Trial Overview

Patients with established coronary artery disease (CAD) requiring on- or off-pump coronary artery bypass grafting (CABG) are still at significant risk of postoperative major adverse cardiocerebral events (MACCE), including periprocedural myocardial infarction (MI), repeat revascularisation, stroke or ultimately death from cardiovascular causes. The presence of increasing co-morbidity in the constantly aging patient population has led to a substantial postoperative increase in the rate of major adverse cardiac events ranging from 5% in low-risk to over 20% in high-risk cohorts of large RCT trials. If outcomes among CABG patients are to be improved, development of better strategies to limit the periprocedural risk for MACCE is imperative.

HMG-CoA reductase inhibitors, commonly called ‘statins’, effectively reduce the risk from atherosclerotic cardiovascular disease through lipid-lowering actions and have gained a pivotal role in primary and secondary prevention of CAD including CABG patients. Beyond their lipid-lowering actions, statins exert multiple additional pleiotropic effects including enhancement of endothelial function, plaque stabilisation, attenuation of inflammation and myocardial ischemia-reperfusion injury. These acute actions have been implicated to offer direct cardiovascular protection and reduce adverse clinical outcomes in patients receiving statins prior to interventional or surgical myocardial revascularisation or non-cardiac surgery. As a consequence statin utilisation in patients with CAD scheduled for PCI or CABG is steadily increasing over the past years to over 70-80%.

The latter, however, is of major clinical relevance as accumulating evidence shows that statin related cardioprotection wanes over time following chronic statin intake, and can be ‘recaptured’ by an increased statin dose given shortly before an ischemia-reperfusion sequence as it occurs during PCI or CABG. Statin recapture therapy before PCI resulted in a significant reduction of major adverse cardiac events (MACE) at 30 days and lowered post-PCI elevation of markers of myocardial injury, implicating substantial lipid-independent cardioprotective. Thus, evaluating this novel approach in patients undergoing CABG, including higher risk patients with recent ACS, prior MI or redo surgery seems particularly promising, since perioperative myocardial injury resulting from inadequate myocardial protection, ischemia-reperfusion injury, surgery-related inflammation and trauma plays a pivotal role for poor clinical outcomes after CABG and may be prevented by simple statin reload treatment before surgery.

The StaRT-CABG trial is the first large-scale, multicentre trial that aims to test whether an acute high-dose statin recapture therapy given shortly before CABG reduces the incidence of MACCE at 30 days after surgery. The trial is expected to provide highly relevant clinical data on the efficacy of this novel therapeutic approach in order to optimize the care for all CAD patients undergoing CABG with broad clinical implications on current clinical practice and existing
Intervention scheme of the clinical trial

The StaRT-CABG trial is a phase 4, multicentre (8 high-volume cardiac surgery centres in Germany), randomised, double-blind and placebo-controlled, parallel-group study in a total of 2,630 patients scheduled for CABG. The trial flow of the StaRT-CABG trial can be subdivided in 5 stages:

**Enrolment of patients**
The StaRT-CABG Trial will recruit CABG patients in 8 high-volume cardiac surgery centres in Germany. Eligible patients must be older than 18 years of age, require isolated on- or off-pump CABG for CAD with stable angina or non-ST segment elevation ACS (NSTE-ACS) and be on chronic statin treatment for at least 30 days before surgery. By protocol, patients on a chronic statin pretreatment must be treated with one of the four commonly prescribed statins (i.e. simvastatin, atorvastatin, pravastatin and fluvastatin). Approximately 15,000 eligible patients scheduled for isolated CABG will be screened for study inclusion over the 36 month recruitment period. Of these, approximately 50% will be excluded for not fulfilling the aforementioned inclusion criteria, for meeting one of the exclusion criteria.

**Allocation to treatment arms**
Of the remaining eligible patients, 2,630 patients will be approached for study participation and enrolled upon providing informed written consent. Eligible patients will be assigned in a 1:1 ratio to treatment arms by a central 24-7 internet randomisation service using permuted blocks of varying length and stratified by statin and study centre. Blinding of patients and investigators will be employed to guarding against performance and detection bias.

**Intervention**
Consenting patients will be randomised to receive either oral statin reloading therapy or matching placebo at two separate doses before CABG surgery. Reload and placebo therapy will be administered twice at 12 hours and 2 hours prior to surgery. The individual preoperative statin regimen will be maintained before surgery in both groups. The example provides the intervention scheme for a patient with a preoperative simvastatin intake at 40 mg (maximal daily dose of simvastatin is 80 mg).

**Procedure**
Routine CABG surgery will be performed as indicated. Anaesthesia, myocardial revascularisation strategy, CPB protocol, applied myocardial protection technique and postoperative care of patients will follow usual practice of the participating centre. Irrespective of the initial randomization assignment, all patients will be treated postoperatively with their standard statin therapy.

**Outcome measures**
The primary outcome measure of the StaRT-CABG Trial is the incidence of a composite consisting of all-cause mortality, non-fatal myocardial infarction and cerebrovascular event (stroke or TIA) at 30 days after CABG (MACCE). In all patients, blood samples will be collected and sent to a core clinical chemistry laboratory located at the University of Cologne to assess perioperative
release of markers of myocardial injury. Routine electrocardiography (ECG) will be performed at baseline and postoperatively and analysed in an electrocardiographic core laboratory. All cause mortality will be assessed at 12 months. All primary and secondary outcomes will be validated by a blinded clinical events committee (CEC) that will adjudicate the primary outcome using standardised definitions. The primary analysis is based on the full-analysis set (intention-to-treat).

Trial flow chart of the StaRT-CABG Trial

Trial flow of the StaRT-CABG trial. CK (-MB): creatine kinase (-myocardial band); CV: cerebrovascular event (TIA or stroke); MI: myocardial infarction; NSTEMI: non-ST-segment elevation acute coronary syndrome; STEMI: ST-segment-elevation myocardial infarction; POD: postoperative day.

Inclusion and exclusion criteria of patients

To facilitate comparisons of patient populations the inclusion and exclusion criteria are closely matched to those of comparable, major RCT in cardiac surgery. The risk profile of the included study population will range from patients that are at low, moderate or high-risk for MACCE after CABG surgery and include redo CABG or patients suffering from diabetes, multivessel disease, ACS or left main stem disease. Given a estimated 70-80% preoperative statin utilisation rate in CABG patients the proposed criteria facilitate a high reproducibility and generalizability of the results as they reflect approximately 60-70% of patients undergoing CABG worldwide. Study subjects must meet all of the inclusion criteria and none of the exclusion criteria to receive treatment assignment as delineated in detail below.

**Inclusion criteria**

The subjects must meet all the criteria listed below for study entry.

1. A patient must be on a chronic statin medication for more than or equal to 30 days (≥30 days) at hospital admission with one of the following four statins and irrespective of the individual dose: simvastatin, atorvastatin, pravastatin or fluvastatin
2. A patient must have relevant CAD with stable angina pectoris or non-ST-segment elevation ACS (NSTEMI) as diagnosed by a cardiologist at least 24 hours before surgery
3. A patient must require isolated CABG including on- or off-pump or Re-do cardiac surgery, for relevant CAD as documented in a recent coronary angiography (performed within the last 6 months)
4. A patient must be ≥18 years of age
5. A patient must not be legally incapacitated
6. A patient must provide written informed consent

**Exclusion criteria**

The subjects will be excluded from study entry if any of the criteria listed below are met.
1. A patient that requires any concomitant cardiovascular procedure to CABG (i.e valve, aortic, atrial ablation or carotid artery surgery).

2. A patient with acute ST-segment-elevation myocardial infarction (STEMI) or NSTE-ACS with cardiogenic shock warranting emergency CABG within 24 hours of hospital admission.

3. A patient with a history of atrial fibrillation or atrial fibrillation documented in the preoperative ECG at Screening.

4. A patient with history or presence of muscle disease (i.e. myopathy, myalgia, myositis, myasthenia, rhabdomyolysis) with or without concomitant CK-elevation > 5 ULN that cannot be ascribed to any other medical condition (i.e. myocardial infarction etc.).

5. A patient with inability of oral drug intake.

6. A patient with known lactose intolerance or contraindication for statins listed in Information Sheet.

7. A patient with current renal failure with serum creatinine concentrations > 2 mg/dL (180 µmol/L), dialysis or history of kidney transplant at screening.

8. A patient with active or chronic liver disease with serum ALT or AST concentrations > 3 ULN, hepatic neoplasm or history of liver transplant at screening.

9. History of HIV infection and/or ongoing antiviral therapy.

10. A patient who participates in other investigational drug trials.

11. A woman who is breast-feeding, pregnant or intends to become pregnant or fails to use highly-effective contraceptive methods. Contraceptive methods with a Pearl Index lower than 1% are regarded as highly-effective.

12. A patient with on-going drug or alcohol abuse or a patient with a psychiatric condition that, in the opinion of the investigator, makes the patient unsuitable for study participation.

13. A patient with any kind of dependency on the investigator or employed by the sponsor or investigator.

14. A patient with inability or unwillingness to abide by the protocol or held in an institution by legal or official order.

Clinical endpoints of the trial

**Primary objective**
The primary objective is to determine the efficacy of an acute statin reloading strategy in patients receiving a chronic statin therapy prior to CABG in reducing the incidence of postoperative MACCE, as measured by the first occurrence of any component of the composite primary endpoint of all-cause mortality, non-fatal MI and non-fatal cerebrovascular event (stroke or TIA) occurring during or following CABG surgery through postoperative day thirty.

**Secondary objectives**
The key secondary objective is to evaluate the efficacy of acute statin reloading with respect to the incidence cardiac mortality and morbidity as measured by the first occurrence of any component of the composite of cardiac death or non-fatal MI (MACE) occurring during or following CABG surgery through postoperative day thirty. Additional secondary efficiency measures include the evaluation of postoperative enzymatic myocardial injury, the incidence of postoperative new-onset atrial fibrillation, the length of stay on the ICU and hospital, the need for repeat coronary revascularisation in both treatment arms. Finally, assessment of the clinical
benefit of statin reloading in reducing the incidence of all-cause mortality at 12 months following CABG surgery will be performed.

Publications

PubMed

Relevant Publications


Other Sources


4. EMEA-Guideline On Data Monitoring Committees: EMEA/CHMP/EWP/5872/03 Corr
