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Efficacy of a glucagon-like peptide-1 agonist and restrictive vs. liberal oxygen supply in patients undergoing coronary artery bypass grafting or aortic valve replacement: Study protocol for a 2-by-2 factorial designed, randomized clinical trial

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Short Title
GLP-1 agonists and restrictive oxygenation for organ protection in heart surgery

Acronym
GLORIOUS

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Trial registration

1. Danish Health and Medicines Authority: Protocol no. HJE-PHARMA-001, EudraCT no. 2015-003050-41, 2nd of October 2015
2. Local ethics committee "Videnskabsetisk komité C, Region Hovedstaden": No. H-15010562
3. www.clinicaltrials.gov: ID no. NCT02673931

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Abstract

Introduction

Coronary artery bypass grafting (CABG) and/or aortic valve replacement (AVR) are associated with risk of death, as well as brain-, heart-, and kidney injury. Glucagon-like peptide-1 (GLP-1) analogs are approved for treatment of type 2 diabetes, and GLP-1 analogs have been suggested to have potential organ-protective and anti-inflammatory effects. During cardiopulmonary bypass (CPB), consensus on the optimal fraction of oxygen is lacking. The objective of the present study is to determine the efficacy of the GLP-1- analog exenatide versus placebo and restrictive oxygenation (50% FiO2) versus liberal oxygenation (100% FiO2) in patients undergoing open heart surgery.

Methods and analysis

A randomized, placebo-controlled, double blind (for the exenatide intervention)/single blind (for the oxygenation strategy), parallel group, 2x2 factorial designed single-center trial on adult patients undergoing elective or subacute CABG and/or surgical AVR. Patients will be randomized in a 1:1 and 1:1 ratio to a 6 hours and 15 minutes infusion of 17.4 µg of exenatide or placebo during CPB and to a FiO2 of 50% versus 100% during and after weaning from CPB. Patients will be followed until 12 months after inclusion of the last participant. The primary composite endpoint consists of time to first event of death, renal failure requiring renal replacement therapy, hospitalization for stroke or heart failure. In addition, the trial will include predefined sub-studies applying more advanced measures of cardiac- and pulmonary dysfunction, renal dysfunction and cerebral dysfunction. The trial is event-driven and aims at 323 primary end-points with a projected inclusion of approximately 1400 patients.

Ethics and dissemination

Eligible patients will provide informed, written consent prior to randomization. The trial is approved by the local ethics committee and is conducted in accordance with Danish legislation and the Declaration of Helsinki. The results will be presented in peer reviewed journals.

Registration

The study was approved by the Danish Health and Medicines Authority (Protocol no. HJE-PHARMA-001, EudraCT no. 2015-003050-41, 2nd of October 2015) and by the institutional review board (No. H-15010562). The trial was registered at www.clinicaltrials.gov (No. NCT02673931).

Strengths and limitations

- First clinical study to investigate the efficacy of a GLP-1 analog and restrictive oxygenation in patients undergoing open heart surgery.
- Randomized, placebo-controlled double/single blind parallel group 2-by-2 factorial trial design conducting analyses on the intention-to-treat population
- Large trial expected to include approximately 1400 patients
- Setting is limited to a single center
- Follow-up is limited to 12 months after inclusion of the last patient.

Introduction

In modern management of coronary artery disease (CAD), coronary artery bypass grafting (CABG) is often indicated, and in management of aortic stenosis, aortic valve replacement (AVR) is often applied. Both procedures require the use of cardiopulmonary bypass (CPB). During CPB, blood is exposed to artificial surfaces and mechanical stress potentially resulting in risk of arterial emboli and a systemic inflammatory response syndrome (SIRS) with the potential of organ damage and multiple organ failure. Patients with CAD have associated atherosclerotic disease and ischemia-induced damage to the brain, kidneys and myocardium is frequent following open heart surgery[1–3].

Following elective open heart surgery the 30-day mortality is 1-2% for CABG[4,5] and 4% for valve surgery[6]. In elderly patients with reduced renal function and comorbidities, the 30-day mortality is as high as 20%[4]. Complications include severe heart failure and cardiogenic shock, graft occlusion or occlusion of coronary arteries, renal failure, stroke, and/or development of severe inflammatory response syndrome (SIRS), which may be lethal.

The risk of acute kidney injury (AKI) requiring temporary dialysis after open heart surgery is 2-3% dependent on the kidney function prior to surgery and patient age. Often, AKI is seen in conjunction with progression or development of heart failure and low cardiac output syndrome (LCOS)[7]. The risk of stroke during and after CABG is 1-5%[1,8]. Factors associated with stroke in cardiac surgery are higher age, previous atherosclerotic-associated diseases and prolonged CPB-time[1]. The risk of cognitive deficits after open heart surgery is above 50% decreasing to approximately 30% after one year[9], however, one study did not find any difference in cognitive decline in atherosclerotic patients undergoing CABG compared to atherosclerotic patients not undergoing CABG[10]. Suggested risk factors for cognitive decline are higher age and duration of bypass, however surgical technique (valve-insertion, CPB etc.), equipment and de-airing techniques may also be of importance. The physiological mechanisms suggested to cause cognitive decline include cerebral microembolism, SIRS and altered cerebral flow including LCOS[11]. Several pharmacological interventions have been tested to mitigate cerebral damage during heart surgery; however, the success has been limited[12–16]. Hence, there are no pharmacological interventions currently in use to hinder ischemic damage during CPB.

Glucagon-like peptide-1 analogs

Glucagon-like peptide-1 (GLP-1) analogs are incretin mimetics and thus increase insulin release and inhibit glucagon release. Several GLP-1 analogs, including exenatide, are approved for the treatment of type 2 diabetes.

Pre-clinical data

GLP-1 analogs have been suggested to have complex neuroprotective effects and anti-inflammatory properties[17]. In rodent models, GLP-1 analogs have been shown to ameliorate neurological diseases such as Alzheimer's disease[18], Parkinson's disease[19], and amyotrophic lateral sclerosis[20]. In animal stroke models, GLP-1 analogs reduce the final infarct size[21], and in models of acute myocardial infarction (MI) GLP-1 analogs reduce the infarct size[22].

Clinical data

In humans, the GLP-1 analog exenatide has been associated with increased myocardial salvage when initiated before revascularization after MI[23], and in patients with a limited time of ischemia, exenatide resulted in a smaller infarct size[24], which has been confirmed by later trials[25,26]. Importantly, exenatide has been administered to severely ill patients with ST-segment elevation MI (STEMI)[24] and to patients resuscitated from out-of-hospital cardiac arrest[27] with no increased risk of adverse events.

Liberal versus restrictive oxygen administration during weaning from CPB

When weaning from CPB, there is currently no consensus on the optimal oxygen fraction, but a majority is offering a high oxygen (FiO2> 50%), which then gradually is reduced to maintain saturations >95% before the patient is transferred to the intensive care unit (ICU).

Pre-clinical data

It has been shown, that hyperoxia increases cerebral damage following brain ischemia in cardiac arrest models of no-flow[28,29].

Clinical data

Hyperoxia has been investigated in several settings, and a final consensus on its hazards and benefits has not been reached. For simplicity, henceforth the term hyperoxia will be used in situations where the FiO_2 is increased above 50%.

Hyperoxia increases the risk of developing lung injury (hyperoxia-induced acute lung injury); however, it seems that several days of hyperoxia is a prerequisite for this[30], and the risk of lung injury caused by shorter periods of hyperoxia is presumably small.

Ischemic reperfusion injury of the lung in relation to CPB has been investigated in smaller trials; however, the impact of different ventilation strategies is questionable[31]. Hyperoxia may be associated with an increase in systemic vascular resistance, and may not be associated with improved tissue oxygenation[32]. Recently, hyperoxia has been associated with a reduced risk of surgical site infection after abdominal surgery in a meta-analysis[33], however a large RCT found an association between hyperoxia and increased mortality in patients with malignancy undergoing abdominal surgery[34]. A single-center RCT and a meta-analysis found that a restrictive oxygenation strategy resulted in reduced mortality in critically ill patients admitted to the ICU[35,36], while a recent multi-center RCT in ICU patients found no difference in higher versus lower oxygen targets[37]. In patients with ST-elevation acute myocardial infarction, routine administration of oxygen was associated with increased myocardial injury in one study[38], however, another study found no effect of routine administration of oxygen in patients with suspected myocardial infarction[39]. In addition, a recent small study has demonstrated, that a restrictive oxygenation strategy in patients undergoing CABG is safe[40]. Further research is warranted, and the risks versus benefits of hyperoxia during CPB and immediately after weaning from CPB are unknown.

Hypothesis

1. Infusion with the GLP-1 analog exenatide started pre-operatively in patients undergoing elective or subacute CABG and/or AVR will reduce mortality and morbidity from heart, brain and kidney injury.
2. Restrictive oxygenation (FIO_2=50%) compared to liberal oxygenation (FiO_2=100%) during CPB and the first hour after weaning from CPB will reduce the mortality and morbidity from heart, brain and kidney injury, without increasing the risk of significant surgical site infection.

In addition to the main hypothesis, three sub-studies will be a part of the trial. These sub-studies will investigate the effects of GLP-1 analogs and oxygenation strategy on cardio- and pulmonary-protection, neuro-protection, and renal-protection, respectively.

Endpoints

Endpoint data will be collected and noted on specific electronic CRFs. Supporting information will be provided to the endpoint adjudication committee for confirmation of events.

Primary endpoint

The efficacy of exenatide versus placebo and restrictive versus liberal oxygenation will be assessed by the time to the first occurring of the following co-primary endpoints within the follow-up period ending 12 months after inclusion of the last included participant:

1) Death from any cause, or
2) The occurrence of any of the following adverse events, adjudicated by an endpoint committee blinded for treatment allocation:
    a. Renal failure requiring any type of renal replacement therapy
    b. Stroke, defined as any sign or symptom of neurological dysfunction persisting for more than 24 hours, determined by the treating physician based on clinical information like CT-scan etc.
    c. New onset or worsening heart failure defined as need for mechanical circulatory support at the ICU, inability to close the sternum due to hemodynamic instability and/or need for inotropic hemodynamic support more than 48 hours after initiation of the first surgical procedure after randomization. In addition, any admission for heart failure during follow-up after discharge from the index admission.

Secondary endpoints

1) Time in days to occurrence of each individual endpoint, within the follow-up period:
    a. Time to death from any cause, or
    b. Time to AKI requiring renal replacement therapy, or
    c. Time to stroke, or
    d. Time to re-hospitalization for heart failure, or time to new onset or worsening in-hospital heart failure

2) Incidence of any of the following safety endpoints:
    a. Surgical site infections with need for antibiotics for more than 48 hours (excluding routine use of antibiotics for open sternum, surgical intervention, and/or endocarditis within 6 months of surgery, or
    b. Doubling of S-creatinine or urine output below 0.5 mL/kg/hour for 12 hours or more at any time point during index admission, or
    c. Hypoglycemia, defined as blood glucose < 3 mmol/L, during index admission, or
    d. Pancreatitis, defined as s-amylase > 3 times upper normal limit, during index admission, or
    e. A relative reduction of LVEF of 50% compared to baseline at any time point during index admission, or
    f. Re-operation for bleeding during index admission, or
    g. Re-operation for any cause during index admission, or
    h. Post-surgery MI (Type 5 MI[41]) during index admission, or
    i. Re-admission for cardiovascular causes within 12 months
3) Change in Cerebral Performance Category (CPC) from baseline to 12 months
4) Change in modified Rankin Scale (mRS) from baseline to 12 months

Methods and analysis

This is a randomized, placebo-controlled, double blind (for the exenatide intervention)/single blind (for the oxygenation strategy), parallel group 2x2 factorial designed single-center trial on adult patients undergoing elective or subacute CABG and/or AVR. Patients are enrolled from a Danish tertiary university hospital with a catchment area of 2.2 million citizens older than 18 years of age.

After completion of screening and baseline procedures, patients will be randomized to receive a GLP-1 analog or placebo and restrictive or liberal oxygenation in a 1:1 and 1:1 ratio. Patients will be followed until 12 months after inclusion of the last participant.

Patient and public involvement

No patient involved.

Inclusion

Patients undergoing elective or subacute CABG and/or AVR will be eligible for screening, irrespective of other concomitant valve surgery All patients will receive oral and written information and must sign the informed consent form, approved by the local ethics committee, prior to randomization This is in accordance with Danish legislation. After provision of informed consent, patients will be registered in the trial database, and will be provided with a unique study ID. A trained study nurse will screen the patients according to the predefined inclusion and exclusion criteria (Table 1) during their preoperative admission. If the criteria are met, the patients will be randomly allocated to one of the four allocation arms (GLP-1 analog vs placebo and restrictive vs. liberal oxygenation) via an internet-based randomization algorithm using permuted blocks of 4, 8 or 12 participants on the trial website. Randomization will be stratified by planned AVR. In addition, baseline characteristics will be noted in the case report forms.

Interventions

GLP-1 analog versus placebo

A GLP-1 analog, exenatide (Byetta®), or placebo will be administered as a 6 hour and 15 minutes infusion starting at the time of anesthesia immediately prior to surgery. The study drug (i.e. either exenatide or placebo) is prepared by trained nurses with experience in preparation and administration of intravenous medications. The trial website lists enrolled patients by study ID, initials, social security number and randomization allocation, i.e. either exenatide or placebo. The study drug infusion kit consists of 1.5 mL of 20% Human Albumin to 248.5 mL of isotonic NaCl, and then 25 µg of exenatide (Byetta®, Lilly) is added to patients allocated to the active study drug arm. The infusion kit is labeled with study ID, social security number as well as date and initials of the manufacturing nurse.

For each included patient, the infusion kit is brought to the coordinating anesthetist by an investigator who is blinded from study drug allocation. The coordinating anesthetist, who is blinded from study drug allocation, is responsible for delivering the correct investigational product to the operating theatre. The attending nurse of anesthesia, also blinded from study drug allocation, is responsible for initiation of the study-drug infusion. The study drug infusion is initiated within one hour of scheduled start of surgery at a rate of 72mL/hour

(0.12 µg/min) for 15 minutes (at a set volume of 18mL), followed by 26mL/hour (0.043 µg/min) for 6 hours (at a set volume of 156mL). Thus, a total of 17.4 µg of exenatide is administered. The infusion can be given in either a central or a peripheral intravenous line. The dosage and infusion rate were based on laboratory data and previously randomized trials of exenatide for cardio protection in STEMI patients, and of exenatide for neuroprotection in patients after out-of-hospital cardiac arrest. Notably, in these two trials enrolling severely ill patients, the infusion rates used were not associated with an increased risk of adverse events including severe hypoglycemia or acute pancreatitis.

The time points for infusion start and end as well as rates for bolus and continuous infusion are described on a paper sheet along with measured blood glucose values from baseline to 12 hours. Any corrective glucose administered intravenously is documented. The specific care of the patients is at the discretion of the treating physician. If clinical signs of an allergic reaction or other life-threatening side effects are suspected the investigational product will be terminated immediately. If necessary, the treatment allocation can be un-blinded and a standard operating procedures manual is available to all clinicians involved in the trial.

Restrictive versus liberal oxygenation

The patient is allocated to either restrictive or liberal oxygenation. The attending nurse preparing the study drug infusion kits registers the allocation of restrictive or liberal oxygenation on the infusion kit labels, by ticking a box labeled 'FiO_2=50%' or a box labeled 'FiO_2=100%'.

The allocated oxygenation strategy is clearly communicated to the perfusionist and the anaesthetic nurse. The intervention period is defined as time on CPB (FiO_2 on oxygenator) and for the first hour after weaning off CPB (FiO2 on the ventilator). Tidal volumes and inspiratory pressures are adjusted according to local guidelines. Positive end-expiratory pressure, peak pressure, respiratory rate, and minute volumes are recorded at 5-minute intervals. In addition, arterial blood gases are analyzed at least once on CPB and once while ventilated during the intervention period.

Dosage adjustments are not intended. However, increasing FiO_2 is allowed if SaO_2 drops below 92% for more than 30 seconds or if deemed necessary to ensure the patients' safety. It is recommended, that FiO_2 is reduced as soon as it is considered safe for the patient, preferably to 50%. Any increase is at the treating physician's discretion, and any dose

adjustments are documented along with the reasons for increasing FiO_2 (SaO_2 < 92%, arrhythmia, concern for cerebral oxygenation etc.). The specific care of the patients is at the discretion of the treating physician, and information on protocol violations and/or concomitant therapy is collected on case report forms. Necessary interventions will not be delayed by the trial intervention.

Assessments

The investigator will be responsible for ensuring that all assessments are performed according to protocol, and that the data are recorded in the electronic case report forms. Specific plans for data entry and security have been described in the trial protocol. Missing data, as well as the reasons, must be reported in the case report forms. All routine laboratory analyses will be performed on point-of-care systems or at the hospital's local laboratory.

Preoperative assessments

Prior to surgery, the following variables will be noted in the case report forms:

- Verified informed consent
- Medical history including previous surgery
- New York Heart Association (NYHA) classification
- Euro Score and STS score (evaluated by the attending surgeon)
- Cerebral Performance Category (CPC)
- Modified Rankin Score (mRS)
- Self-perceived function "two simple questions"
- Left ventricular ejection fraction (LVEF)
- Physical examination including age, sex, height, body weight
- Vital signs including blood pressure (BP), heart rate (HR), respiratory rate (RR) and peripheral oxygenation (SAT)
- Any concomitant therapy

Follow-up assessments

Follow-up assessments will occur during index admission, after 3 and 12 months as well as at end of follow-up. The 3 months assessment will be done during an in-hospital visit, whereas the other assessments will be telephone/registry based.

At each follow-up the following will be recorded:

- The occurrence of any adverse events (AE)
- The occurrence of serious adverse events (SAE)
- NYHA classification
- Patient reported outcome (PRO) questionnaires will be answered at 1 week and 3 months
- Cerebral Performance Category (CPC)
- Modified Rankin Score (mRS)
- Self-perceived function "two simple questions"
- Vital signs will be recorded throughout admission and at 3 months follow-up visit

From the day after surgery all information on serious adverse events (SAE) will be recorded.

Blood sampling

Blood will be drawn for biochemistry at baseline, the morning after surgery, at day three and five after surgery and after three months. The following analyses will be conducted at each blood draw: Sodium, potassium, calcium, glucose, albumin, blood urea nitrogen, uric acid, bilirubin (total), creatinine, S-protein, red blood cell count, white blood cell count, platelet count, HbA1c (solely preoperatively), NT-proBNP, CRP. In addition, 3x10 mL of blood will be drawn and stored in a biobank for up to 20 years.

Substudy assessments

Each of the three substudies will make individual assessments as described below.

Cardio- and pulmonary protection substudy

The potential effect of the two interventions on the heart will be studied by transthoracic echocardiography in a sub-study. The first 1080 included patients will be examined by advanced 2D and 3D echocardiography the day before surgery, 4-6 days after surgery (before discharge) and 3 months after surgery. Besides global, regional and layer-specific circumferential, radial, longitudinal and area strain measures, the echocardiographic assessment will include evaluation of systolic function (2D LVEF, 3D LVEF/RVEF, dp/dt, mitral and tricuspid annular movement), diastolic function (left atrial volume, mitral inflow velocities, early and late diastolic mitral and tricuspid movements), cardiac time intervals,

valve disease, pericardial effusion and constriction, and ventricular, vena caval and aortic dimensions. The primary echocardiographic endpoint regarding both interventions in the trial is global longitudinal strain (GLS). In a subset of patients, a 6-minute hall walk test and serial 12-ECGs were also performed.

For the pulmonary protection substudy, an advanced lung function testing with DLCO is performed using the EasyOne Pro manufactured by ndd Medizintechnik AG, Technoparkstr. 1, 8005 Zürich, Switzerland, www.ndd.ch. The tests consist of spirometry and DLCO (dilution gas technique (10% helium, 0.3% carbon monoxide, and 18 % to 25 % oxygen (normally 21%)). The tests are performed the day before surgery, before discharge and on the follow-up visit after 3 months by trained study personnel where possible in the first 800 patients. Participation in the sub-study is voluntary.

The following hypothesis are investigated:

1) Exenatide infusion during cardiac surgery is associated with less decline DLCO and FEV1/FVC after 3 months compared to placebo.
2) Restrictive oxygenation during cardiac surgery is associated with less decline DLCO and FEV1/FVC after 3 months compared to placebo.

In addition, the association of advanced lung functions tests and prognosis, risk of AE and subsequent heart failure events are evaluated. Correlations to echocardiographic parameters of cardiac systolic and diastolic function are also evaluated.

Neuroprotection substudy

The neuroprotection substudy will be based on the biobank, measuring multiple markers of brain injury, cognitive outcomes at three months follow-up visit, and mRS and CPC scores. Biomarkers will be measured in the entire study cohort, whereas neurologic assessment is performed in the first 1100 patients only due to limited resources. The primary biobank measurement will be markers of cerebral injury measured the first days following surgery (primary endpoint), and secondary endpoints will include the relation to mRS, CPC, and risk of death during follow-up.

Renoprotection substudy

The primary outcome of the renoprotection substudy is acute kidney injury (AKI) defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, which is based on S-creatinine increases and urine output. Secondary outcomes will include glomerular filtration rate (GFR) measured by Cr-EDTA clearance, estimated glomerular filtration rate (eGFR) and novel biomarkers of AKI. The primary endpoint will be based on the entire study cohort.

Safety

The trial population consists of patients with ischemic heart disease and/or aortic valve disease, who undergo CABG and/or AVR. The majority of adverse events (AE) are relatively common irrespective of treatment strategies. The occurrence of any AE will be recorded daily during index admission and at all follow-ups.

Adverse events (AE)

AEs are defined as undesirable medical occurrences or worsening of pre-existing medical conditions that occur after initiation of the investigational product, whether or not considered to be related to the investigational product.

Serious adverse events (SAE)

SAEs are defined as AEs resulting in significant side effects including ones that are fatal, life threatening, require hospitalization of prolongation of hospitalization and/or are persistent or significant.

Suspected unexpected serious adverse reactions (SUSAR)

SUSARs are defined as unexpected, serious AEs with presumed relation to the investigational drug. The term 'unexpected' is defined using the Byetta® Summary of product characteristics (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf, current version 16th of August 2016) and the Conoxia® Summary of product characteristics available at the Danish Medicines Agency (http://www.produktresume.dk/docushare/dsweb/View/Collection-99, current version 11th of February 2016).

Reporting procedures

Safety variables and SAEs will be recorded continuously in the CRF during the first 7 days after surgery. AEs occurring after 7 days will be recorded at the pre-planned follow-up visits. All medically significant AEs considered by the investigator or the sponsor to be related to the investigational product will be followed until resolved or considered stable. The following attributes will be recorded by the investigator: description, dates of onset and resolution, severity, assessment of whether the AE is related to the investigational product, other suspected drugs or devices, and action taken. For each AE reported in the CRF, the investigator will adjudicate whether the event is a SAE. All SAEs will be recorded on a Serious Adverse Event Report form. The sponsor is responsible for reporting all SUSARs to the Danish Health and Medicines Authority as soon as possible and no later than 7 days after awareness.

Data Monitoring

A Data Monitoring and Safety Committee (DMSC) has been assembled and consists of individuals free of any potential conflicts of interests. The DMSC is responsible for ensuring the interests of trial participants, for assessing safety and efficacy of the two trial interventions and for monitoring the conduct of the trial. The DMSC can recommend stopping of continuing the trial to the trial steering committee (TSC). Also, the DMSC can formulate recommendations regarding all elements of the trial conduct, in order to enhance the trial integrity. Any recommendations from the DMSC regarding stopping, continuing or changing the trial will be communicated to the TSC without delay. The TSC is responsible for reviewing any recommendations from the DMSC and to determine, whether changes in trial conduct are required. The sponsor is responsible for reporting the number of SAEs and SUSARs to the DMSC bimonthly until 250 patients have been randomized. The need for further evaluation of SAEs and all-cause mortality will be decided by the DMSC. Interim analyses will be performed by a statistician selected by the DMSC.

An endpoint classification committee will adjudicate primary endpoints in a blinded fashion. Independent good clinical practice (GCP) units will monitor informed written consent forms, data quality and adjudication of endpoints.

Planned statistical analyses

Sample size estimation

This parallel group trial investigates two interventions, and we plan to analyze these two interventions as two separate studies. The effect of the two interventions are not expected to interact, therefore the design og sample size estimation did not account for such interaction. The study involving restrictive versus liberal oxygenation is subordinate to the study involving the GLP-1 analog, and the potential interactions of the two interventions will be analyzed in the GLP-1 analog trial. Thus, the power calculations are based on the GLP-1 analog intervention.

The trial is event driven, aiming at 323 primary endpoints to be able to show a 25% reduction in the primary endpoint with a power of 80% at an α-level of 0.05 (two-sided). Based on event rates from a variety of databases, including reporting from the surgical register at Rigshospitalet, we expect to include approximately 1400 patients in the trial and follow all patients until the last included patient has been followed for 12 months.

General principles

All analyses will be performed according to the intention-to-treat principle[42]. A two-sided significance level of 0.05 will be applied throughout. Missing data will be reported in the publication. In case of more than 5% missing data in outcome variables, multiple imputation with creation of 50 imputed datasets will be analyzed separately and aggregated into an estimate of the intervention's effect on the primary endpoint[43,44]. For non-fatal events, competing risk of events will be accounted for.

Inclusion profile

In accordance with the Consolidated Standards of Reporting Trials (CONSORT) diagram[45], a flowchart of the trial inclusion and exclusion profile will be provided.

Baseline variables

The following baseline variables will be included in table 1.

1) Demographics
    a. Sex
    b. Age per year
    c. BMI
    d. History of smoking

e. Estimated amount of alcohol consumed per week per grams

2) Previous medical history
   a. Comorbidity and function (including CPC-class, previous heart failure, previous myocardial infarction, ischemic heart disease, previous arrhythmia, previous cardiac arrest, arterial hypertension, transient ischemic attack or stroke, epilepsy, diabetes, asthma or chronic obstructive pulmonary disease, chronic hemodialysis or peritoneal dialysis, hepatic cirrhosis, hematological malignancy, other malignancy, AIDS, alcoholism, intravenous drug abuse, or other immunodeficiency)
   b. Previous percutaneous coronary intervention
   c. Previous coronary artery bypass grafting
   d. Previous aortic valve surgery
   e. Implantable cardioverter-defibrillator and/or pacemaker
   f. Current medical therapy at time of surgery
3) Surgical procedure
   a. Indication for surgery
   b. Coronary artery bypass grafting
      i. Number of grafts, stratified by arterial and venous grafts
   c. Aortic valve replacement, stratified by type of valve
   d. Combined coronary artery bypass graft and aortic valve replacement
   e. Duration of surgery (minutes)
   f. Duration of cardiopulmonary bypass (minutes)
   g. Duration of aortic cross clamp time (minutes)

Baseline variables will be stratified according to treatment allocation. Continuous variables will be presented as mean ± SD if normally distributed or otherwise as median (interquartile range). Differences between allocation groups will be tested with the independent sample t-test, potentially after logarithmic transformation for lognormally distributed variables, or the non-parametric Mann-Whitney test as appropriate. Categorical variables will be presented as number (percentage) and differences between allocation groups will be tested with the chi-square test or the Fisher's exact test as appropriate.

Endpoint analyses

Primary endpoint

For each of the two interventions (exenatide and oxygenation), Kaplan-Meier curves will be graphically displayed, and compared using the two-sided log-rank test. In addition, a multivariable analysis of the time to first event will be performed using Cox proportional hazard models. The model will be adjusted for the following covariates: treatment allocation, age, sex, body mass index, indication for surgery, procedure (CABG vs AVR vs CABG+AVR), known alcohol or drug abuse, Charlson comorbidity index, previous PCI, previous CABG, previous AVR, length of procedure, length of cardiopulmonary bypass. The hazard ratio with 95% confidence intervals will be reported.

Since the primary intervention is exenatide versus placebo, the potential interactions between this treatment and the oxygenation-allocation on outcome and treatment will be estimated in the article on exenatide via the Cox proportional hazard models, with oxygenation group as a covariate in the model.

Censoring: Subjects withdrawing from the study early (other than for withdrawal of consent) will be followed for potential development of the primary endpoint. Subjects completing the study and not experiencing the composite event will be censored.

Secondary endpoint

Time to the individual secondary endpoints will be analyzed with Kaplan-Meier estimates for all-cause mortality and cumulative incidence rates for other endpoints taking competing risk of death into account. The censoring mechanism will be similar to the one applied to the primary endpoint. The type 1 error rate associated with multiple comparisons will be controlled with the application of Benjamini-Hochberg adjustment[46].

Differences in the occurrence of pre-defined adverse events between allocation groups will be analyzed with the chi-square test or the Fisher's exact test, as appropriate.

Changes in continuous variables over time will be analyzed using linear mixed models.

Safety endpoint

Incidence rates of adverse events will be graded according to severity and relationship to the investigational product. Tables of deaths, serious and significant adverse events, including ones causing early withdrawal will be provided. Differences in incidence of adverse events, as

well as the cumulative incidence of adverse events between groups, will be analyzed with the chi-square test or the Fisher's exact test, as appropriate.

Ethics and Dissemination

Participation in the trial will not delay routine or therapeutic procedures. The mortality and morbidity after open heart surgery (including CABG and AVR) are mainly caused by organ failure and inflammation. Thus, methods of organ protection are considered essential for reducing the mortality after open heart surgery. In addition, increased knowledge of organ function following surgery will potentially be of benefit to patients undergoing open heart surgery.

Exenatide has been used for treatment of type 2 diabetes for years. In addition, it has been used in STEMI patients and out-of-hospital cardiac arrest patients without increased risk of adverse events compared to placebo. As infusion of study-drug will occur simultaneously with surgery, and the allocated oxygenation strategy will occur during CPB, when weaning from and the following hour after weaning from CPB, the participants will experience no side effects. The organ protective effects of exenatide and restrictive oxygenation during open heart surgery cannot be gained outside the clinical setting, and human experimental models are obviously unethical. All patients will provide oral and written informed consent prior to inclusion in the trial.

Approvals

The trial is conducted in accordance with Danish legislation and the Helsinki declaration. In addition, the trial is conducted in accordance with international standards for good clinical practice (GCP) and is monitored by an independent GCP-unit. The trial is surveyed by a DMSC with full access to the study database upon request. The trial protocol, including any amendments and written information- and consent forms have been approved prior to initiation of the trial by the local ethics committee (ref. no. H-15010562). In addition, The Danish Health and Medicines Authority approved the trial (protocol ref. HJE-PHARMA-001, EudraCT no. 2015-003050-41). The full protocol is published at www.clinicaltrials.gov (ID no. NCT02673931)

Dissemination

All results will be published in international, peer-reviewed journals and presented at international congresses. Co-authorships will be granted in accordance with the Vancouver guidelines. In case the trial demonstrates a significant, positive effect of exenatide or restrictive oxygenation during heart surgery these treatment strategies will be easy to implement.

References

1 Mao Z, Zhong X, Yin J, *et al.* Predictors associated with stroke after coronary artery bypass grafting: A systematic review. *J Neurol Sci* 2015;**357**:1–7. doi:10.1016/j.jns.2015.07.006

2 Wijeysundera D, Karkouti K, Beattie S, *et al.* Improving the Identification of Patients at Risk of Postoperative Renal Failure after Cardiac Surgery. *Anesthesiology* 2005;**104**:65–72.

3 Salamonsen RF, Schneider HG, Bailey M, *et al.* Cardiac troponin I concentrations, but not electrocardiographic results, predict an extended hospital stay after coronary artery bypass graft surgery. *Clin Chem* 2005;**51**:40–6. doi:10.1373/clinchem.2004.041103

4 Houlind K, Kjeldsen BJ, Madsen SN, *et al.* On-Pump Versus Off-Pump Coronary Artery Bypass Surgery in Elderly Patients Results From the Danish On-Pump Versus Off-Pump Randomization Study. *Circulation* 2012;**125**:2431–9. doi:10.1161/CIRCULATIONAHA.111.052571/-/DC1

5 Nicolini F, Vezzani A, Fortuna D, *et al.* Gender differences in outcomes following isolated coronary artery bypass grafting: long-term results. *J Cardiothorac Surg* 2016;**11**:1–12. doi:10.1186/s13019-016-0538-4

6 Thyregod HGH, Steinbrüchel DA, Ihlemann N, *et al.* Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis 1-Year Results From the All-Comers NOTION Randomized Clinical Trial. *J Am Coll Cardiol* 2015;**65**:2184–94.

7 Pannu N, Graham M, Klarenbach S, *et al.* A new model to predict acute kidney injury requiring renal replacement therapy after cardiac surgery. *CMAJ* 2016;**188**:1076–83. doi:10.1503/cmaj.151447

8 Mérie C, Køber L, Olsen PS, *et al.* Risk of Stroke After Coronary Artery Bypass Grafting. *Stroke* 2011;**43**:38–43. doi:10.1161/STROKEAHA.111.620880/-/DC1

9 Newman MF, Kirchner JL, Phillips-Bute B, *et al.* Longitudinal Assessment of Neurocognitive Function after Coronary-Artery Bypass Surgery. *N Engl J Med* 2001;**344**:395–402.

10 Selnes OA, Grega MA, Bailey MM, *et al.* Do Management Strategies for Coronary Artery Disease Influence 6-Year Cognitive Outcomes? *ATS* 2009;**88**:445-454.e3. doi:10.1016/j.athoracsur.2009.04.061

11 Cropsey C, Kennedy J, Han J, *et al.* Cognitive Dysfunction, Delirium, and Stroke in Cardiac Surgery Patients. *Semin Cardiothorac Vasc Anesth* 2015;**19**:309–17. doi:10.1177/1089253215570062

12 Nagels W, Demeyere R, Van Hemelrijck J, *et al.* Evaluation of the Neuroprotective Effects of S(+)-Ketamine During Open-Heart Surgery. *Anesth Analg* 2004;**98**:1595–603. doi:10.1213/01.ANE.0000117227.00820.0C

13 Taggart DP, Browne SM, Wade DT, *et al.* Neuroprotection during cardiac surgery: a randomised trial of a platelet activating factor antagonist. *Heart* 2003;**89**:897–900.

14 Wang D, Wu X, Li J, *et al.* The Effect of Lidocaine on Early Postoperative Cognitive Dysfunction After Coronary Artery Bypass Surgery. *Anesth Analg* 2002;**95**:1134–41. doi:10.1213/01.ANE.0000027870.09122.51

15 Arrowsmith J, Harrison MJG, Newman SP, *et al.* Neuroprotection of the Brain During Cardiopulmonary Bypass: A Randomized Trial of Remacemide During Coronary Artery Bypass in 171 Patients. *Stroke* 2015;**29**:2357–62.

16 Kong RS, Butterworth J, Aveling W, *et al.* Clinical Trial of the Neuroprotectant Clomethiazole in Coronary Artery Bypass Graft Surgery A Randomized Controlled Trial. *Anesthesiology* 2002;**97**:585–91.

17 Holscher C. Potential Role of Glucagon-Like Peptide-1(GLP-1) in Neuroprotection. *CNS Drugs* 2012;**26**:871–82.

18 McClean PL, Parthsarathy V, Faivre E, *et al.* The Diabetes Drug Liraglutide Prevents Degenerative Processes in a Mouse Model of Alzheimer's Disease. *J Neurosci* 2011;**31**:6587–94. doi:10.1523/JNEUROSCI.0529-11.2011

19 Harkavyi A, Abuirmeileh A, Lever R, *et al.* Glucagon-like peptide 1 receptor stimulation by exendin-4 reverses key deficits in distinct rodent models of Parkinson's disease. *J Neuroinflammation* 2008;**5**:19. doi:10.1186/1742-2094-5-19

20 Li Y, Chigurupati S, Holloway HW, *et al.* Exendin-4 Ameliorates Motor Neuron Degeneration in Cellular and Animal Models of Amyotrophic Lateral Sclerosis. *PLoS One* 2012;**7**:e32008-13. doi:10.1371/journal.pone.0032008

21 Teramoto S, Miyamoto N, Yatomi K, *et al.* Exendin-4, a glucagon-like peptide-1 receptor agonist, provides neuroprotection in mice transient focal cerebral ischemia. *J Cereb Blood Flow & Metab* 2011;**31**:1696–705. doi:10.1038/jcbfm.2011.51

22 Timmers L, Henriques JPS, de Kleijn DP V, *et al.* Exenatide Reduces Infarct Size and Improves Cardiac Function in a Porcine Model of Ischemia and Reperfusion Injury. *J Am Coll Cardiol* 2009;**53**:501–10. doi:10.1016/j.jacc.2008.10.033

23 Lonborg J, Vejlstrup N, Kelbaek H, *et al.* Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 2012;**33**:1491–9. doi:10.1093/eurheartj/ehr309

24 Lonborg J, Kelbaek H, Vejlstrup N, *et al.* Exenatide Reduces Final Infarct Size in Patients With ST-Segment-Elevation Myocardial Infarction and Short-Duration of Ischemia. *Circ Cardiovasc Interv* 2012;**5**:288–95. doi:10.1161/CIRCINTERVENTIONS.112.968388

25 Woo J. Cardioprotective Effects of Exenatide in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *Arter Thromb Vasc Biol* 2013;:2252–60. doi:10.1161/ATVBAHA.113.301586/-/DC1

26 Bernink FJP, Timmers L, Diamant M, *et al.* Effect of additional treatment with EXenatide in patients with an Acute Myocardial Infarction: The EXAMI study. *Int J Cardiol* 2013;**167**:289–90. doi:10.1016/j.ijcard.2012.09.204

27 Wiberg S, Hassager C, Schmidt H, *et al.* Neuroprotective Effects of the Glucagon-Like Peptide-1 Analog Exenatide After Out-of-Hospital Cardiac Arrest: A Randomized Controlled Trial. *Circulation* 2016;:CIRCULATIONAHA.116.024088-12. doi:10.1161/CIRCULATIONAHA.116.024088

28 Vereczki V, Martin E, Rosenthal RE, *et al.* Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death. *J Cereb Blood Flow Metab* 2005;**26**:821–35. doi:10.1038/sj.jcbfm.9600234

29 Liu Y, Rosenthal RE, Haywood Y, *et al.* Normoxic Ventilation After Cardiac Arrest Reduces Oxidation of Brain Lipids and Improves Neurological Outcome. *Stroke* 1998;**29**:1679–86. doi:10.1161/01.STR.29.8.1679

30 Kallet RH, Matthay MA. Hyperoxic Acute Lung Injury. *Respir Care* 2012;**58**:123–41. doi:10.4187/respcare.01963

31 Schreiber JU, Lancé MD, de Korte M, *et al.* The Effect of Different Lung-Protective Strategies in Patients During Cardiopulmonary Bypass: A Meta-Analysis and Semiquantitative Review of Randomized Trials. *J Cardiothorac Vasc Anesth* 2012;**26**:448–54. doi:10.1053/j.jvca.2012.01.034

32 Anderson KJ, Harten JM, Booth MG, *et al.* The cardiovascular effects of normobaric hyperoxia in patients with heart rate fixed by permanent pacemaker. *Anaesthesia* 2010;**65**:167–71. doi:10.1111/j.1365-2044.2009.06195.x

33 Hovaguimian F, Lysakowski C, Elia N, *et al.* Effect of Intraoperative High Inspired Oxygen Fraction on Surgical Site Infection, Postoperative Nausea and Vomiting, and Pulmonary Function_Systematic Review and Meta-analysis of Randomized Controlled Trials. *Anesthesiology* 2013;**119**:303–16.

34 Meyhoff CS, Jorgensen LN, Wetterslev J, *et al.* Increased Long-Term Mortality After a High Perioperative Inspiratory Oxygen Fraction During Abdominal Surgery. *Anesth Analg* 2012;**115**:849–54. doi:10.1213/ANE.0b013e3182652a51

35 Girardis M, Busani S, Damiani E, *et al.* Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit. *JAMA* 2016;**316**:1583–7. doi:10.1001/jama.2016.11993

36 Chu DK, Kim LH-Y, Young PJ, *et al.* Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018;**391**:1693–705.http://www.crd.york.ac.uk/

37 Schjørring OL, Klitgaard TL, Perner A, *et al.* Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. *N Engl J Med* 2021;:1–11. doi:10.1056/NEJMoa2032510

38 Stub D, Smith K, Bernard S, *et al.* Air Versus Oxygen in ST-Segment–ElevationMyocardial Infarction. *Circulation* 2015;**131**:2143–50. doi:10.1161/CIRCULATIONAHA.114.014494/-/DC1

39 Hofmann R, James SK, Jernberg T, *et al.* Oxygen Therapy in Suspected Acute Myocardial Infarction. *N Engl J Med* 2017;**377**:1240–9. doi:10.1056/nejmoa1706222

40 Smit B, Smulders YM, de Waard MC, *et al.* Moderate hyperoxic versus near-physiological oxygen targets during and after coronary artery bypass surgery: a randomised controlled trial. *Crit Care* 2016;**20**:1–10. doi:10.1186/s13054-016-1240-6

41 Thygesen K, Alpert JS, Jaffe AS, *et al.* Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–67. doi:10.1093/eurheartj/ehs184

42 Fergusson D, Aaron S, Guyatt G, *et al.* Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *Br Med J* 2002;**325**:652–4.

43 Donders ART, van der Heijden GJMG, Stijnen T, *et al.* Review: A gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006;**59**:1087–91. doi:10.1016/j.jclinepi.2006.01.014

44 Schafer JL, Graham JW. Missing data: Our view of the state of the art. *Psychol Methods* 2002;**7**:147–77. doi:10.1037//1082-989X.7.2.147

45 Moher D, Schulz KF, Altman DG, *et al.* The CONSORT statement: revised recommendations for improvingthe quality of reports of parallel-group randomised trials. *Lancet* 2001;**357**:1191–4.

46 Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc* 1995;**57**:289–300.

Author contributions

Authors SW, JK, RM, CHM, KK, HR, CH, LK, JCN all contributed equally to the conceptualization of the trial or substudies. All authors have contributed to drafting and writing the protocol and sub-study protocols. Author SW wrote the first draft of this design article based on the study protocol. All authors, SW, JK, RM, CHM, KK, HR, CH, LK, JCN have read and approved the final manuscript.

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Competing interests

The authors declare, that they have no competing interests.

Trial status

Inclusion of patients began on February 5th 2016 and is expected to be complete by the end of 2021. Final follow-up is expected to be complete by 2022.

Table 1. Inclusion and exclusion criteria

Inclusion criteria

1. Appropriately obtained written informed consent
2. Age ≥ 18 years
3. Ischemic heart disease requiring CABG and/or aortic valve disease requiring AVR, irrespective of other concomitant valve surgery

Exclusion criteria

1. Active treatment with GLP-1 analogs
2. Obstructive hypertrophic cardiomyopathy, active myocarditis, constrictive pericarditis
3. Hyperthyroidism or untreated hypothyroidism
4. History of, or active pancreatitis
5. Acute surgery; subacute surgery (i.e. the following days) are eligible
6. Known allergy towards exenatide/Byetta or albumin (vehicle)
7. On the urgent waiting list for a heart transplant (UNOS category 1A or 1B or equivalent)
8. Recipient of any major organ transplant (e.g. Heart, lung, liver)
9. Receiving of has received cytotoxic or cytostatic chemotherapy and/or radiation therapy for treatment of malignancy within 6 month before randomization
10. Clinical evidence of current malignancy, with the exceptions of: basal or squamous cell carcinoma, cervical intraepithelial neoplasia, prostate cancer with a life expectancy of > 2.5
11. Currently enrolled in, or within 30 days from ending participation in other investigational drug trials for the treatment of diabetes or malignant obesity. Participation in other non-pharmacological trials is not an exclusion criteria
12. Recent, within 3 months, history of alcohol or drug abuse disorder, based on self-report.
13. Pregnancy or currently breast feeding
14. Any condition or situation that, in the investigator's opinion, could put the subject at significant risk, confound the trial's results or interfere with the subject's participation in the trial
15. Previous participation in the present trial

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 26
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10, table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10-11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17-19
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15-16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16-20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20-21

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20-21
	31b	Authorship eligibility guidelines and any intended use of professional writers	20-21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Efficacy of a glucagon-like peptide-1 agonist and restrictive vs. liberal oxygen supply in patients undergoing coronary artery bypass grafting or aortic valve replacement: Study protocol for a 2-by-2 factorial designed, randomized clinical trial

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Efficacy of a glucagon-like peptide-1 agonist and restrictive vs. liberal oxygen supply in patients undergoing coronary artery bypass grafting or aortic valve replacement: Study protocol for a 2-by-2 factorial designed, randomized clinical trial

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Short Title
GLP-1 agonists and restrictive oxygenation for organ protection in heart surgery

Acronym
GLORIOUS

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Trial registration

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2. Local ethics committee "Videnskabsetisk komité C, Region Hovedstaden": No. H-15010562
3. www.clinicaltrials.gov: ID no. NCT02673931

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Abstract

Introduction

Coronary artery bypass grafting (CABG) and/or aortic valve replacement (AVR) are associated with risk of death, as well as brain-, heart-, and kidney injury. Glucagon-like peptide-1 (GLP-1) analogs are approved for treatment of type 2 diabetes, and GLP-1 analogs have been suggested to have potential organ-protective and anti-inflammatory effects. During cardiopulmonary bypass (CPB), consensus on the optimal fraction of oxygen is lacking. The objective of the present study is to determine the efficacy of the GLP-1- analog exenatide versus placebo and restrictive oxygenation (50% FiO2) versus liberal oxygenation (100% FiO2) in patients undergoing open heart surgery.

Methods and analysis

A randomized, placebo-controlled, double blind (for the exenatide intervention)/single blind (for the oxygenation strategy), parallel group, 2x2 factorial designed single-center trial on adult patients undergoing elective or subacute CABG and/or surgical AVR. Patients will be randomized in a 1:1 and 1:1 ratio to a 6 hours and 15 minutes infusion of 17.4 µg of exenatide or placebo during CPB and to a FiO2 of 50% versus 100% during and after weaning from CPB. Patients will be followed until 12 months after inclusion of the last participant. The primary composite endpoint consists of time to first event of death, renal failure requiring renal replacement therapy, hospitalization for stroke or heart failure. In addition, the trial will include predefined sub-studies applying more advanced measures of cardiac- and pulmonary dysfunction, renal dysfunction and cerebral dysfunction. The trial is event-driven and aims at 323 primary end-points with a projected inclusion of 1400 patients.

Ethics and dissemination

Eligible patients will provide informed, written consent prior to randomization. The trial is approved by the local ethics committee and is conducted in accordance with Danish legislation and the Declaration of Helsinki. The results will be presented in peer reviewed journals.

Registration

The study was approved by the Danish Health and Medicines Authority (Protocol no. HJE-PHARMA-001, EudraCT no. 2015-003050-41, 2nd of October 2015) and by the institutional review board (No. H-15010562). The trial was registered at www.clinicaltrials.gov (No. NCT02673931).

Strengths and limitations

- First clinical study to investigate the efficacy of a GLP-1 analog and restrictive oxygenation in patients undergoing open heart surgery.
- Randomized, placebo-controlled double/single blind 2-by-2 factorial trial design conducting analyses on the intention-to-treat population
- Large trial expected to include 1400 patients
- Setting is limited to a single center

Introduction

In modern management of coronary artery disease (CAD), coronary artery bypass grafting (CABG) is often indicated, and in management of aortic stenosis, aortic valve replacement (AVR) is often applied. Both procedures require the use of cardiopulmonary bypass (CPB). During CPB, blood is exposed to artificial surfaces and mechanical stress potentially resulting in risk of arterial emboli and a systemic inflammatory response syndrome (SIRS) with the potential of organ damage and multiple organ failure. Patients with CAD have associated atherosclerotic disease and ischemia-induced damage to the brain, kidneys and myocardium is frequent following open heart surgery[1–3].

Following elective open heart surgery the 30-day mortality is 1-2% for CABG[4,5] and 4% for valve surgery[6]. In elderly patients with reduced renal function and comorbidities, the 30-day mortality is as high as 20%[4]. Complications include severe heart failure and cardiogenic shock, graft occlusion or occlusion of coronary arteries, renal failure, stroke, and/or development of severe inflammatory response syndrome (SIRS), which may be lethal.

The risk of acute kidney injury (AKI) requiring temporary dialysis after open heart surgery is 2-3% dependent on the kidney function prior to surgery and patient age. Often, AKI is seen in conjunction with progression or development of heart failure and low cardiac output syndrome (LCOS)[7]. The risk of stroke during and after CABG is 1-5%[1,8]. Factors associated with stroke in cardiac surgery are higher age, previous atherosclerotic-associated diseases and prolonged CPB-time[1]. The risk of cognitive deficits after open heart surgery is above 50% decreasing to approximately 30% after one year[9], however, one study did not find any difference in cognitive decline in atherosclerotic patients undergoing CABG compared to atherosclerotic patients not undergoing CABG[10]. Suggested risk factors for cognitive decline are higher age and duration of bypass, however surgical technique (valve-insertion, CPB etc.), equipment and de-airing techniques may also be of importance. The physiological mechanisms suggested to cause cognitive decline include cerebral microembolism, SIRS and altered cerebral flow including LCOS[11]. Several pharmacological interventions have been tested to mitigate cerebral damage during heart surgery; however, the success has been limited[12–16]. Hence, there are no pharmacological interventions currently in use to hinder ischemic damage during CPB.

Glucagon-like peptide-1 analogs

Glucagon-like peptide-1 (GLP-1) analogs are incretin mimetics and thus increase insulin release and inhibit glucagon release. Several GLP-1 analogs, including exenatide, are approved for the treatment of type 2 diabetes.

Pre-clinical data

GLP-1 analogs have been suggested to have complex neuroprotective effects and anti-inflammatory properties[17]. In rodent models, GLP-1 analogs have been shown to ameliorate neurological diseases such as Alzheimer's disease[18], Parkinson's disease[19], and amyotrophic lateral sclerosis[20]. In animal stroke models, GLP-1 analogs reduce the final infarct size[21–24]. The mechanisms are suggested to be mediated by the intracellular AMP/PKA/CREB and the PI3K/Akt pathways, and to include reduced inflammation, oxidative stress, and apoptosis that occur secondary to stroke[25]. In models of acute myocardial infarction (MI) GLP-1 analogs reduce the infarct size[26,27]. While the understanding of the underlying mechanisms is incomplete, cardio protection induced by activation of GLP-1 receptors has been suggested to be mediated by a mechanism involving muscarinic receptors[28]. Further, GLP-1 receptor activation has been demonstrated to oppose the effects of beta-adrenoceptor stimulation of cardiac ventricular excitability and to reduce ventricular arrhythmic potential[29].

Clinical data

In humans, the GLP-1 analog exenatide has been associated with increased myocardial salvage when initiated before revascularization after MI[30], and in patients with a limited time of ischemia, exenatide resulted in a smaller infarct size[31], which has been confirmed by later trials[32,33]. Importantly, exenatide has been administered to severely ill patients with ST-segment elevation MI (STEMI)[31] and to patients resuscitated from out-of-hospital cardiac arrest[34] with no increased risk of adverse events.

Liberal versus restrictive oxygen administration during weaning from CPB

When weaning from CPB, there is currently no consensus on the optimal oxygen fraction, but a majority is offering a high oxygen (FiO2> 50%), which then gradually is reduced to maintain saturations >95% before the patient is transferred to the intensive care unit (ICU).

Pre-clinical data

Several pre-clinical studies have suggested potential beneficial effects of hyperoxia in the pre-clinical setting. Conversely, it has been shown, that hyperoxia increases cerebral damage following brain ischemia in cardiac arrest models of no-flow[35,36], as well as after deep hypothermic circulatory arrest[37].

Clinical data

During and after CPB, one of the main perioperative goals is to maintain end-organ oxygenation. Accordingly, high FiO_2 levels have routinely been administered during and after CPB to protect against the risk of hypoxia and consequently organ ischemia.

Hyperoxia has been investigated in several settings, and a final consensus on its hazards and benefits has not been reached. For simplicity, henceforth the term hyperoxia will be used in situations where the FiO_2 is increased above 50%. In addition to the avoidance of ischemia, suggested beneficial effects of hyperoxia during cardiac surgery include preconditioning of the myocardium to better tolerate ischemia, and a reduction in gaseous microemboli generated during CBP[38,39]. While hyperoxia has previously been suggested to reduce the risk of surgical site infection[40], contemporary results have been conflicting. Hyperoxia increases the risk of developing lung injury (hyperoxia-induced acute lung injury); however, it seems that several days of hyperoxia is a prerequisite for this[41], and the risk of lung injury caused by shorter periods of hyperoxia is presumably small. Ischemic reperfusion injury of the lung in relation to CPB has been investigated in smaller trials; however, the impact of different ventilation strategies is questionable[42]. Hyperoxia may be associated with an increase in systemic vascular resistance, and may not be associated with improved tissue oxygenation[43,44]. Recently, hyperoxia has been associated with a reduced risk of surgical site infection after abdominal surgery in a meta-analysis[45], however a large RCT found an association between hyperoxia and increased mortality in patients with malignancy undergoing abdominal surgery[46]. A single-center RCT and a meta-analysis found that a restrictive oxygenation strategy resulted in reduced mortality in critically ill patients admitted to the ICU[47,48], while a recent multi-center RCT in ICU patients found no difference in higher versus lower oxygen targets[49]. In patients with ST-elevation acute myocardial infarction, routine administration of oxygen was associated with increased myocardial injury in one study[50], however, another study found no effect of routine

administration of oxygen in patients with suspected myocardial infarction[51]. Importantly, a recent small study has demonstrated, that a restrictive oxygenation strategy in patients undergoing CABG is safe[52]. Further research is warranted, and the risks versus benefits of hyperoxia during CPB and immediately after weaning from CPB are unknown.

Hypothesis

1. Infusion with the GLP-1 analog exenatide started pre-operatively in patients undergoing elective or subacute CABG and/or AVR will reduce mortality and morbidity from heart, brain and kidney injury.
2. Restrictive oxygenation (FIO_2=50%) compared to liberal oxygenation (FiO_2=100%) during CPB and the first hour after weaning from CPB will reduce the mortality and morbidity from heart, brain and kidney injury, without increasing the risk of significant surgical site infection.

As no consensus on oxygenation targets exists, the two oxygenation strategies were based on expert opinion and endorsed by the trial steering committee. No substantial interaction between the two interventions are expected[53]. In addition to the main hypothesis, three sub-studies will be a part of the trial. These sub-studies will investigate the effects of GLP-1 analogs and oxygenation strategy on cardio- and pulmonary-protection, neuro-protection, and renal-protection, respectively.

Endpoints

Endpoint data will be collected and noted on specific electronic CRFs. Supporting information will be provided to the endpoint adjudication committee for confirmation of events.

Primary endpoint

The efficacy of exenatide versus placebo and restrictive versus liberal oxygenation will be assessed by the time to the first occurring of the following co-primary endpoints within the follow-up period ending 12 months after inclusion of the last included participant:

1) Death from any cause, or
2) The occurrence of any of the following adverse events, adjudicated by an endpoint committee blinded for treatment allocation:
    a. Renal failure requiring any type of renal replacement therapy

b. Stroke, defined as any sign or symptom of neurological dysfunction persisting for more than 24 hours, determined by the treating physician based on clinical information like CT-scan etc.
c. New onset or worsening heart failure defined as need for mechanical circulatory support at the ICU, inability to close the sternum due to hemodynamic instability and/or need for inotropic hemodynamic support more than 48 hours after initiation of the first surgical procedure after randomization. In addition, any admission for heart failure during follow-up after discharge from the index admission.

Secondary endpoints

1) Time in days to occurrence of each individual endpoint, within the follow-up period:
   a. Time to death from any cause, or
   b. Time to AKI requiring renal replacement therapy, or
   c. Time to stroke, or
   d. Time to re-hospitalization for heart failure, or time to new onset or worsening in-hospital heart failure
2) Incidence of any of the following safety endpoints:
   a. Surgical site infections with need for antibiotics for more than 48 hours (excluding routine use of antibiotics for open sternum, surgical intervention, and/or endocarditis within 6 months of surgery, or
   b. Doubling of S-creatinine or urine output below 0.5 mL/kg/hour for 12 hours or more at any time point during index admission, or
   c. Hypoglycemia, defined as blood glucose < 3 mmol/L, during index admission, or
   d. Pancreatitis, defined as s-amylase > 3 times upper normal limit, during index admission, or
   e. A relative reduction of LVEF of 50% compared to baseline at any time point during index admission, or
   f. Re-operation for bleeding during index admission, or
   g. Re-operation for any cause during index admission, or
   h. Post-surgery MI (Type 5 MI[54]) during index admission, or
   i. Re-admission for cardiovascular causes within 12 months

3) Change in Cerebral Performance Category (CPC) from baseline to 12 months
4) Change in modified Rankin Scale (mRS) from baseline to 12 months

Methods and analysis

This is a randomized, placebo-controlled, double blind (for the exenatide intervention)/single blind (for the oxygenation strategy), 2x2 factorial designed single-center trial on adult patients undergoing elective or subacute CABG and/or AVR. Patients are enrolled from a Danish tertiary university hospital with a catchment area of 2.2 million citizens older than 18 years of age.

After completion of screening and baseline procedures, patients will be randomized to receive a GLP-1 analog or placebo and restrictive or liberal oxygenation in a 1:1 and 1:1 ratio. By design, the factorial design of the trial can be used to test two different interventions, and as such, the trial can be regarded as two independent trials. Patients will be followed until 12 months after inclusion of the last participant.

Patient and public involvement

No patient involved.

Inclusion

Patients undergoing elective or subacute CABG and/or AVR will be eligible for screening, irrespective of other concomitant valve surgery All patients will receive oral and written information and must sign the informed consent form, approved by the local ethics committee, prior to randomization This is in accordance with Danish legislation. After provision of informed consent, patients will be registered in the trial database, and will be provided with a unique study ID. A trained study nurse will screen the patients according to the predefined inclusion and exclusion criteria (Table 1) during their preoperative admission. If the criteria are met, the patients will be randomly allocated to one of the four allocation arms (GLP-1 analog vs placebo and restrictive vs. liberal oxygenation) via an internet-based randomization algorithm using permuted blocks of 4, 8 or 12 participants on the trial website. Randomization will be stratified by planned AVR. In addition, baseline characteristics will be noted in the case report forms.

Interventions

GLP-1 analog versus placebo

A GLP-1 analog, exenatide (Byetta®), or placebo will be administered as a 6 hour and 15 minutes infusion starting at the time of anesthesia immediately prior to surgery. The study drug (i.e. either exenatide or placebo) is prepared by trained nurses with experience in preparation and administration of intravenous medications. The trial website lists enrolled patients by study ID, initials, social security number and randomization allocation, i.e. either exenatide or placebo. The study drug infusion kit consists of 1.5 mL of 20% Human Albumin to 248.5 mL of isotonic NaCl, and then 25 µg of exenatide (Byetta®, Lilly) is added to patients allocated to the active study drug arm. The infusion kit is labeled with study ID, social security number as well as date and initials of the manufacturing nurse.

For each included patient, the infusion kit is brought to the coordinating anesthetist by an investigator who is blinded from study drug allocation. The coordinating anesthetist, who is blinded from study drug allocation, is responsible for delivering the correct investigational product to the operating theatre. The attending nurse of anesthesia, also blinded from study drug allocation, is responsible for initiation of the study-drug infusion. The study drug infusion is initiated within one hour of scheduled start of surgery at a rate of 72mL/hour (0.12 µg/min) for 15 minutes (at a set volume of 18mL), followed by 26mL/hour (0.043 µg/min) for 6 hours (at a set volume of 156mL). Thus, a total of 17.4 µg of exenatide is administered. The infusion can be given in either a central or a peripheral intravenous line. The dosage and infusion rate were based on laboratory data and previously randomized trials of exenatide for cardio protection in STEMI patients, and of exenatide for neuroprotection in patients after out-of-hospital cardiac arrest [55,56]. Notably, in these two trials enrolling severely ill patients, the infusion rates used were not associated with an increased risk of adverse events including severe hypoglycemia or acute pancreatitis.

The time points for infusion start and end as well as rates for bolus and continuous infusion are described on a paper sheet along with measured blood glucose values from baseline to 12 hours. Any corrective glucose administered intravenously is documented. The specific care of the patients is at the discretion of the treating physician. If clinical signs of an allergic reaction or other life-threatening side effects are suspected the investigational product will be

terminated immediately. If necessary, the treatment allocation can be un-blinded and a standard operating procedures manual is available to all clinicians involved in the trial.

Restrictive versus liberal oxygenation

The patient is allocated to either restrictive or liberal oxygenation. The attending nurse preparing the study drug infusion kits registers the allocation of restrictive or liberal oxygenation on the infusion kit labels, by ticking a box labeled 'FiO_2=50%' or a box labeled 'FiO_2=100%'.

The allocated oxygenation strategy is clearly communicated to the perfusionist and the anaesthetic nurse. The intervention period is defined as time on CPB (FiO_2 on oxygenator) and for the first hour after weaning off CPB (FiO2 on the ventilator). Tidal volumes and inspiratory pressures are adjusted according to local guidelines. Positive end-expiratory pressure, peak pressure, respiratory rate, and minute volumes are recorded at 5-minute intervals. In addition, arterial blood gases are analyzed at least once on CPB and once while ventilated during the intervention period.

Dosage adjustments are not intended. However, increasing FiO_2 is allowed if SaO_2 drops below 92% for more than 30 seconds or if deemed necessary to ensure the patients' safety. It is recommended, that FiO_2 is reduced as soon as it is considered safe for the patient, preferably to 50%. Any increase is at the treating physician's discretion, and any dose adjustments are documented along with the reasons for increasing FiO_2 (SaO_2 < 92%, arrhythmia, concern for cerebral oxygenation etc.). The specific care of the patients is at the discretion of the treating physician, and information on protocol violations and/or concomitant therapy is collected on case report forms. Necessary interventions will not be delayed by the trial intervention.

Assessments

The investigator will be responsible for ensuring that all assessments are performed according to protocol, and that the data are recorded in the electronic case report forms. Specific plans for data entry and security have been described in the trial protocol. Missing data, as well as the reasons, must be reported in the case report forms. All routine laboratory analyses will be performed on point-of-care systems or at the hospital's local laboratory.

Preoperative assessments

Prior to surgery, the following variables will be noted in the case report forms:

- Verified informed consent
- Medical history including previous surgery
- New York Heart Association (NYHA) classification
- Euro Score and STS score (evaluated by the attending surgeon)
- Cerebral Performance Category (CPC)
- Modified Rankin Score (mRS)
- Self-perceived function "two simple questions"
- Left ventricular ejection fraction (LVEF)
- Physical examination including age, sex, height, body weight
- Vital signs including blood pressure (BP), heart rate (HR), respiratory rate (RR) and peripheral oxygenation (SAT)
- Any concomitant therapy

Follow-up assessments

Follow-up assessments will occur during index admission, after 3 and 12 months as well as at end of follow-up. The 3 months assessment will be done during an in-hospital visit, whereas the other assessments will be telephone/registry based.

At each follow-up the following will be recorded:

- The occurrence of any adverse events (AE)
- The occurrence of serious adverse events (SAE)
- NYHA classification
- Patient reported outcome (PRO) questionnaires will be answered at 1 week and 3 months
- Cerebral Performance Category (CPC)
- Modified Rankin Score (mRS)
- Self-perceived function "two simple questions"
- Vital signs will be recorded throughout admission and at 3 months follow-up visit

From the day after surgery all information on serious adverse events (SAE) will be recorded.

Blood sampling

Blood will be drawn for biochemistry at baseline, the morning after surgery, at day three and five after surgery and after three months. The following analyses will be conducted at each blood draw: Sodium, potassium, calcium, glucose, albumin, blood urea nitrogen, uric acid, bilirubin (total), creatinine, S-protein, red blood cell count, white blood cell count, platelet count, HbA1c (solely preoperatively), NT-proBNP, CRP. In addition, 3x10 mL of blood will be drawn and stored in a biobank for up to 20 years.

Substudy assessments

Each of the three substudies will make individual assessments as described below.

Cardio- and pulmonary protection substudy

The potential effect of the two interventions on the heart will be studied by transthoracic echocardiography in a sub-study. The first 1080 included patients will be examined by advanced 2D and 3D echocardiography the day before surgery, 4-6 days after surgery (before discharge) and 3 months after surgery. Besides global, regional and layer-specific circumferential, radial, longitudinal and area strain measures, the echocardiographic assessment will include evaluation of systolic function (2D LVEF, 3D LVEF/RVEF, dp/dt, mitral and tricuspid annular movement), diastolic function (left atrial volume, mitral inflow velocities, early and late diastolic mitral and tricuspid movements), cardiac time intervals, valve disease, pericardial effusion and constriction, and ventricular, vena caval and aortic dimensions. The primary echocardiographic endpoint regarding both interventions in the trial is global longitudinal strain (GLS). In a subset of patients, a 6-minute hall walk test and serial 12-ECGs were also performed.

For the pulmonary protection substudy, an advanced lung function testing with DLCO is performed using the EasyOne Pro manufactured by ndd Medizintechnik AG, Technoparkstr. 1, 8005 Zürich, Switzerland, www.ndd.ch. The tests consist of spirometry and DLCO (dilution gas technique (10% helium, 0.3% carbon monoxide, and 18 % to 25 % oxygen (normally 21%)). The tests are performed the day before surgery, before discharge and on the follow-up visit after 3 months by trained study personnel where possible in the first 800 patients. Participation in the sub-study is voluntary.

The following hypothesis are investigated:

1) Exenatide infusion during cardiac surgery is associated with less decline DLCO and FEV1/FVC after 3 months compared to placebo.
2) Restrictive oxygenation during cardiac surgery is associated with less decline DLCO and FEV1/FVC after 3 months compared to placebo.

In addition, the association of advanced lung functions tests and prognosis, risk of AE and subsequent heart failure events are evaluated. Correlations to echocardiographic parameters of cardiac systolic and diastolic function are also evaluated.

Neuroprotection substudy

The neuroprotection substudy will be based on the biobank, measuring multiple markers of brain injury, cognitive outcomes at three months follow-up visit, and mRS and CPC scores. Biomarkers will be measured in the entire study cohort, whereas neurologic assessment is performed in the first 1100 patients only due to limited resources. The primary biobank measurement will be markers of cerebral injury measured the first days following surgery (primary endpoint), and secondary endpoints will include the relation to mRS, CPC, and risk of death during follow-up.

Renoprotection substudy

The primary outcome of the renoprotection substudy is acute kidney injury (AKI) defined according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria, which is based on S-creatinine increases and urine output. Secondary outcomes will include glomerular filtration rate (GFR) measured by Cr-EDTA clearance, estimated glomerular filtration rate (eGFR) and novel biomarkers of AKI. The primary endpoint will be based on the entire study cohort.

Safety

The trial population consists of patients with ischemic heart disease and/or aortic valve disease, who undergo CABG and/or AVR. The majority of adverse events (AE) are relatively common irrespective of treatment strategies. The occurrence of any AE will be recorded daily during index admission and at all follow-ups.

Adverse events (AE)

AEs are defined as undesirable medical occurrences or worsening of pre-existing medical conditions that occur after initiation of the investigational product, whether or not considered to be related to the investigational product.

Serious adverse events (SAE)

SAEs are defined as AEs resulting in significant side effects including ones that are fatal, life threatening, require hospitalization of prolongation of hospitalization and/or are persistent or significant.

Suspected unexpected serious adverse reactions (SUSAR)

SUSARs are defined as unexpected, serious AEs with presumed relation to the investigational drug. The term 'unexpected' is defined using the Byetta® Summary of product characteristics (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000698/WC500051845.pdf, current version 16th of August 2016) and the Conoxia® Summary of product characteristics available at the Danish Medicines Agency (http://www.produktresume.dk/docushare/dsweb/View/Collection-99, current version 11th of February 2016).

Reporting procedures

Safety variables and SAEs will be recorded continuously in the CRF during the first 7 days after surgery. AEs occurring after 7 days will be recorded at the pre-planned follow-up visits. All medically significant AEs considered by the investigator or the sponsor to be related to the investigational product will be followed until resolved or considered stable. The following attributes will be recorded by the investigator: description, dates of onset and resolution, severity, assessment of whether the AE is related to the investigational product, other suspected drugs or devices, and action taken. For each AE reported in the CRF, the investigator will adjudicate whether the event is a SAE. All SAEs will be recorded on a Serious Adverse Event Report form. The sponsor is responsible for reporting all SUSARs to the Danish Health and Medicines Authority as soon as possible and no later than 7 days after awareness.

Data Monitoring

A Data Monitoring and Safety Committee (DMSC) has been assembled and consists of individuals free of any potential conflicts of interests. The DMSC is responsible for ensuring the interests of trial participants, for assessing safety and efficacy of the two trial interventions and for monitoring the conduct of the trial. The DMSC can recommend stopping of continuing the trial to the trial steering committee (TSC). Also, the DMSC can formulate recommendations regarding all elements of the trial conduct, in order to enhance the trial integrity. Any recommendations from the DMSC regarding stopping, continuing or changing the trial will be communicated to the TSC without delay. The TSC is responsible for reviewing any recommendations from the DMSC and to determine, whether changes in trial conduct are required. The sponsor is responsible for reporting the number of SAEs and SUSARs to the DMSC bimonthly until 250 patients have been randomized. The need for further evaluation of SAEs and all-cause mortality will be decided by the DMSC. Interim analyses will be performed by a statistician selected by the DMSC.

An endpoint classification committee will adjudicate primary endpoints in a blinded fashion. Independent good clinical practice (GCP) units will monitor informed written consent forms, data quality and adjudication of endpoints.

Planned statistical analyses

Sample size estimation

This parallel group trial investigates two interventions, and we plan to analyze these two interventions as two separate studies. The effect of the two interventions are not expected to interact, therefore the design and sample size estimation did not account for such interaction. The study involving restrictive versus liberal oxygenation is subordinate to the study involving the GLP-1 analog, and the potential interactions of the two interventions will be analyzed in the GLP-1 analog trial. Thus, the power calculations are based on the GLP-1 analog intervention.

The trial is event driven, aiming at 323 primary endpoints to be able to show a 25% reduction in the primary endpoint with a power of 80% at an α-level of 0.05 (two-sided). Based on cumulative event rates from the surgical register at Rigshospitalet (unpublished), a total of 1400 patients are needed to reach a total of 323 events during follow-up. We will include 1400 patients in the trial. We will follow all patients until 323 events have been reached and the last patient has been followed for a minimum of 12 months. Accordingly, the follow-

up period will vary from approximately 6 years from the earliest included patients to 12 months for the last included patient.

General principles

All analyses will be performed according to the intention-to-treat principle[57]. A two-sided significance level of 0.05 will be applied throughout. Missing data will be reported in the publication. In case of more than 5% missing data in outcome variables, multiple imputation with creation of 50 imputed datasets will be analyzed separately and aggregated into an estimate of the intervention's effect on the primary endpoint[58,59]. For non-fatal events, competing risk of events will be accounted for.

Inclusion profile

In accordance with the Consolidated Standards of Reporting Trials (CONSORT) diagram[60], a flowchart of the trial inclusion and exclusion profile will be provided.

Baseline variables

The following baseline variables will be included in table 1.

1) Demographics
    a. Sex
    b. Age per year
    c. BMI
    d. History of smoking
    e. Estimated amount of alcohol consumed per week per grams
2) Previous medical history
    a. Comorbidity and function (including CPC-class, previous heart failure, previous myocardial infarction, ischemic heart disease, previous arrhythmia, previous cardiac arrest, arterial hypertension, transient ischemic attack or stroke, epilepsy, diabetes, asthma or chronic obstructive pulmonary disease, chronic hemodialysis or peritoneal dialysis, hepatic cirrhosis, hematological malignancy, other malignancy, AIDS, alcoholism, intravenous drug abuse, or other immunodeficiency)
    b. Previous percutaneous coronary intervention

c. Previous coronary artery bypass grafting
d. Previous aortic valve surgery
e. Implantable cardioverter-defibrillator and/or pacemaker
f. Current medical therapy at time of surgery

3) Surgical procedure
   a. Indication for surgery
   b. Coronary artery bypass grafting
      i. Number of grafts, stratified by arterial and venous grafts
   c. Aortic valve replacement, stratified by type of valve
   d. Combined coronary artery bypass graft and aortic valve replacement
   e. Duration of surgery (minutes)
   f. Duration of cardiopulmonary bypass (minutes)
   g. Duration of aortic cross clamp time (minutes)

Baseline variables will be stratified according to treatment allocation. Continuous variables will be presented as mean ± SD if normally distributed or otherwise as median (interquartile range). Differences between allocation groups will be tested with the independent sample t-test, potentially after logarithmic transformation for lognormally distributed variables, or the non-parametric Mann-Whitney test as appropriate. Categorical variables will be presented as number (percentage) and differences between allocation groups will be tested with the chi-square test or the Fisher's exact test as appropriate.

Endpoint analyses

Primary endpoint

For each of the two interventions (exenatide and oxygenation), Kaplan-Meier curves will be graphically displayed, and compared using the two-sided log-rank test. In addition, a multivariable analysis of the time to first event will be performed using Cox proportional hazard models. The model will be adjusted for the following covariates: treatment allocation, age, sex, body mass index, indication for surgery, year of inclusion, procedure (CABG vs AVR vs CABG+AVR), known alcohol or drug abuse, Charlson comorbidity index, previous PCI, previous CABG, previous AVR, length of procedure, length of cardiopulmonary bypass. The hazard ratio with 95% confidence intervals will be reported. Since the primary intervention is

exenatide versus placebo, the potential interactions between this treatment and the oxygenation-allocation on outcome and treatment will be estimated in the article on exenatide via the Cox proportional hazard models, with oxygenation group as a covariate in the model.

Censoring: Subjects withdrawing from the study early (other than for withdrawal of consent) will be followed for potential development of the primary endpoint. Subjects completing the study and not experiencing the composite event will be censored.

Secondary endpoint

Time to the individual secondary endpoints will be analyzed with Kaplan-Meier estimates for all-cause mortality and cumulative incidence rates for other endpoints taking competing risk of death into account. The censoring mechanism will be similar to the one applied to the primary endpoint. The type 1 error rate associated with multiple comparisons will be controlled with the application of Benjamini-Hochberg adjustment[61]. Differences in the occurrence of pre-defined adverse events between allocation groups will be analyzed with the chi-square test or the Fisher's exact test, as appropriate. Changes in continuous variables over time will be analyzed using linear mixed models.

Safety endpoint

Incidence rates of adverse events will be graded according to severity and relationship to the investigational product. Tables of deaths, serious and significant adverse events, including ones causing early withdrawal will be provided. Differences in incidence of adverse events, as well as the cumulative incidence of adverse events between groups, will be analyzed with the chi-square test or the Fisher's exact test, as appropriate.

Ethics and Dissemination

Participation in the trial will not delay routine or therapeutic procedures. The mortality and morbidity after open heart surgery (including CABG and AVR) are mainly caused by organ failure and inflammation. Thus, methods of organ protection are considered essential for reducing the mortality after open heart surgery. In addition, increased knowledge of organ function following surgery will potentially be of benefit to patients undergoing open heart surgery.

Exenatide has been used for treatment of type 2 diabetes for years. In addition, it has been used in STEMI patients and out-of-hospital cardiac arrest patients without increased risk of adverse events compared to placebo. As infusion of study-drug will occur simultaneously with surgery, and the allocated oxygenation strategy will occur during CPB, when weaning from and the following hour after weaning from CPB, the participants will experience no side effects. The organ protective effects of exenatide and restrictive oxygenation during open heart surgery cannot be gained outside the clinical setting, and human experimental models are obviously unethical. All patients will provide oral and written informed consent prior to inclusion in the trial.

Approvals

The trial is conducted in accordance with Danish legislation and the Helsinki declaration. In addition, the trial is conducted in accordance with international standards for good clinical practice (GCP) and is monitored by an independent GCP-unit. The trial is surveyed by a DMSC with full access to the study database upon request. The trial protocol, including any amendments and written information- and consent forms have been approved prior to initiation of the trial by the local ethics committee (ref. no. H-15010562). In addition, The Danish Health and Medicines Authority approved the trial (protocol ref. HJE-PHARMA-001, EudraCT no. 2015-003050-41). The full protocol is published at www.clinicaltrials.gov (ID no. NCT02673931)

Dissemination

All results will be published in international, peer-reviewed journals and presented at international congresses. Co-authorships will be granted in accordance with the Vancouver guidelines. In case the trial demonstrates a significant, positive effect of exenatide or restrictive oxygenation during heart surgery these treatment strategies will be easy to implement.

References

1 Mao Z, Zhong X, Yin J, *et al.* Predictors associated with stroke after coronary artery bypass grafting: A systematic review. *J Neurol Sci* 2015;**357**:1–7. doi:10.1016/j.jns.2015.07.006

2 Wijeysundera D, Karkouti K, Beattie S, *et al.* Improving the Identification of Patients at Risk of Postoperative Renal Failure after Cardiac Surgery. *Anesthesiology* 2005;**104**:65–72.

3 Salamonsen RF, Schneider HG, Bailey M, *et al.* Cardiac troponin I concentrations, but not electrocardiographic results, predict an extended hospital stay after coronary artery bypass graft surgery. *Clin Chem* 2005;**51**:40–6. doi:10.1373/clinchem.2004.041103

4 Houlind K, Kjeldsen BJ, Madsen SN, *et al.* On-Pump Versus Off-Pump Coronary Artery Bypass Surgery in Elderly Patients Results From the Danish On-Pump Versus Off-Pump Randomization Study. *Circulation* 2012;**125**:2431–9. doi:10.1161/CIRCULATIONAHA.111.052571/-/DC1

5 Nicolini F, Vezzani A, Fortuna D, *et al.* Gender differences in outcomes following isolated coronary artery bypass grafting: long-term results. *J Cardiothorac Surg* 2016;**11**:1–12. doi:10.1186/s13019-016-0538-4

6 Thyregod HGH, Steinbrüchel DA, Ihlemann N, *et al.* Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis 1-Year Results From the All-Comers NOTION Randomized Clinical Trial. *J Am Coll Cardiol* 2015;**65**:2184–94.

7 Pannu N, Graham M, Klarenbach S, *et al.* A new model to predict acute kidney injury requiring renal replacement therapy after cardiac surgery. *CMAJ* 2016;**188**:1076–83. doi:10.1503/cmaj.151447

8 Mérie C, Køber L, Olsen PS, *et al.* Risk of Stroke After Coronary Artery Bypass Grafting. *Stroke* 2011;**43**:38–43. doi:10.1161/STROKEAHA.111.620880/-/DC1

9 Newman MF, Kirchner JL, Phillips-Bute B, *et al.* Longitudinal Assessment of Neurocognitive Function after Coronary-Artery Bypass Surgery. *N Engl J Med* 2001;**344**:395–402.

10 Selnes OA, Grega MA, Bailey MM, *et al.* Do Management Strategies for Coronary Artery Disease Influence 6-Year Cognitive Outcomes? *ATS* 2009;**88**:445-454.e3. doi:10.1016/j.athoracsur.2009.04.061

11 Cropsey C, Kennedy J, Han J, *et al.* Cognitive Dysfunction, Delirium, and Stroke in Cardiac Surgery Patients. *Semin Cardiothorac Vasc Anesth* 2015;**19**:309–17. doi:10.1177/1089253215570062

12 Nagels W, Demeyere R, Van Hemelrijck J, *et al.* Evaluation of the Neuroprotective Effects of S(+)-Ketamine During Open-Heart Surgery. *Anesth Analg* 2004;**98**:1595–603. doi:10.1213/01.ANE.0000117227.00820.0C

13 Taggart DP, Browne SM, Wade DT, *et al.* Neuroprotection during cardiac surgery: a randomised trial of a platelet activating factor antagonist. *Heart* 2003;**89**:897–900.

14 Wang D, Wu X, Li J, *et al.* The Effect of Lidocaine on Early Postoperative Cognitive Dysfunction After Coronary Artery Bypass Surgery. *Anesth Analg* 2002;**95**:1134–41. doi:10.1213/01.ANE.0000027870.09122.51

15 Arrowsmith J, Harrison MJG, Newman SP, *et al.* Neuroprotection of the Brain During Cardiopulmonary Bypass: A Randomized Trial of Remacemide During Coronary Artery Bypass in 171 Patients. *Stroke* 2015;**29**:2357–62.

16 Kong RS, Butterworth J, Aveling W, *et al.* Clinical Trial of the Neuroprotectant Clomethiazole in Coronary Artery Bypass Graft Surgery A Randomized Controlled Trial. *Anesthesiology* 2002;**97**:585–91.

17 Holscher C. Potential Role of Glucagon-Like Peptide-1(GLP-1) in Neuroprotection. *CNS Drugs* 2012;**26**:871–82.

18 McClean PL, Parthsarathy V, Faivre E, *et al.* The Diabetes Drug Liraglutide Prevents Degenerative Processes in a Mouse Model of Alzheimer's Disease. *J Neurosci* 2011;**31**:6587–94. doi:10.1523/JNEUROSCI.0529-11.2011

19 Harkavyi A, Abuirmeileh A, Lever R, *et al.* Glucagon-like peptide 1 receptor stimulation by exendin-4 reverses key deficits in distinct rodent models of Parkinson's disease. *J Neuroinflammation* 2008;**5**:19. doi:10.1186/1742-2094-5-19

20 Li Y, Chigurupati S, Holloway HW, *et al.* Exendin-4 Ameliorates Motor Neuron Degeneration in Cellular and Animal Models of Amyotrophic Lateral Sclerosis. *PLoS One* 2012;**7**:e32008-13. doi:10.1371/journal.pone.0032008

21 Teramoto S, Miyamoto N, Yatomi K, *et al.* Exendin-4, a glucagon-like peptide-1 receptor agonist, provides neuroprotection in mice transient focal cerebral ischemia. *J Cereb Blood Flow & Metab* 2011;**31**:1696–705. doi:10.1038/jcbfm.2011.51

22 Briyal S, Gulati K, Gulati A. Repeated administration of exendin-4 reduces focal cerebral ischemia-induced infarction in rats. *Brain Res* 2012;**1427**:23–34. doi:10.1016/j.brainres.2011.10.026

23 Jiang D, Wang Y, Zang Y, *et al.* Neuroprotective Effects of rhGLP-1 in Diabetic Rats with Cerebral Ischemia/Reperfusion Injury. *Drug Dev Res* 2016;**77**:124–33. doi:10.1002/ddr.21297

24 Zhang H, Meng J, Zhou S, *et al.* Intranasal Delivery of Exendin-4 Confers Neuroprotective Effect Against Cerebral Ischemia in Mice. *AAPS J* 2016;**18**:385–94. doi:10.1208/s12248-015-9854-1

25 Marlet IR, Ölmestig JNE, Vilsbøll T, *et al.* Neuroprotective Mechanisms of Glucagon-like Peptide-1-based Therapies in Ischaemic Stroke: A Systematic Review based on Pre-Clinical Studies. Basic Clin. Pharmacol. Toxicol. 2018;**122**:559–69.

doi:10.1111/bcpt.12974

26 Timmers L, Henriques JPS, de Kleijn DP V, *et al.* Exenatide Reduces Infarct Size and Improves Cardiac Function in a Porcine Model of Ischemia and Reperfusion Injury. *J Am Coll Cardiol* 2009;**53**:501–10. doi:10.1016/j.jacc.2008.10.033

27 Ravassa S, Zudaire A, Díez J. GLP-1 and cardioprotection: From bench to bedside. Cardiovasc. Res. 2012;**94**:316–23. doi:10.1093/cvr/cvs123

28 Basalay M V., Mastitskaya S, Mrochek A, *et al.* Glucagon-like peptide-1 (GLP-1) mediates cardioprotection by remote ischaemic conditioning. *Cardiovasc Res* 2016;**112**:669–76. doi:10.1093/cvr/cvw216

29 Ang R, Mastitskaya S, Hosford PS, *et al.* Modulation of Cardiac Ventricular Excitability by GLP-1 (Glucagon-Like Peptide-1). *Circ Arrhythm Electrophysiol* 2018;**11**:e006740. doi:10.1161/CIRCEP.118.006740

30 Lonborg J, Vejlstrup N, Kelbaek H, *et al.* Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 2012;**33**:1491–9. doi:10.1093/eurheartj/ehr309

31 Lonborg J, Kelbaek H, Vejlstrup N, *et al.* Exenatide Reduces Final Infarct Size in Patients With ST-Segment-Elevation Myocardial Infarction and Short-Duration of Ischemia. *Circ Cardiovasc Interv* 2012;**5**:288–95. doi:10.1161/CIRCINTERVENTIONS.112.968388

32 Woo J. Cardioprotective Effects of Exenatide in Patients With ST-Segment–Elevation Myocardial Infarction Undergoing Primary Percutaneous Coronary Intervention. *Arter Thromb Vasc Biol* 2013;:2252–60. doi:10.1161/ATVBAHA.113.301586/-/DC1

33 Bernink FJP, Timmers L, Diamant M, *et al.* Effect of additional treatment with EXenatide in patients with an Acute Myocardial Infarction: The EXAMI study. *Int J Cardiol* 2013;**167**:289–90. doi:10.1016/j.ijcard.2012.09.204

34 Wiberg S, Hassager C, Schmidt H, *et al.* Neuroprotective Effects of the Glucagon-Like Peptide-1 Analog Exenatide After Out-of-Hospital Cardiac Arrest: A Randomized Controlled Trial. *Circulation* 2016;:CIRCULATIONAHA.116.024088-12. doi:10.1161/CIRCULATIONAHA.116.024088

35 Vereczki V, Martin E, Rosenthal RE, *et al.* Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death. *J Cereb Blood Flow Metab* 2005;**26**:821–35. doi:10.1038/sj.jcbfm.9600234

36 Liu Y, Rosenthal RE, Haywood Y, *et al.* Normoxic Ventilation After Cardiac Arrest Reduces Oxidation of Brain Lipids and Improves Neurological Outcome. *Stroke* 1998;**29**:1679–86. doi:10.1161/01.STR.29.8.1679

37 Nollert G, Nagashima M, Bucerius J, *et al.* Oxygenation strategy and neurologic damage after deep hypothermic circulatory arrest. II. Hypoxic versus free radical injury. *J Thorac Cardiovasc Surg* 1999;**117**:1172–9.

38 Heinrichs J, Lodewyks C, Neilson C, *et al.* The impact of hyperoxia on outcomes after cardiac surgery: a systematic review and narrative synthesis. *Can J Anesth* 2018;**65**:923–35. doi:10.1007/s12630-018-1143-x

39 Young RW. Hyperoxia: A Review of the Risks and Benefits in Adult Cardiac Surgery. *J Extracorpor Technol* 2012;**44**:241–9.

40 Greif R, Akça O, Horn E-P, *et al.* Supplemental Perioperative Oxygen to Reduce the Incidence of Surgical-Wound Infection. *N Engl J Med* 2000;**342**:161–7.

41 Kallet RH, Matthay MA. Hyperoxic Acute Lung Injury. *Respir Care* 2012;**58**:123–41. doi:10.4187/respcare.01963

42 Schreiber JU, Lancé MD, de Korte M, *et al.* The Effect of Different Lung-Protective Strategies in Patients During Cardiopulmonary Bypass: A Meta-Analysis and Semiquantitative Review of Randomized Trials. *J Cardiothorac Vasc Anesth* 2012;**26**:448–54. doi:10.1053/j.jvca.2012.01.034

43 Waring S, Thomson AJ, Adwani SH, *et al.* Cardiovascular Effects of Acute Oxygen Administration in Healthy Adults. *J Cardiovasc Pharmacol* 2003;**42**:245–50.

44 Anderson KJ, Harten JM, Booth MG, *et al.* The cardiovascular effects of normobaric hyperoxia in patients with heart rate fixed by permanent pacemaker. *Anaesthesia* 2010;**65**:167–71. doi:10.1111/j.1365-2044.2009.06195.x

45 Hovaguimian F, Lysakowski C, Elia N, *et al.* Effect of Intraoperative High Inspired Oxygen Fraction on Surgical Site Infection, Postoperative Nausea and Vomiting, and Pulmonary Function_Systematic Review and Meta-analysis of Randomized Controlled Trials. *Anesthesiology* 2013;**119**:303–16.

46 Meyhoff CS, Jorgensen LN, Wetterslev J, *et al.* Increased Long-Term Mortality After a High Perioperative Inspiratory Oxygen Fraction During Abdominal Surgery. *Anesth Analg* 2012;**115**:849–54. doi:10.1213/ANE.0b013e3182652a51

47 Girardis M, Busani S, Damiani E, *et al.* Effect of Conservative vs Conventional Oxygen Therapy on Mortality Among Patients in an Intensive Care Unit. *JAMA* 2016;**316**:1583–7. doi:10.1001/jama.2016.11993

48 Chu DK, Kim LH-Y, Young PJ, *et al.* Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018;**391**:1693–705.http://www.crd.york.ac.uk/

49 Schjørring OL, Klitgaard TL, Perner A, *et al.* Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure. *N Engl J Med* 2021;:1–11. doi:10.1056/NEJMoa2032510

50 Stub D, Smith K, Bernard S, *et al.* Air Versus Oxygen in ST-Segment–ElevationMyocardial Infarction. *Circulation* 2015;**131**:2143–50. doi:10.1161/CIRCULATIONAHA.114.014494/-/DC1

51 Hofmann R, James SK, Jernberg T, *et al.* Oxygen Therapy in Suspected Acute Myocardial Infarction. *N Engl J Med* 2017;**377**:1240–9. doi:10.1056/nejmoa1706222

52 Smit B, Smulders YM, de Waard MC, *et al.* Moderate hyperoxic versus near-physiological oxygen targets during and after coronary artery bypass surgery: a randomised controlled trial. *Crit Care* 2016;**20**:1–10. doi:10.1186/s13054-016-1240-6

53 Reade MC, Bass F, Howe B, *et al.* POINT OF VIEW 110 Considerations for co-enrolment in randomised controlled effectiveness trials in critical care: the SPICE-8 co-enrolment guidelines. 2017.

54 Thygesen K, Alpert JS, Jaffe AS, *et al.* Third universal definition of myocardial infarction. *Eur Heart J* 2012;**33**:2551–67. doi:10.1093/eurheartj/ehs184

55 J L, Vejlstrup N, Kelbaek H, *et al.* Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 2012;:1–9. doi:10.1093/eurheartj/ehr309

56 Wiberg S, Hassager C, Thomsen JH, *et al.* GLP-1 analogues for neuroprotection after out-of-hospital cardiac arrest: study protocol for a randomized controlled trial. *Trials* 2016;:1–9. doi:10.1186/s13063-016-1421-2

57 Fergusson D, Aaron S, Guyatt G, *et al.* Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *Br Med J* 2002;**325**:652–4.

58 Donders ART, van der Heijden GJMG, Stijnen T, *et al.* Review: A gentle introduction to imputation of missing values. *J Clin Epidemiol* 2006;**59**:1087–91. doi:10.1016/j.jclinepi.2006.01.014

59 Schafer JL, Graham JW. Missing data: Our view of the state of the art. *Psychol Methods* 2002;**7**:147–77. doi:10.1037//1082-989X.7.2.147

60 Moher D, Schulz KF, Altman DG, *et al.* The CONSORT statement: revised recommendations for improvingthe quality of reports of parallel-group randomised trials. *Lancet* 2001;**357**:1191–4.

61 Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc* 1995;**57**:289–300.

Author contributions

Authors SW, JK, RM, CHM, KK, HR, CH, LK, JCN all contributed equally to the conceptualization of the trial or substudies. All authors have contributed to drafting and writing the protocol and sub-study protocols. Author SW wrote the first draft of this design article based on the study protocol. All authors, SW, JK, RM, CHM, KK, HR, CH, LK, JCN have read and approved the final manuscript.

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Competing interests

The authors declare, that they have no competing interests.

Trial status

Inclusion of patients began on February 5th 2016 and is expected to be complete by the end of 2021. Final follow-up is expected to be complete by 2022.

Table 1. Inclusion and exclusion criteria

Inclusion criteria

1. Appropriately obtained written informed consent
2. Age ≥ 18 years
3. Ischemic heart disease requiring CABG and/or aortic valve disease requiring AVR, irrespective of other concomitant valve surgery

Exclusion criteria

1. Active treatment with GLP-1 analogs
2. Obstructive hypertrophic cardiomyopathy, active myocarditis, constrictive pericarditis
3. Hyperthyroidism or untreated hypothyroidism
4. History of, or active pancreatitis
5. Acute surgery; subacute surgery (i.e. the following days) are eligible
6. Known allergy towards exenatide/Byetta or albumin (vehicle)
7. On the urgent waiting list for a heart transplant (UNOS category 1A or 1B or equivalent)
8. Recipient of any major organ transplant (e.g. Heart, lung, liver)
9. Receiving of has received cytotoxic or cytostatic chemotherapy and/or radiation therapy for treatment of malignancy within 6 month before randomization
10. Clinical evidence of current malignancy, with the exceptions of: basal or squamous cell carcinoma, cervical intraepithelial neoplasia, prostate cancer with a life expectancy of > 2.5
11. Currently enrolled in, or within 30 days from ending participation in other investigational drug trials for the treatment of diabetes or malignant obesity. Participation in other non-pharmacological trials is not an exclusion criteria
12. Recent, within 3 months, history of alcohol or drug abuse disorder, based on self-report.
13. Pregnancy or currently breast feeding
14. Any condition or situation that, in the investigator's opinion, could put the subject at significant risk, confound the trial's results or interfere with the subject's participation in the trial (specific reasons will be provided)
15. Previous participation in the present trial

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	26
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 26
	5b	Name and contact information for the trial sponsor	1
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	26
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	16

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9-10, table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11-12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10-12
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-10

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10-11
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9-10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10-11
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-14
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	N/A

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17-19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	17-19
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	16
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	16
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15-16
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	16-20
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20-21

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	26
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20-21
	31b	Authorship eligibility guidelines and any intended use of professional writers	20-21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.