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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 monotherapy, 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.