high-risk patients undergoing vascular surgery. Dutch Echocardiography Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. *N Engl J Med*. 1999;341(24):1789-1794.

46. 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(4): 349-361.

47. Devereaux PJ, Yang H, Yusuf S, et al; POISE Study Group. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet*. 2008;371(9627):1839-1847.

48. 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(5):983-990.

49. Brady AR, Gibbs JS, Greenhalgh RM, Powell JT, Sydes MR; POB-BLE trial investigators. Perioperative beta-blockade (POBBLE) for patients undergoing infrarenal vascular surgery: results of a randomized double-blind controlled trial. *J Vasc Surg*. 2005;41(4):602-609.

50. Juul AB, Wetterslev J, Gluud C, et al. Effect of perioperative beta blockade in patients with diabetes undergoing major non-cardiac surgery: randomised placebo controlled, blinded multicentre trial. *BMJ*. 2006;332(7556):1482.

51. Zaugg M, Bestmann L, Wacker J, et al. Adrenergic receptor genotype but not perioperative bisoprolol therapy may determine cardiovascular outcome in at-risk patients undergoing surgery with spinal block: the Swiss Beta Blocker in Spinal Anesthesia (BBSA) study: a double-blinded, placebo-controlled, multicenter trial with 1-year follow-up. *Anesthesiology*. 2007;107(1):33-44.

52. Flu WJ, van Kuijk JP, Chonchol M, et al. Timing of pre-operative Beta-blocker treatment in vascular surgery patients: influence on post-operative outcome. *J Am Coll Cardiol*. 2010;56(23): 1922-1929.

53. Poldermans D, Schouten O, van Lier F, et al. Perioperative strokes and beta-blockade. *Anesthesiology*. 2009;111(5):940-945.

54. Poldermans D, Bax JJ, Boersma E, et al. Guidelines for pre-operative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and endorsed by the European Society of Anaesthesiology (ESA). *Eur J Anaesthesiol*. 2010;27(2): 92-137.

55. Fleischmann KE, Beckman JA, Buller CE, et al. 2009 ACCF/AHA focused update on perioperative beta blockade. *J Am Coll Cardiol*. 2009;54(22):2102-2128.

56. Poldermans D, Boersma E, Bax JJ, et al. for the Dutch Cardiac Risk Evaluation Applying Stress Echocardiography Group. Bisoprolol reduces cardiac death and myocardial infarction in high-risk patients as long as 2 years after successful major vascular surgery. *Eur Heart J*. 2001;22(15):1353-1358.

57. Frishman W. Beta-adrenergic blocker withdrawal. *Am J Cardiol*. 1987;59(13):26F-32F.

58. Psaty B, Koepsell T, Wagner E, et al. The relative risk of incident coronary heart disease associated with recently stopping the use of B-blockers. *JAMA*. 1990;263(12):1653-1657.

59. Langou RA, Wiles JC, Peduzzi PN, Hammond GL, Cohen LS. Incidence and mortality of perioperative myocardial infarction in patients undergoing coronary artery bypass grafting. *Circulation*. 1977;56(suppl 3):II54-II58.

60. Shammash JB, Trost JC, Gold JM, et al. Perioperative β-blocker withdrawal and mortality in vascular surgical patients. *Am Heart J*. 2001;141(1):148-153.

61. Priebe HJ. Perioperative myocardial infarction—aetiology and prevention. *Br J Anaesth*. 2005;95(1):3-19.

62. Poldermans D. Statins and noncardiac surgery: current evidence and practical considerations. *Cleve Clin J Med*. 2009;76(suppl 4): S79-S83.

63. Ridker PM, Cannon CP, Morrow D, et al. C-Reactive protein levels and outcomes after statin therapy. *N Engl J Med*. 2005;352(1): 20-28.

64. Schouten O, Boersma E, Hoeks SE, et al. for the Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography Study Group. Fluvastatin and perioperative events in patients undergoing vascular surgery. *N Engl J Med*. 2009; 361(10):980-989.

65. 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(5):967-976.

66. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. *JAMA*. 2004;291(17):2092-2099.

67. 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(4):343-352.

68. Heeschen C, Hamm CW, Laufs U, Snapinn S, Bohm M, White HD. Withdrawal of statins increases event rates in patients with acute coronary syndromes. *Circulation*. 2002;105(12):1446-1452.