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Liraglutide for perioperative management of hyperglycaemia in cardiac surgery patients: a multicentre randomized superiority trial

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Abstract

Aims: Most cardiac surgery patients, with or without diabetes, develop perioperative hyperglycaemia, for which intravenous insulin is the only therapeutic option. This is labour-intensive and carries a risk of hypoglycaemia. We hypothesized that preoperative administration of the glucagon-like peptide-1 receptor agonist liraglutide reduces the number of patients requiring insulin for glycaemic control during cardiac surgery.

Materials and methods: In this randomized, blinded, placebo-controlled, parallel-group, balanced (1:1), multicentre randomized, superiority trial, adult patients undergoing cardiac surgery in four Dutch tertiary hospitals were randomized to receive 0.6 mg subcutaneous liraglutide on the evening before surgery and 1.2 mg after induction of anaesthesia or matching placebo. Blood glucose was measured hourly and controlled using an insulin-bolus algorithm. The primary outcome was insulin administration for blood glucose >8.0 mmol/L in the operating theatre. Research pharmacists used centralized, stratified, variable-block, randomization software. Patients, care providers and study personnel were blinded to treatment allocation.

Results: Between June 2017 and August 2018, 278 patients were randomized to liraglutide (139) or placebo (139). All patients receiving at least one study drug injection were included in the intention-to-treat analyses (129 in the liraglutide group, 132 in the placebo group). In the liraglutide group, 55 (43%) patients required additional insulin compared with 80 (61%) in the placebo group and absolute difference 18% (95% confidence interval 5.9–30.0, $P = 0.003$). Dose and

Parts of this study were presented in abstract form at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, California, 8-11 June 2019.

Deidentified patients' data can be requested by researchers for use in independent scientific research and will be provided following review and approval of the research proposal and completion of a data-sharing agreement with the University of Amsterdam. Data requests can be made any time after the publication of this trial for up to 5 years (extendable). Requests should be sent to the corresponding author.

number of insulin injections and mean blood glucose were all significantly lower in the liraglutide group. We observed no difference in the incidence of hypoglycaemia, nausea and vomiting, mortality or postoperative complications.
Conclusions: Preoperative liraglutide, compared with placebo, reduces insulin requirements while improving perioperative glycaemic control during cardiac surgery.

1 | INTRODUCTION

The majority of patients undergoing cardiac surgery develop hyperglycaemia in the perioperative period.[1] The association between hyperglycaemia and postoperative complications is firmly established in this population.[2] The Society of Thoracic Surgeons guidelines recommend blood glucose (BG) to be controlled <10 mmol/L in cardiac surgery patients.[2] Randomized controlled trials indicated a benefit of an even lower BG target, <7.8 mmol/L.[1,3] However, implementation of strict perioperative glucose regulation is hindered by low adherence to labour-intensive protocols requiring frequent BG measurements and insulin administrations, as well as the risk of hypoglycaemia.[4,5] Therefore, clinicians need alternatives to insulin to improve glycaemic control, which are easy to use and carry a low risk of hypoglycaemia.[6] The American Diabetes Association acknowledged the potential of incretin therapies in this regard while awaiting evidence from randomized clinical trials.[7]

Glucagon-like peptide 1 (GLP1) stimulates insulin release and suppresses glucagon secretion in a glucose-dependent manner, thereby reducing BG concentrations without increasing the risk of hypoglycaemia.[8] GLP1 receptor agonists (GLP-1RA) are an established therapy for type 2 diabetes mellitus and because of their efficacy, ease of once-daily administration, and safety profile seem to be an attractive alternative to insulin in the perioperative period.[8,9] However, their main side effect, gastrointestinal intolerance, could be problematic in this setting. In a recent systematic review, we found only small single-centre trials studying incretin-based therapies in the perioperative period.[9] Therefore, we performed a multicentre randomized trial to evaluate the efficacy of a GLP1RA as an alternative to perioperative insulin administration in patients undergoing elective cardiac surgery. We hypothesized that preoperative liraglutide administration reduces the number of patients requiring insulin for glycaemic control during surgery.

2 | MATERIALS AND METHODS

2.1 | Study design

We performed a multicentre, triple-blind, placebo-controlled, parallel-group, phase 3, randomized superiority clinical trial in four Dutch tertiary care centres. Participating hospitals were Amsterdam UMC (Amsterdam), Amphia Hospital (Breda), Catharina Hospital (Eindhoven) and OLVG (Amsterdam). The study protocol was approved by the medical ethics committee of the Amsterdam UMC (registration number: 2017012) and by the Dutch competent authority before initiation of the trial. The trial was carried out according to the initially approved protocol except for one approved amendment to the eligibility criteria as mentioned below. The trial protocol (Appendix S1) was published open access[10] and registered with www.trialregister.nl, number NTR6323. A contracted, independent study monitor validated good clinical practice adherence and quality of data collection. This paper follows the CONSORT recommendations for reporting of randomized trials.[11] The study workflow is summarized in Figure 1.

2.2 | Participants

Patients planned to undergo elective cardiac surgery aged between 18 and 80 years were eligible for inclusion. We excluded patients with type 1 diabetes, current treatment with insulin >0.5 IU/kg daily, GLP1RAs or corticosteroids, history of heart failure [New York Heart Association (NYHA) class III and IV; on November 6, 2017, this was amended to NYHA class IV only after an update in the summary of products characteristics (SPC) of liraglutide], impaired renal function (creatinine ≥133 μmol/L for men and ≥115 μmol/L for women), allergies to trial products, history of pancreatic surgery, acute or chronic pancreatitis, personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2, and (possibly) pregnant or breastfeeding women. All participants provided written informed consent before any trial-related procedures.

2.3 | Randomization and masking

Research pharmacists co-ordinated the randomization and treatment assignment at each institution. Patients were randomly assigned to either liraglutide or placebo, using the randomization module implemented in the data management system Castor EDC (Ciwit BV, Amsterdam, The Netherlands).[12] We used a balanced, stratified, block randomization, with variable random computer-generated blocks of four, six or eight, an allocation ratio of 1:1 and stratification per centre and for type 2 diabetes mellitus. Research pharmacists (not involved in any other part of the trial) randomized patients at a location distant from patient wards, operating room, offices of care providers or study personnel. The pharmacy distributed the study medication in identical pen-injectors (containing liraglutide or placebo with solvents and water for injections, visually identical, equal in appearance and weight; provided by Novo Nordisk A/S, Bagsvaerd, Denmark), to trained research personnel, responsible for the administration of the study

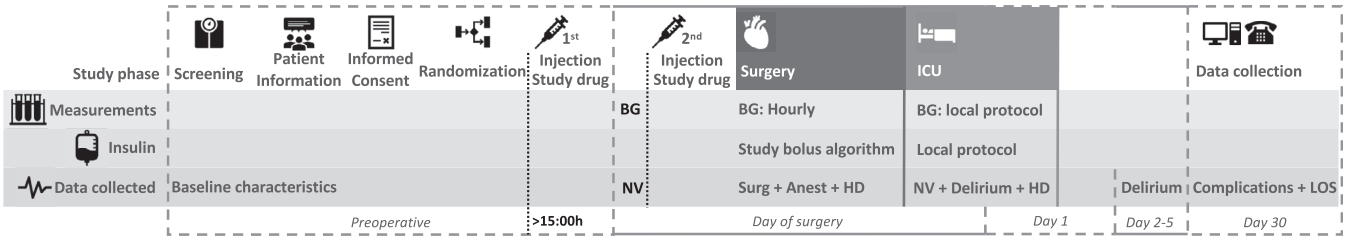

FIGURE 1 Workflow patients through the study. Abbreviations: BG, blood glucose; HD, haemodynamics; LOS, length of stay; NV, nausea and vomiting

medication. All patients, care providers and study personnel were thus blinded to treatment allocation.

2.4 | Procedures

Patients received a first subcutaneous injection with liraglutide 0.6 mg (Novo Nordisk A/S) or placebo, on the evening before surgery (after 15:00 h). Patients were fasted and received no oral or intravenous carbohydrates from the evening before surgery (00:00 h). In the morning before surgery, all patients were asked to score nausea on a numeric rating scale (0–10). A second dose of 1.2 mg of the study drug was administered after the induction of anaesthesia unless the patient reported a nausea score >4 preoperatively. Researchers measured BG hourly, starting just before induction of anaesthesia and until transfer to the intensive care unit (ICU). BG concentrations were measured in arterial blood samples by point-of-care equipment for blood gas analysis. Insulin was administered as intravenous bolus injections according to a previously published algorithm, with a BG target range between 4.0 and 8.0 mmol/L (Appendix S1).[10] After transfer to the ICU, all study interventions stopped, and only data collection continued. BG control was left to the discretion of the treating intensivist. Of note, all participating centres had a nurse-driven glycaemic control protocol in place employing continuous insulin infusions to achieve BG levels <10 mmol/L. We recorded BG measurements, the total dose of insulin and the presence of nausea and vomiting within the first 24 postoperative hours. We collected postoperative outcomes and complications up to 30 days after surgery, by review of in-hospital health records and retrieval of any out-of-hospital health care documentation.

2.5 | Outcomes

The primary endpoint was the difference between groups for any insulin given to control BG <8.0 mmol/L between entrance and exit from the operating room. Secondary endpoints were differences between groups in any of the following measures: total dose of insulin administered, number of insulin administrations, mean intraoperative BG concentration, number of hyperglycaemic events (BG >11.0 mmol/L), number of mild (BG <4.0 mmol/L) or severe (<2.3 mmol/L) hypoglycaemic events, postoperative nausea and vomiting, postoperative delirium, length of hospital stay, length of ICU stay and three composite endpoints, for cardiac, infectious or other complications. The cardiac composite endpoint comprised cardiovascular death, cardiac arrhythmia, myocardial infarction and cerebrovascular accident. The infectious composite included sternal wound infection, pneumonia, sepsis or bacteraemia, and urinary tract infection; the other complications composite endpoint comprised non-cardiac death, reoperation, deep venous thrombosis, pulmonary embolus, major bleeding, renal failure and any other reported serious adverse events.

2.6 | Statistical analysis

Based on the glycaemic control in patients undergoing coronary artery bypass graft surgery (GLUCO-CABG) trial, we expected 97% of patients to require insulin during cardiac surgery when targeting BG <8.0 mmol/L.[1] To detect a clinically relevant between-group difference of 10%, with 80% power, alpha at 0.05, and accounting for an 8% drop-out rate we required 137 patients per group.[13] Dropouts because of logistical reasons were replaced. No interim analyses were planned or performed. We based our primary analyses on the intention-to-treat population, including all patients receiving at least one study medication dose. We included patients who received both study drug administrations in a per-protocol analysis. Discrete data are presented as count (%) and compared between groups using χ^2-tests or Fisher's exact test. Continuous variables are presented as mean ± SD or median (interquartile range) and compared using Student's *t*-test or Mann–Whitney *U*-tests, depending on the distribution of the data. Absolute differences between groups are presented with their 95% confidence intervals (CIs). Normality of distributions was assessed visually with histograms, Q-Q plots and the Shapiro–Wilk test. P <0.05 was considered significant. Statistical analyses were performed using SPSS (IBM version 24; IBM Corp., Armonk, New York).

3 | RESULTS

Between June 12, 2017 and August 29, 2018, we enrolled 278 patients planned to undergo cardiac surgery (Figure 2). We randomly assigned 139 patients to liraglutide and 139 to placebo. After randomization, but unaware of group allocation, nine patients withdrew their consent. Surgery was rescheduled, cancelled or performed emergently for six patients. For two patients, an exclusion criterion was noted after randomization, and the researchers withdrew them from the study. None

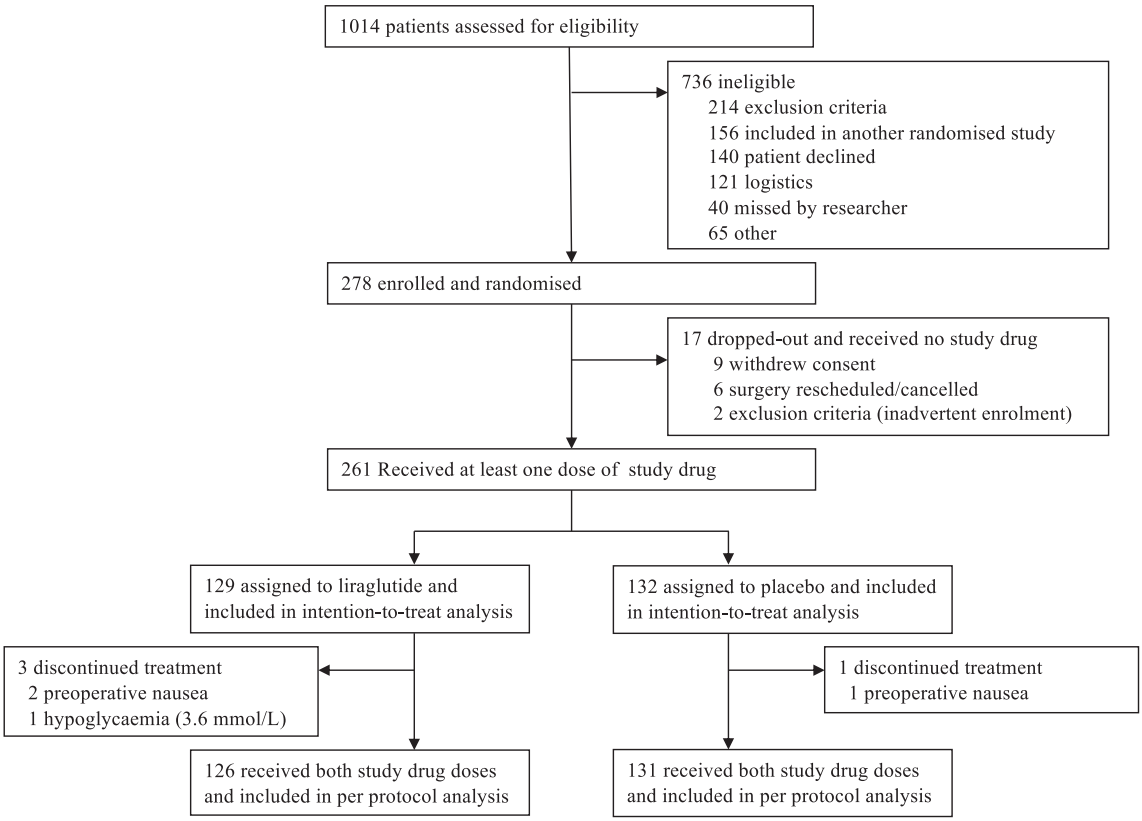

FIGURE 2 CONSORT flowchart of patients in the study

of these 17 patients received any study drug, and no data were collected after their withdrawal from the study (Figure 2). All patients receiving at least one study drug administration were included in the primary intention-to-treat analyses (129 in the liraglutide group, 132 in the placebo group). The second study drug administration was withheld in four patients (liraglutide: three; placebo: one); patients receiving both study drug administrations were included in a per-protocol analysis. The trial ended after completion of follow-up and data collection of the last patient on November 9, 2018. No crossovers between groups and no unblinding procedure occurred during the trial.

3.1 | Baseline variables

Patients were well balanced between groups, as we observed no notable differences in baseline characteristics between the two groups (Table 1). The mean ± SD for age was 65 ± 11 years, 81% of patients were men, and mean BMI was 27.5 ± 4.2 kg/m^2. Type 2 diabetes mellitus was present in 42 (16%) patients, six (2%) of whom used insulin. The mean ± SD of glycated haemoglobin of patients with type 2 diabetes mellitus was 7.2% ± 3.2% (55 ± 12 mmol/mol), and 5.6 ± 0.5 (38 ± 5 mmol/mol) in patients without a history of diabetes mellitus. The median euroSCORE II was 1.27% (0.89–1.97), and the mean duration of surgery was 222 min (165–293), resulting in a median (interquartile range) of 5 (4–6) intraoperative BG measurements per patient.

3.2 | Insulin requirements

The primary outcome of any insulin administration differed significantly between treatment groups; 55 (43%) for liraglutide and 80 (61%) for placebo, with a difference of 18% between groups (95% CI 5.9–30.0, P = 0.003). In the liraglutide group, the total intraoperative insulin doses and number of insulin administrations were lower compared with placebo-treated patients (both with a median of 0 in the liraglutide group; Table 2). The number of patients that required insulin in the first 24 postoperative hours was not different [liraglutide: 48 patients (37%) vs. placebo: 54 (41%) patients, difference 4% (95% CI −8 to 15, P = 0.54)], nor was the median total dose of insulin administered [liraglutide 0 IU (0–20) vs. placebo 0 IU (0–22), P = 0.63].

3.3 | Glycaemic control

The incidence of BG measurements >8.0 mmol/L (requiring insulin) and the mean hourly BG concentrations are depicted in Figure 3. The mean intraoperative BG concentration was lower in the liraglutide group, difference 0.66 mmol/L (6.3 vs. 7.0, 95% CI 0.39–0.93, P < 0.0001). There was no difference in the incidence of hypoglycaemia (BG <4.0 mmol/L) with four (3%) patients in the liraglutide group versus 3 (2%) patients in the placebo group (P = 0.72). Hyperglycaemia (BG >11.0 mmol/L) and mild or severe hypoglycaemia (between 4.0 and 2.3 or <2.3 mmol/L,

TABLE 1 Baseline characteristics of the intention-to-treat population

	All	Liraglutide	Placebo
	261	129	132
Age, mean ± SD, years	65.0 ± 10.9	64.6 ± 11.2	65.3 ± 10.7
Male sex, n (%)	211 (81)	105 (81)	106 (80)
Ethnic origin, n (%)			
Caucasian	250 (96)	123 (95)	127 (96)
Other	11 (4)	6 (5)	5 (4)
BMI, mean ± SD, kg/m^2	27.5 ± 4.2	27.3 ± 4.0	27.7 ± 4.4
Diabetes, n (%)			
No	219 (84)	108 (84)	111 (84)
Type 2 non-insulin	36 (14)	18 (14)	18 (14)
Type 2 insulin	6 (2)	3 (2)	3 (2)
HbA1c, mean ± SD, %	5.8 ± 0.8	5.8 ± 0.9	5.8 ± 0.8
HbA1c, mean ± SD, mmol/mol	40 ± 8.9	40 ± 9.7	40 ± 8.1
ASA score, n (%)			
II	36 (14)	22 (17)	14 (11)
III	189 (72)	94 (73)	95 (72)
IV	36 (14)	13 (10)	23 (17)
Smoker past year, n (%)	54 (21)	26 (20)	28 (21)
Creatinine clearance, mean ± SD, mL/min	80.4 ± 16.6	80.6 ± 17.0	80.2 ± 16.2
EuroSCORE II, median (IQR), %	1.27 (0.89–1.97)	1.22 (0.84–1.93)	1.34 (0.90–2.05)
Duration of surgery, median (IQR), min	222 (165–293)	222 (162–276)	219 (169–308)
Type of surgery, n (%)			
CABG procedure	92 (35)	46 (36)	46 (35)
Single non-CABG procedure	102 (39)	52 (40)	50 (38)
Two or more procedures	67 (26)	31 (24)	36 (27)
Type of anaesthesia, n (%)			
Propofol	16 (6)	8 (6)	8 (6)
Sevoflurane	245 (94)	121 (94)	124 (94)

respectively) all occurred with an incidence of ≤5%, and rates did not differ between groups (Table 2). In the first 24 postoperative hours, the mean ± SD BG concentrations increased to 9.0 ± 1.4 mmol/L, while the remaining 0.49 mmol/L was lower in the liraglutide group (95% CI 0.15–0.84, $P < 0.0001$).

3.4 | Adverse events

We observed no between-group difference in the incidence of nausea or vomiting, neither before nor after surgery. Patients had significantly higher heart rates in the liraglutide group compared with placebo, whereas the mean arterial pressures were comparable. Lengths of ICU or hospital stay were not different between groups, nor were any of the composite endpoints of complications. Within 30 days after surgery three patients died (two in the placebo and one in the liraglutide group). We noted five patients with a postoperative myocardial infarction (liraglutide: three; placebo: two) and eight with a cerebrovascular accident (liraglutide: four; placebo: four). Other significant complications included postoperative cardiac stunning and postoperative hypoperfusion syndrome (Appendix S1). The per-protocol analysis revealed similar results to the intention-to-treat analysis for all outcomes (Appendix S1).

3.5 | Potential confounders

The 42 (16%) patients with a history of type 2 diabetes mellitus were evenly distributed between groups. These patients required more insulin and had higher perioperative BG concentrations (Appendix S1). None the less, between-group differences were similar for patients with or without type 2 diabetes mellitus and no different effect on the primary endpoint (requiring any perioperative insulin) was found ($P_{interaction} = 0.945$).

According to the local protocol in three participating centres, 164 (63%) patients received intraoperative corticosteroids, 81 of these patients had been allocated to liraglutide and 83 to placebo. Patients receiving corticosteroids were administered a median (interquartile range) dose of 0.95 mg/kg (0.49–1.02) dexamethasone. Compared with patients not receiving any corticosteroids, insulin requirements and BG concentrations were higher in patients having corticosteroid injection during surgery (Appendix S1). No different effect on the primary endpoint (requiring any perioperative insulin) was found ($P_{interaction} = 0.794$).

We also found no significant interaction effect for the type of surgery ($P_{interaction} = 0.457$ for coronary bypass only vs. more complex procedures) nor the type of anaesthesia ($P_{interaction} = 0.072$ for propofol vs. sevoflurane maintenance of anaesthesia).

4 | DISCUSSION

Liraglutide treatment resulted in a lower number of patients requiring any insulin during cardiac surgery. Furthermore, preoperative liraglutide resulted in a lower number and dose of insulin administrations, as well as lower perioperative BG concentrations, without an increase in the incidence of hypoglycaemia. We observed no differences in adverse outcomes such as hyperglycaemia, nausea and vomiting, length of hospital or ICU stay, or postoperative complications.

The first trials studying a continuous infusion of GLP1 in cardiac surgery patients all found either lower BG concentrations or fewer insulin requirements with comparable glycaemic control.[14-16] While three trials studied a GLP1RA in cardiac surgery,[17-19] all used the short-acting GLP1RA exenatide, and only two[17,18] reported on BG concentrations or insulin requirements. One of these studies, including 38 patients, reported lower average BG concentrations with a trend towards fewer insulin requirements.[18] However, the other trial,

TABLE 2 Insulin therapy, glycaemic control, nausea and vomiting, and postoperative complications

	Liraglutide 129	Placebo 132	Absolute difference	95% CI	*P* value[a]
Insulin therapy					
Any insulin administered, n (%)	55 (43)	80 (61)	18%	6–30	0.003
Total intraoperative dose, median (IQR)	0 (0–3)	2 (0–5)	2	0.9–3.1	0.003
Number of administrations, median (IQR)	0 (0–1)	1 (0–2)	1	0.5–1.5	0.001
Glycaemic control					
Intraoperative					
Mean blood glucose, mean ± SD	6.3 ± 1.1	7.0 ± 1.1	0.66	0.39–0.93	<0.001
Hyperglycaemia (>11 mmol/L), n (%)	7 (5)	5 (4)	−2%	−7% to 3%	0.57
Hypoglycaemia mild (2.3–4 mmol/L), n (%)	3 (2)	2 (2)	−1%	−4% to 3%	0.68
Hypoglycaemia severe (<2.3 mmol/L), n (%)	1 (1)	1 (1)	0%	−2% to 2%	1.00
Postoperative					
Mean blood glucose, mean ± SD	8.8 ± 1.4	9.2 ± 1.4	0.49	0.15–0.84	0.006
Hyperglycaemia (>11 mmol/L), n (%)	42 (33)	50 (38)	5%	−7% to 18%	0.36
Hypoglycaemia mild (2.3–4 mmol/L), n (%)	0 (0)	0 (0)	NA	NA	NA
Hypoglycaemia severe (<2.3 mmol/L), n (%)	0 (0)	0 (0)	NA	NA	NA
Nausea and vomiting, n (%)					
Preoperative	4 (3)	1 (1)	−2%	−6% to 1%	0.21
Postoperative	33 (26)	27 (20)	−5%	−15% to 6%	0.37
Haemodynamics, mean ± SD					
Heart rate preoperative (beats/min)	77 ± 16	68 ± 17	−10	−13 to −5.5	<0.001
Heart rate postoperative (beats/min)	78 ± 13	72 ± 18	−6	−9.8 to −2.1	0.003
Heart rate ICU 1 h postoperative (beats/min)	81 ± 12	73 ± 13	−8	−11 to −4.6	<0.001
Mean arterial pressure preoperative (mmHg)	92 ± 18	88 ± 20	−4	−9 to 0.39	0.07
Mean arterial pressure postoperative (mmHg)	71 ± 13	67 ± 15	−4	7.6 to −0.77	0.02
Mean arterial pressure ICU 1 h postoperative (mmHg)	77 ± 16	77 ± 13	0	−3.9 to 3.2	0.85
Complications, n (%)					
Composite endpoint cardiac	53 (41)	58 (44)	3%	−9% to 15%	0.64
Composite endpoint infectious	12 (9)	11 (8)	−1%	−8% to 6%	0.78
Composite endpoint other	23 (18)	28 (21)	3%	−6% to 13%	0.49
Any complications	68 (53)	76 (58)	5%	−7% to 17%	0.43
Delirium (ICU + Ward)	4 (3)	10 (8)	4%	−1% to 10%	0.17
Delirium (CAM-ICU only)	2 (2)	7 (5)	4%	−1% to 8%	0.17

Abbreviations: CAM-ICU, confusion assessment method for the ICU; ICU, intensive care unit; NA, not applicable.
[a]*P* values represent comparisons among the treatment groups.

including 104 patients, showed no difference in the number of patients requiring any insulin, total insulin dose or glycaemic control, although this study used a slightly higher dose of exenatide.[17] A trial comparing exenatide once weekly to liraglutide once daily in patients with type 2 diabetes mellitus found liraglutide to be more effective for improvement of glycaemic control and reduction of body weight.[20] However, liraglutide resulted in higher rates of nausea and vomiting at initiation of therapy, with differences dissolving after 4–6 weeks.[20] In a systematic review, 18 of 19 trials studying a GLP1RA in the perioperative or ICU setting, found either improved glycaemic control or reduced insulin requirements.[9] A previous trial from our own group in a non-cardiac surgery population showed improved glycaemic control with fewer insulin requirements after preoperative liraglutide administration.[21] Our current data extend these results to patients undergoing cardiac surgery.

The Joint Commission on Accreditation of Healthcare Organizations marked insulin as one of five high-alert medications.[22] Although its use is directly correlated to hypoglycaemia, so far there were no alternatives to insulin for the treatment of perioperative hyperglycaemia.[2] With hyperglycaemia and hypoglycaemia both having been linked to postoperative complications,[23] an impasse exists. In the search for a way out, many experts have pointed to the use of

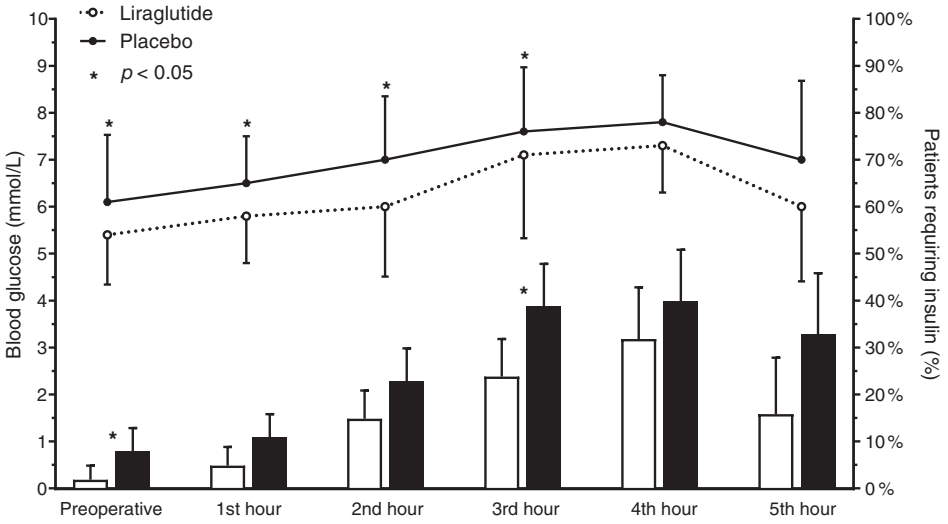

FIGURE 3 Mean intraoperative blood glucose concentrations and incidence of hyperglycaemia requiring insulin administration. Blood glucose concentrations during surgery (mean ± SD, lines, top of figure) and incidence of blood glucose >8 mmol/L [% (95% CI), bars, bottom of the figure]

non-insulin alternatives for in-hospital glycaemic control.[7,9,24] Our trial shows that liraglutide is indeed an effective alternative to insulin for the treatment of hyperglycaemia induced by the stress of cardiac surgery. Reassuringly, the lower BG attained in the liraglutide group was not accompanied by a higher hypoglycaemia rate. This is in line with a meta-analysis of perioperative and intensive care trials, studying incretin therapies.[9]

Liraglutide is a dipeptidyl peptidase-4-resistant GLP1 analogue that stimulates insulin and inhibits glucagon secretion, thereby reducing BG levels.[8] GLP1 also acts on other organs such as the liver, fat and muscle tissue, stimulating glucose uptake and glycogen synthesis.[8] GLP1 also has a direct effect on the heart. GLP1 receptors have been found in the sinus node, increasing the heart rate, as also observed in our study.[8] In addition, various studies have postulated cardioprotective properties of GLP1 therapy such as reducing ischaemia-reperfusion injury, reducing infarction size and improving ischaemic left ventricular function.[25] These effects stem mostly from small pilot studies. Future well-designed larger trials will have to evaluate the effectiveness of these cardioprotective mechanisms to improve outcomes.

To quantify the effect on insulin requirements, we used an insulin bolus algorithm that was proven effective in controlling perioperative BG concentrations.[21] Besides the intervention group in this study, glycaemic control in the placebo group was also quite good, with a mean intraoperative BG of 7.0 mmol/L and only 4% of patients experiencing hyperglycaemia >11.0 mmol/L. It is probable that the glycaemic control in the placebo group was positively influenced by a clinical trial effect, because outside of clinical trials, non-compliance with insulin protocols results in poorer glycaemic control.[4,22] Considering the relatively modest contrast in glycaemic control, it is perhaps not surprising that we found no difference in any of the composite endpoints of complications, whereas studies with interventions resulting in larger differences in BG concentrations did report significant differences in complications.[1,26,27] Importantly, this trial was not powered to find a reduction in complications.

Gastrointestinal complications, including nausea and vomiting, are commonly reported with the use of GLP1RAs.[8] The American Diabetes Association highlighted this as a potential concern for the in-hospital use of GLP1RAs.[7] Although few studies on incretin-therapies in (post)surgical patients have reported on postoperative nausea and vomiting, none have found a difference in its incidence compared with placebo.[9] To reduce the risk of preoperative nausea, and based on previous trial experience, we administered the second dose of liraglutide after the induction of anaesthesia.[21] The emetic effects of anaesthesia and surgery probably outweigh any additional impact of liraglutide.[21] Of note, the comparable incidences of postoperative nausea and vomiting in the liraglutide (26%) and placebo groups (20%, P = 0.37) were both considerably lower than the 54% reported in a recent systematic review of postoperative nausea and vomiting after cardiac surgery.[28]

Administering prophylactic corticosteroids to treat the systemic inflammatory reaction associated with cardiopulmonary bypass is common practice,[29] as it was in three of the four participating centres in our trial. Therefore, we stratified our randomization per centre. Consistent with the literature, we observed higher BG concentrations in the patients treated with corticosteroids.[30] None the less, the efficacy of liraglutide was comparable, whether patients received intraoperative corticosteroids or not.

Our study has some limitations. Of the 1014 patients screened, 214 (21%) could not be enrolled because of exclusion criteria, most commonly heart and kidney failure. At the commencement of this trial, we excluded patients with heart failure NYHA class III and IV because of limited experience with liraglutide in this population. After reassuring results from the Liraglutide Effect and Action in Diabetes Evaluation of Cardiovascular Outcome Results (LEADER) trial, the summary of product characteristics for liraglutide was updated, and exclusion from our trial was adapted to NYHA class IV only.[31] The safety of liraglutide in patients with NYHA class IV heart failure remains to be evaluated. For similar reasons, we excluded patients with chronic kidney disease from this trial. However,

researchers postulated BG-independent renoprotective effects for liraglutide.[32,33] Currently, liraglutide is only contraindicated in patients with end-stage renal disease. Furthermore, this study also excluded patients with other contraindications for GLP1RA therapy, such as a history of pancreatitis. Finally, in this trial liraglutide was administered preoperatively only, and while the duration of action is 24 h,[8] a considerable rise in BG was still observed postoperatively. While we found a statistically significant difference in glycaemic control, a greater difference is probably required to result in further reductions in postoperative complications, for which our trial was not powered. Hence, higher doses and more potent or longer-acting preparations could further improve glycaemic control postoperatively.

In conclusion, liraglutide reduced insulin requirements and improved glycaemic control, without an increase in hypoglycaemia. These effects should be viewed in combination to appreciate the potential of GLP1RAs to improve perioperative care safely in a health care provider- and patient-friendly way. This multicentre trial validates previous smaller studies and provides support for the use of liraglutide in the perioperative setting. We expect future in-hospital glycaemic control studies to focus on the potential of GLP1RAs to reduce complications.

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AUTHOR CONTRIBUTIONS

A.H.H. and J.H. had full access to all the data in the study and take final responsibility for the integrity of the data and the accuracy of the data analysis as well as the decision to submit for publication. J.H. and J.H.D. wrote the initial research proposal. A.H.H. and J.H. drafted the initial manuscript. M.J.V., B.M.G., T.S., R.A.B., M.G.W., M.B.G., B.T., M.W.H., B.P. and J.H.D. reviewed and edited the manuscript, and contributed to the discussion. A.H.H. did the statistical analysis. A.H.H., M.J.V., B.M.G., T.S., R.A.B., M.G.W. and B.T. recruited patients and collected research data.

CONFLICT OF INTEREST

M.J.V., M.B.G., B.T., M.B.G., T.S. and M.G.W. have no conflicts to declare. A.H.H. and J.H. have received a grant from the European Society of Anaesthesiology. R.A.B. acts as a consultant for Philips Research. M.W.H. is Executive Section Editor Pharmacology with *Anesthesia & Analgesia*, Section Editor Anesthesiology with *Journal of Clinical Medicine* and acts as a consultant for Eurocept, MSD and CSL Behring. B.P. has received research support from GE Healthcare, Edwards, Air Liquide; he has received lecture fees from Abbott, Abbvie, Orion Pharma, Philips Healthcare and grants from SCA, ESA and ZonMW. J.H.D. has received research support from Sanofi, acts as a consultant for Novo Nordisk. As the funder of the study, Novo Nordisk, had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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