BMJ Open Study protocol of the randomised placebo-controlled GLOBE trial: GLP-1 for bridging of hyperglycaemia during cardiac surgery

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ABSTRACT

Introduction Perioperative hyperglycaemia is common during cardiac surgery and associated with postoperative complications. Although intensive insulin therapy for glycaemic control can reduce complications, it carries the risk of hypoglycaemia. GLP-1 therapy has the potential to lower glucose without causing hypoglycaemia. We hypothesise that preoperative liraglutide (a synthetic GLP-1 analogue) will reduce the number of patients requiring insulin to achieve glucose values <8 mmol L⁻¹ in the intraoperative period.

Methods and analysis We designed a multi-centre randomised parallel placebo-controlled trial and aim to include 274 patients undergoing cardiac surgery, aged 18–80 years, with or without diabetes mellitus. Patients will receive 0.6 mg liraglutide or placebo on the evening before, and 1.2 mg liraglutide or placebo just prior to surgery. Blood glucose is measured hourly and controlled with an insulin bolus algorithm, with a glycaemic target between 4–8 mmol L⁻¹. The primary outcome is the percentage of patients requiring insulin intraoperatively.

Ethics and dissemination This study protocol has been approved by the medical ethics committee of the Academic Medical Centre (AMC) in Amsterdam and by the Dutch competent authority. The study is investigator-initiated and the AMC, as sponsor, will remain owner of all data and have all publication rights. Results will be submitted for publication in a peer-reviewed international medical journal.

Trial registration number NTR6323; Pre-results.

BACKGROUND

Perioperatively, the incidence of hyperglycaemia (glucose >8 mmol/L) is over 90% in patients undergoing cardiac surgery.¹ Several studies describe a clear association between hyperglycaemia and complications in this population.^{2–3} In addition, keeping glucose <8 mmol/L reduced complications in randomised controlled trials in patients with and without diabetes mellitus (DM).¹⁴ However, stricter glucose control is also complicated by increasing incidence of hypoglycaemia.^{5–6}

Strengths and limitations of this study

- The first study using a glucagon-like peptide 1 analogue to improve glycaemic control during cardiac surgery.
- Double-blind, multicentre, randomised and placebo-controlled trial.
- Intervention aimed at improving glycaemic control without increased risk of hypoglycaemia.
- Use of a simple, minimally invasive, placebo-controlled intervention.
- Not powered on clinical outcome, however, using a relevant surrogate endpoint for complications and including complications as secondary endpoint.

For this reason, the American Diabetes Association currently recommends a perioperative glucose target range of 4.4–10 mmol/L.⁷ Above this range, insulin therapy should be initiated using short acting insulin. This management strategy requires frequent glucose measurements and insulin adjustments, and is thus labour intensive. This likely contributes to the surprisingly low adherence to insulin protocols and failure to achieve these targets in practice.^{8–9}

Glucagon-like peptide 1 (GLP-1) is the main enteroendocrine hormone and is secreted by L-cells in the intestine.¹⁰ In the pancreas, GLP-1 stimulates insulin secretion via its receptor while inhibiting glucagon secretion, leading to lower blood glucose levels. This antihyperglycaemic effect of GLP-1 is glucose dependent. As such, GLP-1-based therapy has the potential to lower glucose without causing hypoglycaemia.^{11–12} Liraglutide is a synthetic GLP-1 analogue made resistant to the GLP-1 breakdown enzyme dipeptidyl peptidase, thereby prolonging its duration of action up to 24 hours.¹⁰ With a one time daily dosage, this therapy is safer (preventing

hypoglycaemia) and considerably less time consuming for perioperative caregivers.

Other forms of GLP-1 (analogue) therapy have been studied in small trials in the intraoperative period. Intraoperative addition of exenatide to insulin therapy during cardiac surgery resulted in lower glucose values (0.83 mmol/L (95% CI 0.40 to 1.25)) and a higher percentage of time spent in glucose target range, compared with placebo.¹³ A continuous intravenous GLP-1 infusion during cardiac surgery also lowered glucose levels by 0.8–0.9 mmol/L, as compared with placebo.¹⁴ In non-cardiac surgery, a trial in our own centre showed that liraglutide lowered glucose levels with reduced total insulin doses as compared with continuous or bolus insulin regimens.¹⁵ While the American Diabetes Association currently recommends an upper glucose target limit of 10 mmol/L perioperatively, recent trials indicated benefit of a moderate glycaemic control below <8 mmol/L.^{1 16}

We hypothesise that liraglutide administration before surgery reduces the number of patients that need any insulin to achieve glycaemic control <8 mmol/L in the intraoperative period.

METHODS/DESIGN

The manuscript was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials guideline on reporting of intervention trial protocols.¹⁷

Trial design

The study is a multicentre randomised parallel placebo-controlled (1:1) superiority trial in patients undergoing cardiac surgery, evaluating the potential of liraglutide to reduce the need for insulin. The study is investigator initiated with the Academic Medical Center (AMC) Amsterdam as local sponsor. The trial will recruit patients in the AMC, a tertiary academic centre, and three large cardiac surgery centres of secondary district hospitals in the Netherlands (OLVG, Amsterdam; Amphia, Breda; Catharina, Eindhoven).

Eligibility criteria

Adult patients scheduled to undergo an elective cardiac surgical procedure will be eligible for inclusion. Detailed inclusion and exclusion criteria are listed below. We set a maximum preoperative daily insulin dose because we expect all patients to require intraoperative insulin, when already treated with a daily dose of insulin >0.5 IU/kg bodyweight, despite receiving an additional GLP-1 receptor agonist. Chronic oral corticosteroid treatment is an exclusion criterion because of its hyperglycaemic effect. Emergency surgery is excluded to ensure sufficient time for the informed consent process. All other exclusion criteria are in accordance with the summary of product characteristics of liraglutide.

Inclusion criteria

- ▶ Signed informed consent.
- ▶ Aged 18–80 years (inclusive).
- ▶ Scheduled for elective cardiac surgery.

Exclusion criteria

- ▶ Type 1 DM.
- ▶ Type 2 DM on total daily insulin dose >0.5 IU/kg bodyweight.
- ▶ Current treatment with GLP-1 analogues.
- ▶ Known or suspected allergy to trial products or other drugs in the same class.
- ▶ Emergency surgery, defined as in need of surgery for medical reasons within 72 hours.
- ▶ Heart failure New York Heart Association class IV.
- ▶ Serum-creatinine ≥133 µmol/L for men and ≥115 µmol/L for women.
- ▶ Receiving oral corticosteroid therapy.
- ▶ History of pancreatic surgery or acute or chronic pancreatitis.
- ▶ Personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2.
- ▶ Woman of childbearing potential who is pregnant, breast feeding or intend to become pregnant or is not using adequate contraceptive methods.

Researchers will screen all patients presenting for elective cardiac surgery, and patients will be contacted and informed in case of eligibility.

Study outline

Patients will be contacted either by telephone or at the preoperative assessment clinic, and written information and oral explanation will be provided. After written consent is obtained, patients will be randomised by the local pharmacy department. Patient characteristics (age, gender, ethnicity), length, height, body mass index, medical history, medication use and American Society of Anesthesiologists physical score classification will be recorded. The study drug will be administered two times: first on the evening before surgery, and a second injection after induction of anaesthesia. Date and time of all study drug administrations will be recorded. Preoperative fasting is prescribed in accordance with European guidelines in all participating centres.¹⁸ In case of preoperative nausea induced by the first liraglutide injection, the second dose will be omitted. In case an operation is rescheduled, the patient will receive the first dose again, on the evening before surgery. This will be at least 24 hours later, similar to the period of action of a single dose of liraglutide. Blood glucose will be measured before the induction of anaesthesia and then every hour until discharge from the operating room (OR). Insulin will be administered in bolus dosages according to the study algorithm. All study interventions will be performed by trained study personnel or the treating anaesthetist following instructions from the researchers.

Surgical and anaesthetic details will be recorded. It is common practice to administer prophylactic

Table 1 Recorded composites of outcomes

Composite of:	Timing	Outcome	Definition
Cognitive outcomes	Day 1–5	Delirium	According to CAM-ICU method ²⁰
		Other cognitive dysfunction	Recorded in patient file
Cardiovascular outcomes	<30 days	Cardiovascular death	Death with primary cardiac cause
		Cardiac arrhythmia	New onset cardiac arrhythmia
		Myocardial infarction	According to the third universal definition of myocardial infarction task force
		Cerebrovascular event	Diagnosed by CT scan
Infectious complications	<30 days	Sternal wound infection	CDC definition
		Pneumonia	CDC definition
		Sepsis/bacteraemia	CDC definition
		Cystitis/UTI	CDC definition
Other postoperative outcomes	<30 days	Death	30-day mortality of any cause other than cardiovascular
		Reoperation	Unplanned surgical intervention within 30 days after discharge
		Deep venous thrombosis	Diagnosed by Doppler and treatment started
		Lung embolus	Diagnosed by spiral CT scan
		Bleeding	Requiring intervention or transfusion of RBC's
		Renal failure	Requiring dialysis
		ICU and hospital LoS	Days of ICU and hospital admission after surgery
		Other	All reported SAEs not listed as secondary outcomes

CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; CDC, Centre for Disease Control and Prevention; ICU, intensive care unit; LoS, length of stay; RBC, red blood cell; SAE, serious adverse event; UTI, urinary tract infection.

corticosteroids before cardiac surgery to attenuate the inflammatory response associated to cardiopulmonary bypass and surgery.¹⁹ However, evidence for this therapy is conflicting and no longer standard of care in one of the four participating centres. Intraoperative treatment with glucocorticoids is left to the discretion of the anaesthetist, but this will be recorded.

Nausea measured on a numeric rating scale (0–10) is recorded before surgery and on the first postoperative day. Daily assessment of the presence of postoperative delirium will be recorded using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)²⁰ until the fifth postoperative day. We will assess the presence of all complications listed in [table 1](#), until 30 days after surgery. For the Consolidated Standards of Reporting Trials flow diagram of the study, see [figure 1](#). All data will be entered using an electronic clinical report form build in Castor EDC, Amsterdam, a good clinical practice compliant data management system.²¹

Randomisation

Randomisation will be done using online software provided by Castor EDC.²¹ We use block randomisation with computer generated blocks of 4, 6 or 8, with a block size unknown to the investigators, an allocation ratio of 1:1 and stratification per centre and for DM type 2.

Allocation concealment and blinding

Randomisation will be performed at the local pharmacy department, distant from patient wards, the OR,

or offices for healthcare providers or researchers. Only pharmacy employees will be responsible for randomisation, distribution of study medication and drug accountability. Allocation of patients will only be disclosed in case of a suspected unexpected serious adverse reaction. Study drug will be provided by Novo Nordisk as 'pen injectors', identical for placebo and liraglutide. Patients, healthcare providers and outcome assessors are thus all blinded to intervention status until database lock.

Study procedures and interventions

We will administer 0.6 mg liraglutide or placebo subcutaneously in the evening (after 15:00) before surgery, and a second dose of 1.2 mg liraglutide or placebo after the induction of anaesthesia. Our research group successfully applied this therapeutic scheme for perioperative glucose control in major non-cardiac surgery.¹⁵ Glucose will be measured before the induction of anaesthesia and every 60 min thereafter until transfer to the intensive care unit (ICU). We will attempt to maintain blood glucose within a target range of 4–8 mmol/L using the insulin bolus algorithm in [table 2](#). Our research group has previous trial experience with this algorithm, which proved effective in maintaining perioperative glucose levels <8 mmol/L.¹⁵

Laboratory measurements

A creatinine measurement within 6 months of the day of surgery will be recorded or determined if not present in the health records. Blood for **glycated hemoglobin** (HbA1c) and fasting glucose determination will be

Figure 1 Consolidated Standards of Reporting Trials flow diagram of glucagon-like peptide 1 for bridging of hyperglycaemia trial.

sampled before the induction of anaesthesia. Glucose will be measured every hour after the first measurement with an acceptable range of 15 min from that time. All glucose measurements will be done by point of care blood gas analysis equipment after sampling from the intra-arterial catheter, which is placed prior to the induction of anaesthesia.

Postoperative complications

Delirium is marked present on any day the CAM-ICU score²⁰ is positive, as long as the patient is admitted to the ICU; thereafter, delirium is recorded as present if explicitly mentioned in the patient's file. Complications mentioned in the composite endpoints listed in [table 1](#) are assessed by review of the patient file. If the patient is transferred to another hospital, the hospital will be

requested to provide discharge letters and applicable follow-up notes.

Outcome measures

Our primary outcome measure is the proportion of patients needing insulin therapy to maintain blood glucose within the preset range in the period from entrance to discharge from the OR. The secondary outcome measures are the total number of units of insulin used perioperatively, the number of insulin administrations, the mean perioperative glucose value, number of hyperglycaemic (>11 mmol/L) events, the number of mild (<4 mmol/L) and severe (<2.3 mmol/L) hypoglycaemic events, proportion of patients with postoperative nausea and vomiting, and four composites of complications (listed in [table 1](#)).

Table 2 Glucose correction study algorithm

Blood glucose (mmol/L)	First insulin bolus (IU)	Second insulin bolus, if glucose increases after first bolus (IU)	Third insulin bolus, if glucose increases after second bolus (IU)
<4*	–	–	–
4–8	–	–	–
8–9	2	4	6
9–10	3	5	7
10–11	4	8	12
11–12	5	9	13
12–13	6	12	18
13–14	7	13	19
14–15	8	15	20
15–16	9	16	21
>16†	10	17	22

*Glucose is 2.3–4 mmol/L, give 4 g glucose IV.
 Glucose <2.3 mmol/L: give 50 g glucose IV. In both cases, measure again after 10 min and consult research physician.
 †Consult research physician.

Safety

All serious adverse events will be collected and reviewed by the Principal Investigator and reported to the medical ethics committee of the AMC. Insurance is provided for all participating subjects by the AMC.

Sample size calculation

Difference in primary outcome will be compared using the Fisher's exact test, based on an intention-to-treat analysis. Based on the data of the glucose control in patients undergoing coronary artery bypass graft surgery (GLUCO-CABG) trial, we assume an expected proportion of 97% of patients needing insulin therapy during cardiac surgery when aiming for plasma glucose of <8 mmol/L.¹ To be able to detect a clinically relevant between group difference of at least 10%, we need a sample size of 137 patients per group, accounting for a drop-out rate of 8% (two sided, power 80%, alpha 0.05). The sample size calculation is based on a final analysis using the Fisher exact test.²² Sample size was calculated using nQuery (Statsol, Boston, Massachusetts, USA).

Statistical analyses

The difference in primary outcome will be compared using Fisher's exact test, based on an intention-to-treat analysis. The intention-to-treat population is defined as anyone who receives at least one dose of the investigational product followed by surgery the next day (figure 1). All patients receiving at least one dose of the investigational product will be analysed in the safety population, independent of receiving surgery the following day. A per-protocol analysis will be performed for all patients receiving

both investigational product doses along with surgery the day after the first dose. No interim analyses are planned.

Number and dose of insulin administrations, and perioperative mean glucose will be analysed using the Student's *t*-test or Mann-Whitney U test, depending on the distribution of the data. Normality of distribution will be assessed visually with histograms, Q-Q plots and using the Shapiro-Wilk test. Between group differences in composites of complications, hyperglycaemic and hypoglycaemic events, and nausea and vomiting will be calculated using the χ^2 test.

Prophylactic corticosteroid administration before cardiac surgery to attenuate the inflammatory response associated to cardiopulmonary bypass and surgery is standard of care in three of four participating centres. To investigate any interaction effect of routine prophylactic corticosteroid administration in one of the centres, as mentioned above, on the intervention, a subanalysis per centre will be performed for all outcomes. Also, because of an expected effect on glucose values and insulin requirements in patients with DM2, we will perform a subanalysis according to preoperative diagnosis of DM2. All analyses will be done using SPSS (IBM, V.24).

Monitoring

The trial will be monitored by the Clinical Research Unit from the AMC. Every participating centre will be subject to a start-up visit after three included patients, a second visit after 30 inclusions or after 1 year and one close-out visit after the data collection of all patients is complete. The monitor will confirm all written informed consents, check all serious adverse events and investigate data collection and data quality for a random subset of patients.

Patient and public involvement

Patients were not involved in the design of this study.

ETHICS AND DISSEMINATION

Written informed consent will be obtained by trained study personnel; all subjects will receive a written patient information letter and informed consent form (online supplementary material S1). A subject screening and enrolment log will be kept on a secure server only accessible to study personnel. Participation in the trial will be recorded in the electronic patient health records, visible for all other care providers.

Planning and dissemination

The study started with inclusion of the first patient in June 2017. The planned duration of the trial is 3 years. Protocol amendments will be subjected to the Medical Ethics Committee for approval and thereafter communicated to all investigators and trial registries. The AMC Amsterdam is the trial sponsor and will remain owner of all data and rights to publication. No publication restrictions apply. The manuscript will be drafted by the principal investigators from the participating centres. Full

protocol, dataset and statistical analysis plan will be available on request to the corresponding author.

Study results will be submitted in abstract form, to be presented at national and international conferences and submitted as an original paper for publication in a peer-reviewed international medical journal.

Contributors AHH: study design and writing of the manuscript, future acquisition, analysis and interpretation of study data. MJV: critically reviewing the manuscript, future acquisition and analysis of study data. MBG, BT, BMG, TVS, RAB, MGAW: critically reviewing the manuscript, future acquisition and interpretation of study data. MWH: critically reviewing the manuscript, future analysis and interpretation of study data. JHdV: conception and design of study, writing of the manuscript, future analysis and interpretation of study data. BP: study design and writing of the manuscript, future analysis and interpretation of study data. JH: conception and design of study, writing of the manuscript, future acquisition, analysis and interpretation of study data. All authors approved this final version of the manuscript to be published and are accountable for all aspects of the work.

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Competing interests Novo Nordisk, the manufacturer of liraglutide, was contacted after design of the trial. After approving the protocol, Novo Nordisk provided financial support. The Department of Anaesthesiology of the Academic Medical Centre received financial support for this project from Novo Nordisk. JHdV sits on a GLP-1 advisory board and speaker bureau for Novo Nordisk.

Patient consent Next of kin consent obtained.

Ethics approval Medical Ethics Committee Academic Medical Center Amsterdam.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1. Umpierrez G, Cardona S, Pasquel F, et al. Randomized controlled trial of intensive versus conservative glucose control in patients undergoing coronary artery bypass graft surgery: GLUCO-CABG trial. *Diabetes Care* 2015;38:1665–72.
2. Doenst T, Wijesundera D, Karkouti K, et al. Hyperglycemia during cardiopulmonary bypass is an independent risk factor for mortality in patients undergoing cardiac surgery. *J Thorac Cardiovasc Surg* 2005;130:1144.e1–1144.e8.
3. Lazar HL, McDonnell M, Chipkin SR, et al. The Society of Thoracic Surgeons practice guideline series: Blood glucose management during adult cardiac surgery. *Ann Thorac Surg* 2009;87:663–9.
4. Lazar HL, Chipkin SR, Fitzgerald CA, et al. Tight glycemic control in diabetic coronary artery bypass graft patients improves perioperative outcomes and decreases recurrent ischemic events. *Circulation* 2004;109:1497–502.
5. Lazar HL, McDonnell MM, Chipkin S, et al. Effects of aggressive versus moderate glycemic control on clinical outcomes in diabetic coronary artery bypass graft patients. *Ann Surg* 2011;254:458–64.
6. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009;360:1283–97.
7. Moghissi ES, Korytkowski MT, DiNardo M, et al. American association of clinical endocrinologists and american diabetes association consensus statement on inpatient glycemic control. *Diabetes Care* 2009;32:1119–31.
8. Ley SC, Preckel B, Schlack W. Perioperative Behandlung von Patienten mit Diabetes Mellitus. *Anästhesiol Intensivmed Notfallmed Schmerzther* 2005;40:230–49.
9. Polderman JA, de Groot FA, Zamanbin A, et al. An automated reminder for perioperative glucose regulation improves protocol compliance. *Diabetes Res Clin Pract* 2016;116:80–2.
10. Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006;368:1696–705.
11. Meier JJ, Weyhe D, Michaely M, et al. Intravenous glucagon-like peptide 1 normalizes blood glucose after major surgery in patients with type 2 diabetes. *Crit Care Med* 2004;32:848–51.
12. Besch G, Perrotti A, Mauny F, et al. Clinical effectiveness of intravenous exenatide infusion in perioperative glycemic control after coronary artery bypass graft surgery: a phase II/III randomized trial. *Anesthesiology* 2017;127:775–87.
13. Lipš M, Mráz M, Kloučková J, et al. Effect of continuous exenatide infusion on cardiac function and peri-operative glucose control in patients undergoing cardiac surgery: A single-blind, randomized controlled trial. *Diabetes Obes Metab* 2017;19:1818–22.
14. Kohl BA, Hammond MS, Cucchiara AJ, et al. Intravenous GLP-1 (7–36) amide for prevention of hyperglycemia during cardiac surgery: a randomized, double-blind, placebo-controlled study. *J Cardiothorac Vasc Anesth* 2014;28:618–25.
15. Polderman JAW, van Steen SCJ, Thiel B, et al. Peri-operative management of patients with type-2 diabetes mellitus undergoing non-cardiac surgery using liraglutide, glucose-insulin-potassium infusion or intravenous insulin bolus regimens: a randomised controlled trial. *Anaesthesia* 2018;73:332–9.
16. de Vries FE, Gans SL, Solomkin JS, et al. Meta-analysis of lower perioperative blood glucose target levels for reduction of surgical-site infection. *Br J Surg* 2017;104:e95–e105.
17. Chan AW, Tetzlaff JM, Gøtzsche PC, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586–42.
18. Smith I, Kranke P, Murat I, et al. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2011;28:556–69.
19. Dieleman JM. Intraoperative high-dose dexamethasone for cardiac surgery. *JAMA* 2012;308:1761.
20. Inouye SK, van Dyck CH, Alessi CA, et al. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med* 1990;113:941–8.
21. Amsterdam, Ciwit BV the N. Castor electronic data capture. 2017.
22. Jung S-H. Stratified Fisher's exact test and its sample size calculation. *Biometrical Journal* 2014;56:129–40.