A Randomised Study of Perioperative Esmolol Infusion for Haemodynamic Stability during Major Vascular Surgery; Rationale and Design of DECREASE-XIII

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Abstract *Objectives:* This article describes the rationale and design of the DECREASE-XIII trial, which aims to evaluate the potential of esmolol infusion, an ultra-short-acting beta-blocker, during surgery as an add-on to chronic low-dose beta-blocker therapy to maintain perioperative haemodynamic stability during major vascular surgery.
Design: A double-blind, placebo-controlled, randomised trial.
Materials & methods: A total of 260 vascular surgery patients will be randomised to esmolol or placebo as an add-on to standard medical care, including chronic low-dose beta-blockers. Esmolol is titrated to maintain a heart rate within a target window of 60—80 beats per minute for 24 h from the induction of anaesthesia. Heart rate and ischaemia are assessed by continuous 12-lead electrocardiographic monitoring for 72 h, starting 1 day prior to surgery. The primary outcome measure is duration of heart rate outside the target window during infusion of the study drug. Secondary outcome measures will be the efficacy parameters of occurrence of cardiac ischaemia, troponin T release, myocardial infarction and cardiac death within 30 days after surgery and safety parameters such as the occurrence of stroke and hypotension.
Conclusions: This study will provide data on the efficacy of esmolol titration in chronic beta-blocker users for tight heart-rate control and reduction of ischaemia in patients undergoing vascular surgery as well as data on safety parameters.
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Only 8% of patients undergoing major vascular surgery have a normal coronary angiogram.[1] Albeit coronary artery disease (CAD) is asymptomatic in the vast majority of these patients, the risk of perioperative cardiac mortality and morbidity is increased.[2–7] Major cardiac complications occur in 2–3.5% of major surgery patients. The predominant risk factor is CAD, and complications are usually preceded by a prolonged haemodynamic instability, leading to myocardial ischaemia and infarction. The pathophysiology of perioperative cardiac events is complex. Haemodynamic instability may lead to coronary plaque rupture, initiating coronary artery thrombosis, occlusion and myocardial infarction (type 1 MI).[8–10] In the presence of stable CAD, myocardial oxygen supply/demand mismatch due to tachycardia and increased contractility, induced by perioperative catecholamine surge, may lead to myocardial ischaemia, ST segment depression and type 2 MI.[8,11–13] Perioperative myocardial infarction (PMI) is one of the most important predictors of short- and long-term morbidity and mortality associated with non-cardiac surgery.[14] Therefore, it is of vital importance to prevent myocardial ischaemia by providing haemodynamic stability and adequate heart-rate control throughout the perioperative period.

Beta-blockers are widely prescribed perioperatively for perioperative heart-rate control. The proposed mechanism of the beneficial effect of beta-blockers consists of a decreased myocardial oxygen demand by reducing heart rate and contractility, also resulting in a lengthening of the diastolic filling period and reduced shear stress.[15] Additional cardioprotective factors are redistribution of coronary blood flow to the subendocardium and an increase in the threshold for ventricular fibrillation. Beta-blockers are thought to have an anti-inflammatory and plaque-stabilising effect, which might only be achieved after prolonged treatment.[16–18]

Beta-blocker therapy is recommended in patients with known ischaemic heart disease (IHD) and for patients scheduled for high-risk surgery, based on a reduction in perioperative cardiac mortality and PMI in several trials.[6,19,20] However, this beneficial effect might be offset by the induction of serious side effects.

In the randomised Perioperative Ischaemic Evaluation (POISE) trial, metoprolol succinate was initiated shortly prior to surgery.[7] Patients could receive up to 400 mg of metoprolol succinate on the day of surgery. This regimen was associated with a decreased risk of PMI and an increase in overall mortality and stroke.

A factor to be considered when initiating beta-blockers prior to vascular surgery is the frequent presence of asymptomatic left ventricular (LV) dysfunction.[21] Patients with LV dysfunction might respond unfavourably to a fixed dose of beta-blocker. Therefore, beta-blockers are commonly titrated over a prolonged period of time in conditions such as hypertension, angina pectoris and heart failure.[22] In the DECREASE I and IV trials, using a regimen of bisoprolol, titrated for heart rate, initiated 30 days before surgery, no increased rate of stroke was observed.[6,23]

A simple approach of chronic low-dose long-acting cardioselective beta-blocker therapy titrated for heart rate, combined with the perioperative use of a short-acting, easily titratable beta-blocker, can provide superior haemodynamic stability. Heart-rate control might be improved compared to low-dose long-acting beta-blocker mono-

therapy, without the adverse effects such as hypotension, bradycardia, progression of asymptomatic LV dysfunction, stroke and mortality associated with high-dose long-acting beta-blockers without titration for heart rate. Low-dose long-acting beta-blockers can be initiated 1 week prior to surgery, as titration of long-acting beta-blocker for tight heart rate control is not mandatory. If low-dose long-acting beta-blockers cannot be initiated prior to surgery, esmolol can provide haemodynamic control, although the additional effect of chronic beta-blocker therapy is lacking.

We propose a randomised, placebo-controlled trial of esmolol, titrated for heart rate, as an add-on to standard medical care, including chronic beta-blockade with metoprolol succinate. Esmolol is an ultra-short-acting beta-blocker with a distribution and elimination half-life of 2 and 9 min and, therefore, easily titratable.[24] Esmolol is highly beta-1 selective and has no intrinsic sympathomimetic activity.[25]

Materials and Methods

Study design and objective

This single-centre, randomised, placebo-controlled study compares a group receiving esmolol (Brevibloc®) as an add-on to metoprolol succinate versus a group receiving metoprolol succinate and placebo. The primary objective is to assess the efficacy of esmolol versus placebo as an add-on to standard medical care for target heart-rate control. Secondary objectives are to assess the efficacy of esmolol for reducing the occurrence and duration of myocardial ischaemia and to assess safety parameters. Approval from the Medical Ethical Committee was obtained. This trial was registered as NTR2615 on www.trialregister.nl.

Study population

Patients scheduled for major vascular surgery will be enrolled after providing informed consent, if none of the exclusion criteria presented in Table 1 is met.

Randomisation, blinding and treatment allocation

The randomisation for active drug or placebo will be performed by the hospital pharmacist in a 1:1 ratio, using a computer-generated randomisation list. Patient, research fellow, nursing and medical staff are blinded, with the exception of the attending anaesthesiologist and intensivist, for safety reasons.

Preoperative risk evaluation and initiation of medical therapy

Patients are screened before vascular surgery using the recently published European Society of Cardiology (ESC) guidelines on perioperative care.[19] In short, patients with unstable cardiac symptoms and patients with >2 points on the revised cardiac risk index[3] will be sent for additional cardiac evaluation and treatment if indicated. In all patients proceeding to surgery, standard medical therapy will be initiated.

Table 1 Inclusion and exclusion criteria.

Inclusion criteria	
Major vascular surgery	Open or endovascular Abdominal Aortic Aneurysm repair, infrarenal aortic occlusive disease repair, open lower limb arterial reconstruction, open carotid artery repair
Age $\geq$ 18 years	
Exclusion criteria	
Active bleeding	
Untreated left main disease	
Active cardiac conditions	Unstable angina pectoris, active heart failure, serious cardiac arrhythmias, symptomatic valvular disease, myocardial infarction <6 months
Preoperative positive Troponin T	
Contraindication for esmolol use	
Previous allergy or intolerance for esmolol	
Cancer	With an expected life expectancy <6 months
Failure to monitor heart rate	With continuous 12-lead electrocardiography because of surgery or baseline electrocardiographic abnormalities
Excessive alcohol abuse	
Pregnancy or planning to become pregnant	
Failure to provide informed consent	

Beta-blockers

All patients will be receiving metoprolol succinate according to the ESC guidelines on perioperative care.[19] Patients on beta-blocker therapy other than metoprolol succinate switch to metoprolol succinate 50 mg once daily at the screening visit. Beta-blocker-naive patients start with metoprolol succinate 50 mg once daily at the screening visit at least 1 week prior to surgery. The beta-blocker dose is adjusted after 7 days of treatment and prior to surgery to achieve a resting heart rate of 60—70 beats per minute (bpm) if tolerated. The same dose is continued the day after surgery.

Statins

Patients on chronic statin therapy will continue medication, while statin-naive patients will be treated with fluvastatin extended release at a dose of 80 mg once daily.

Aspirin

All patients are on perioperative aspirin therapy, 80 mg daily, according to recommendations in the American Heart Association / American College of Cardiology guidelines on peripheral arterial disease.[26]

Angiotensin-converting enzyme inhibitors

Patients on chronic therapy will continue their medication. When LV dysfunction (left ventricular ejection fraction (LVEF) < 40%) is assessed during preoperative evaluation in untreated patients in stable condition, angiotensin-converting enzyme (ACE) inhibitors are initiated as recommended by the ESC guidelines on heart failure.[22]

Anaesthesia technique

During surgery, patients will receive standard of care (hypnotics, opiates and muscle relaxant) in both groups to provide optimal anaesthetic and surgical conditions. Balanced anaesthesia should adequately control depth of anaesthesia with minor intra-operative haemodynamic changes.

Anaesthesia technique (intubation, mechanical ventilation parameters, SaO$_2$, end-tidal carbon dioxide partial pressure) and all medication used during surgery will be noted, including local or regional technique combined to general anaesthesia and with special focus on anaesthesia depth (Mean Alveolar Concentration, MAC), opiate consumptions and duration of anaesthesia. Patients will have standard postoperative pain management. BIS (bispectral index) monitoring will be applied in all patients.

Haemodynamic monitoring

Perioperative haemodynamic monitoring will include continuous measurement of hazard ratio (HR) and ischaemia detection using 12-lead Holter monitoring. Holter monitoring will start 12 h prior to surgery and continue during esmolol infusion and after discontinuation of esmolol infusion for a total of 72 h. Blood pressure will be measured continuously during surgery and at least every 15 min for 48 h postoperatively, depending on the haemodynamic condition of the patient. After surgery, patients will be admitted to the Intensive Care Unit, the Post Anaesthesia (High) Care Unit, or the post-vascular surgery medium care unit for at least 24 h, at the discretion of the attending anaesthesiologist and vascular surgeon. All of these units can provide the level of monitoring and care needed for the current study. Admission to one of these units is customary in our centre after vascular surgery. In patients with an LVEF <35%, additional haemodynamic monitoring using a pulmonary artery catheter is performed during surgery for goal-directed fluid and vasoactive drug therapy, as per hospital protocol.

Haemodynamic management

Tachycardia will be managed with additional beta-blockers only after excluding and treating underlying causes such as

pain, bleeding, hypovolaemia and infection. If tachycardia is likely to be induced by hypovolaemia, a fluid challenge will be administered. If tachycardia does not resolve, it is deemed not to be induced by hypovolaemia. Perioperative bradycardia (HR < 40 bpm) will be managed with intravenous (i.v.) injection of atropine. Hypertension (>20% increase from baseline systolic blood pressure) will be managed with i.v. administration of standard care of vasodilating agent. Hypotension (mean arterial pressure < 60 mmHg) is managed with fluids or vasopressor medication at the discretion of the attending physician.

If heart rate is >80 bpm intra-operatively, a bolus of 0.25 mg kg^{-1} of esmolol or placebo will be administered and a 25 mcg kg^{-1} min^{-1} continuous infusion will be initiated. If heart-rate control is not regained in 5 min, an additional 0.25 mg kg^{-1} bolus will be administered. Continuous infusion will be titrated in steps of 25% of the current dose at 15-min intervals to maintain a heart rate of 60–80 bpm with a maximum of 300 mcg kg^{-1} min^{-1}. If heart rate does not exceed 80 bpm during surgery, the 25 mcg kg^{-1} min^{-1} continuous infusion of esmolol or placebo is initiated before extubation without bolus infusion and titrated as described earlier. The study drug will be withheld if systolic blood pressure is below 100 mmHg.

If heart rate is outside the target window with no signs of cardiac ischaemia detected by continuous electrocardiographic monitoring, after providing the maximum dose of study drug, no additional action will be taken. However, if signs of cardiac ischaemia do not resolve rapidly with uptitration of esmolol or placebo, rescue treatment with i.v. injection of beta-blocker is provided according to good clinical practice.

Outcome

Primary end point

The primary end point is total duration of heart rate outside the target window presented in minutes. The target window is defined as a heart rate between 60 and 80 bpm.

Secondary end points

The secondary study outcome for the efficacy of esmolol is the occurrence of cardiac death and myocardial ischaemia, defined as either transient electrocardiographic signs of ischaemia or troponin T release or both, within 30 days of surgery. In patients with tachycardia and ischaemia, the prescription of rescue medication will be considered a secondary study end point. Serial troponin T levels and electrograph (ECG) recordings will be obtained prior to surgery and on day 1, 3, 7 and 30.

Secondary outcome will also include other safety parameters such as the occurrence of bradycardia (i.e., HR < 50 bpm) hypotension (SBP < 100) and transient ischaemic attack (TIA) confirmed by neurologic examination or stroke as confirmed by neurologic examination and computed tomography (CT) scan.

Sample-size calculation

Based on the results of the DECREASE III trial,[27] the estimated total length of heart rate outside the target window

(60–80 bpm) in the control group will be 8.1 ± 5.8 h. It is anticipated that using esmolol, the total duration of heart rate outside the target window will be reduced by 33%. This estimation is based on the placebo-controlled study in 26 patients published by Raby et al.[28] This means that a group of 260 patients, 130 in each arm, is necessary to have a power of 80% and an alpha of 0.05 to detect this difference. We expect that 10% of the population will be excluded from the study based on the exclusion criteria.

Data analysis

Categorical data are described as numbers and percentages and analyzed using the chi-square test. Continuous data are expressed as medians with interquartile ranges (IQRs) and compared using Kruskal–Wallis test. Logistic and Cox regression analyses will used to evaluate the short- and long-term prognosis of haemodynamic instability. In multivariate analysis, adjustments will be made for cardiac risk factors, type of surgery and open or endovascular procedure. Odds ratio and HRs are given with 95% confidence intervals. For all tests, a p-value <0.05 (two-sided) is considered significant. All analysis will be performed using SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA).

Discussion

This trial is primarily designed to assess the efficacy and safety of perioperative esmolol infusion versus placebo as an add-on to chronic low-dose beta-blocker use for heart-rate control. Prevention of perioperative tachycardia reduces perioperative cardiac ischaemia.[28] Perioperative ischaemia is related to cardiac adverse events and remains an important cause of morbidity and mortality in patients undergoing vascular surgery.[3,4,7,11,12,29] For risk reduction, a perioperative regimen consisting of beta-blockers and a statin, both initiated at least a week prior to surgery, is recommended in this population.[19] Of note, the perioperative period is characterised by haemodynamic fluctuations. This warrants the use of a placebo and creates a situation where it is difficult for the treating physician to assess treatment allocation of an individual patient.

Randomised controlled trials that assessed the effect of beta-blockers in the perioperative period reported divergent results, as shown in Fig. 1. The DECREASE-I trial observed a 10-fold reduction in the incidence of perioperative death and MI in vascular surgery patients with evidence of myocardial ischaemia on preoperative dobutamine stress-echocardiography, treated with bisoprolol compared to placebo.[6] In a trial by Mangano, perioperative atenolol therapy was not associated with an improved in-hospital outcome; however, it was associated with a 50% reduction in ECG evidence of myocardial ischaemia and significantly lower mortality rates at 6 and 24 months after discharge.[20]

The Metoprolol after Vascular Surgery (MaVS), Peri-Operative Beta-BLockadE (POBBLE) and DIabetic POst-operative Mortality (DIPOM) trials did not find a significant effect of perioperative metoprolol.[30–32] All of these studies included many low-risk patients, in contrast to the DECREASE-I trial, which only included patients with inducible ischaemia. In a retrospective cohort study of 782 969
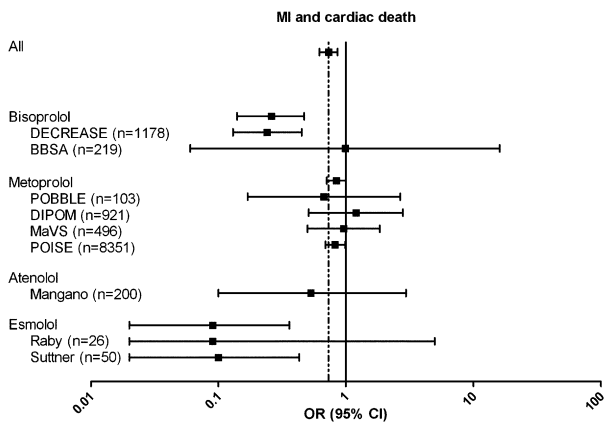
Figure 1 Odds ratios (OR) of randomised beta-blocker trails for perioperative myocardial infarction (MI) and cardiac death. BBSA = Beta Blocker in Spinal Anaesthesia; CI = confidence interval; DECREASE = Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echocardiography; DIPOM = Diabetes Postoperative Mortality and Morbidity; MaVS = Metoprolol after Vascular Surgery; POBBLE = PeriOperative Beta-BLockadE; POISE = PeriOperative Ischaemic Evaluation trial.

patients undergoing major non-cardiac surgery, beta-blocker use was associated with a significant beneficial effect in high-risk patients but showed no effect or possible harm in low-risk patients.[33]

The DECREASE-XIII trial will include only patients undergoing major vascular surgery, including open lower extremity arterial repair, open and endovascular abdominal aortic repair and open carotid stenosis repair. These patients are all at either intermediate or high-risk of cardiac complications. Beta-blocker use in these patients was previously demonstrated to be of benefit and is in accordance with the 2009 ESC guidelines on perioperative care.[6,19,23]

Studies by Raby[28] and Feringa[34] observed that higher doses of beta-blockers and lower heart rates were associated with a marked reduction in the incidence of ischaemia. These data suggest that early initiation of beta-blocker therapy, monitoring of the heart rate and subsequent dose adjustment are of critical importance for the likelihood that a patient will benefit from beta-blockade.

Controversy exists on the appropriate dosing regimen. In the POISE study, patients were randomised for perioperative metoprolol succinate or placebo. Metoprolol succinate was initiated 2−4 h before surgery in a dose of 100 mg. A second dose of 100 mg was administered if heart rate was >80 and systolic blood pressure was >100 mmHg anytime within the first 6 h after surgery. If this situation did not occur, the second dose was administered 6 h after surgery, if heart rate was 50 bpm or more and systolic blood pressure was >100 mmHg. Then, a maintenance dose of 200 mg of metoprolol succinate once daily was started 12 h after the second gift for 30 days. Patients could receive up to 400 mg of metoprolol succinate on the first day of treatment. The incidence of cardiac death, PMI and cardiac arrest in patients randomised to metoprolol compared to placebo was significantly reduced. However, this was offset by an increased incidence of intra-operative hypotension,

bradycardia and 30-day stroke and overall mortality in the treatment group when compared to placebo, as shown in Fig. 2.[7,35,36] The hypothesis is that the frequently observed ischaemic stroke was due to watershed infarction due to hypotension and bradycardia in patients with a diseased cerebrovascular tree.[37,38] In the non-surgical setting, lower starting doses are recommended, for instance, an initial daily dose of 25−100 mg for hypertension, usually uptitrated at weekly intervals.

Feringa et al. demonstrated that a 10 bpm increase in both pre- and postoperative heart rate is associated with a significantly increased risk of perioperative myocardial ischaemia and cardiac troponin release and long-term cardiac events and mortality (HR ranging from 1.4 to 2.6 per 10 bpm increase, $p < 0.05$ in all cases), after adjusting for risk factors, medication use and preoperative cardiac stress test results.[34]

Both bradycardia and increased heart rate are associated with a significantly increased risk of cardiac complications. These data support the importance of the maintenance of tight heart-rate control as a primary end point.

A recent meta-analysis by Landoni et al. showed no increase in the incidence of hypotension or bradycardia during perioperative esmolol infusion. No data on the incidence of stroke were reported in the trials included in this meta-analysis.[39]

Titration of beta-blocker dose requires that treatment be initiated optimally 30 days prior to surgery, or at least 1 week. Early initiation of beta-blocker therapy poses a logistic difficulty in the United States, where patients are commonly admitted to the hospital only on the day prior to surgery. Perioperative esmolol infusion offers a possibility for tight heart-rate control in this clinical condition, although patients do not benefit from the additional cardioprotective anti-inflammatory effect of chronic beta-blocker therapy.
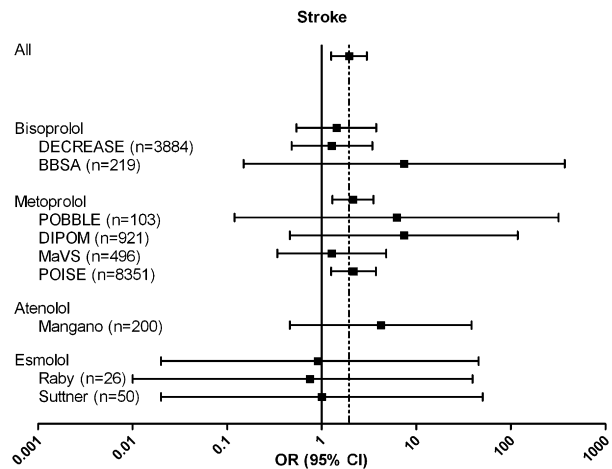

Figure 2 Odds ratios (OR) of randomised beta-blocker trails for stroke, BBSA = Beta Blocker in Spinal Anaesthesia; CI = confidence interval; DECREASE = Dutch Echocardiographic Cardiac Rick Evaluation Applying Stress Echocardiography; DIPOM = Diabetes Postoperative Mortality and Morbidity; MaVS = Metoprolol after Vascular Surgery; POBBLE = PeriOperative Beta-BlockadE; POISE = PeriOperative Ischaemic Evaluation trial.

In conclusion, the optimal perioperative beta-blocker dosing regimen is still controversial. Although proven to be effective in the non-surgical setting in patients with heart failure and CAD, safety issues such as hypotension and bradycardia leading to stroke are potential deleterious consequences. The use of low-dose regimens with careful uptitration and intra-operative use of ultra-short-acting beta-blockers might be the optimal treatment. A sufficiently powered randomised clinical trial is warranted to prove the safety and efficacy of these treatment regimens.

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