Glucose control therapies in the perioperative period

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Glucose control therapies in the perioperative period

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Preface

Introduction

Abraham H. Hulst

Glucose is the primary energy source for most cells in the human body. Because of its central role in human physiology, the blood glucose concentration can be considered a vital parameter. As such, blood glucose regulation is an important factor for the anaesthesiologist during the perioperative period as well as the subject of this thesis.

In healthy conditions, the blood glucose concentration varies between approximately 3.5 mmol/l to 7 mmol/l. Patients with diabetes mellitus have lost the ability to adequately maintain this blood glucose homeostasis. Diabetes mellitus is either a result of an absolute deficit of insulin such as in type 1 diabetes mellitus, or based on a relative deficit of insulin in combination with insulin resistance in target cells, as present in type 2 diabetes mellitus. The chronic loss of appropriate glucose control eventually leads to organ disease such as nefropathy, retinopathy, neuropathy and micro- and macrovascular complications.

Chronic hyperglycaemia due to diabetes mellitus needs to be differentiated from acute hyperglycaemia during severe physiological stress, such as myocardial infarction or surgery. This transient rise in blood glucose concentration in otherwise healthy patients, or as an exacerbation of poor glucose control in patients with diabetes mellitus, is often called “stress hyperglycaemia”.

Glucose dysregulation

The loss of normal insulin release and function, either acute or chronically, leads to hyperglycaemia. Attempts by clinicians to normalize these elevated blood glucose values have the risk of overcorrection, leading to hypoglycaemia. Unfortunately, both extremes on this spectrum can lead to acute and chronic complications.
Because acute stress causes a rise in glucose, most efforts in the perioperative period are made to prevent potentially harmful levels of hyperglycaemia. Although the definition of the optimal target range glycaemia is still a matter of ongoing debate, currently the most widely accepted consensus in clinical guidelines is to prevent acute hyperglycaemia above 10 mmol/l.[1,2]

Complications of acute hyperglycaemia

The rise of glucose in the setting of illness can be seen as an evolutionary adaptive response during stress, by providing more fuel to the cells of the body in extreme situations. All vertebrates and even insects exhibit a hyperglycaemic response to stress.[3] The majority of blood glucose is taken up by non-insulin dependent tissues such as the heart, nervous system and blood cells.[4] Glucose uptake in these tissues is through facilitated transport across the cell membrane following a diffusion gradient. Thus, increasing extracellular glucose increases uptake of glucose in many of the essential cells of the body. Glucose rich environments have been shown to improve cardiovascular function in stress[5] as well as macrophage (white cell) function,[6] indicating that moderate hyperglycaemia is likely part of the body’s mechanism to meet its needs during stress, e.g. after trauma or during an infection.

On the other hand, several maladaptive or harmful consequences have also been shown that question the net beneficial effect of hyperglycaemia during stress and acute illness. The immune system is disturbed through abnormalities in neutrophil function, decreased intracellular bactericidal effects and glycosylation of immunoglobins.[7] Coagulation is activated through increases of prothrombin and platelet aggregation, increasing the risk of thrombosis.[8] Proinflammatory cytokines are released in response to hyperglycaemia, stimulating the inflammation response.[9] Furthermore, cardioprotective effects such as ischaemic preconditioning are negatively affected by higher blood glucose concentrations.[10] Given these discovered mechanisms it seems possible that hyperglycaemia could lead to further complications following critical illness or surgery.

There are many studies showing a correlation between the extent of hyperglycaemia and worse outcomes.[11,12] However, these observations cannot differentiate between an epiphenomenon or causal link. In case hyperglycaemia is a normal response to illness, then more severe illness is related to more hyperglycaemia, and that is then logically related to worse outcomes. Whereas, if hyperglycaemia is an independent contributor to complications, hyperglycaemia itself would lead to a higher incidence in complications. The most compelling arguments for the latter theory came from the "Leuven Intensive Insulin Therapy Trails". These studies demonstrated that stringent control of blood glucose between 3.9 and 6.1 mmol/l with insulin reduced mortality and morbidity in ICU patients.[13,14] However, these results could not be reproduced in a multicentre randomized trial, showing even increased harm with the practice of intensive insulin therapy.[15,16] Currently, a moderate glucose control strategy is practiced in most hospitals, targeting blood glucose concentrations between 4 mmol/l and 10 mmol/l.[1]

Glucose management in the perioperative period

Despite unresolved questions on what level of glucose control is appropriate in different patient populations and settings, in the perioperative period patients remain at risk of significant deterioration of glucose control. From a pragmatic standpoint, glucose control cannot be ignored, leaving many unanswered questions for the clinician, and Part I of this thesis aimed to answer some of the relevant questions.

For chronic treatment in out of hospital patients, a myriad of glucose lowering therapies have come to market. Due to unfavourable side effects, risk of hypoglycaemia during fasting, and other reasons, most of these medications have been deemed unsuitable for treatment in hospitalised patients. As such, intravenous insulin titration remains the treatment of choice for management of glucose in patients in the perioperative period. This requires frequent monitoring of blood glucose and is therefore considerably labour-intensive, while carrying the risk of inducing hypoglycaemia. A recently marketed alternative to insulin are the Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RA).

Glucagon-Like Peptide-1

GLP-1 is a hormone secreted by cells in the digestive tract in response to enteral nutrition. GLP-1 stimulates the beta cells of the pancreas to secrete insulin and inhibits alpha cells of the pancreas resulting in reduced glucagon release.[17] The described mechanisms act in a glucose dependent manner, having a lower activity in a context of lower glucose concentration and more potency during hyperglycaemia.[17] This means that GLP-1 RA can control glucose with a lower risk for hypoglycaemia. In addition, various other beneficial effects of GLP-1 have been described, such as cardiovascular[18] and renal protective properties,[19] with relatively few, mainly gastrointestinal side effects. As such, these GLP-1 RA have a potential to improve glucose control in the perioperative period without the risk for hypoglycaemia, which is investigated in Part II of this thesis.

The Aims of this thesis are to describe

1. how we treat patients with diabetes mellitus in the perioperative period, and
2. whether there is a role for Glucagon-Like Peptide-1 receptor agonists to improve perioperative glucose homeostasis.

Thesis outline

PART I covers issues in patients with diabetes mellitus. Chapter 1 provides an overview of the current perioperative treatment of patients with diabetes mellitus, as reported by Dutch anaesthesiologists. Chapter 2 focusses on one of the many variables influencing treatment decisions, namely the type of diabetes mellitus and their associated perioperative glucose control. The results of a randomized trial on withholding or continuing metformin, a first-line glucose lowering drug, are reported in Chapter 3.

PART II focusses on the potential of a novel glucose lowering medication class (GLP-1 RA) to treat patients at risk of acute hyperglycaemia, with or without diabetes mellitus. Chapter 4 provides an overview of the use and efficacy of GLP-1 during the perioperative period and intensive care treatment. Chapter 5 reports on the methodology of a multicentre randomized trial applying the GLP-1 RA liraglutide to patients undergoing cardiac surgery and the results are presented in Chapter 6, focussing mainly on perioperative glucose control. Chapter 7 reports the results on postoperative cardiac function after application of GLP-1 RA in these cardiac surgery patients. In Chapter 8, we discuss the new, long-acting GLP-1 RAs and their potential use in the perioperative period.

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Part I

Diabetes and anaesthesia

One

Peri-operative management of patients with diabetes mellitus in Dutch hospitals, a nation-wide survey of protocols

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Abstract

Background

Evidence regarding the optimal treatment of patients with diabetes mellitus in the peri-operative period is scarce and variable. We surveyed diabetes protocols in Dutch hospitals hypothesising that these would show considerable variability, reflecting the diverse literature on this topic.

Methods

We contacted all hospitals in the Netherlands by phone and (e-)mail to request their peri-operative treatment protocol for patients with diabetes mellitus. In addition, we sent out a survey to gather information on preoperative preparation, diabetes medication management, glucose measurements and glucose targets, potassium co-administration and blood sugar control-strategies.

Results

Out of the 80 hospitals in the Netherlands, 72 responded to our request (response rate: 90%). We received 55 protocols, 17 hospitals answered the questions in our survey, and 14 hospitals provided both. The median upper peri-operative glucose target was 10 mmol l^{-1} (range 6-20), and the median lower target was 4 mmol l^{-1} (range 2-8). Long acting insulin was reduced by 25-50 % on the day before surgery in 26 hospitals (38%) and continued in full dosage in the others. On the day of surgery, insulin was stopped in 42 hospitals (60%), in 6 (9%) insulin was continued as normal, and in 13 (22%) the insulin dose was reduced by 25-66% (others unknown). The glucose measurement interval varied between once per 1- 6 hours. Forty-nine hospitals (70%) administered a peri-operative glucose infusion (2-10 g h^{-1}), 46 (66%) also administered continuous insulin (0.5-3 IE h^{-1}), and 23 (33%) co-administered potassium (0.8-6 mmol h^{-1}).

Conclusions

We found a large variability between hospital protocols for peri-operative diabetes mellitus management. This reflects the variability and paucity of literature on peri-operative diabetes management and stresses the need for clinical research on this topic to improve clinical guidelines.

Introduction

With increasing prevalence and attention for patients with diabetes mellitus (DM), many guidelines have been published on the inpatient treatment of DM. However, most are written by societies of endocrine and diabetes specialists,[1–4] and their recommendations on peri-operative care are often limited. Societies of anaesthetists such as the American Society of Anesthesiology (ASA) and the European Society of Anaesthesiology (ESA) have no guideline for treatment of patients with DM. In contrast, some national anaesthesiology societies published a guideline on peri-operative DM management, such as in the UK and Australia, and the Netherlands.[5–7] Many of the recommendations in these guidelines are supported by low quality evidence.[1,7] In addition to these guidelines, numerous review articles have been published on the peri-operative treatment of DM.[8,9] In this myriad of literature summarising low quality evidence, conflicting and non-specific recommendations are likely to emerge.

Prevalence of DM in the Netherlands is estimated between 7.0 – 7.4% of the population aged 50-70 years, and increases with age.[10,11] Prevalence of DM is known to be even higher in patients admitted to the hospital for surgery.[12] For this reason, we expected most hospitals to have a standardised (and protocolised) approach to care for surgical patients with DM. To evaluate this local practice, we invited all Dutch hospitals by survey to share their peri-operative treatment of patients with DM. Some of the results have previously been published in the European Journal of Anaesthesiology[13] and are reproduced here with permission from the publisher.

Methods

We sent out a survey to the anaesthesia department of every public hospital in the Netherlands. Via this survey, we requested their physicians to send us the most recent peri-operative DM protocol in each clinic. We also provided a questionnaire in case the responding clinic either had no protocol or was unwilling to share it. The questionnaire is available as online-only supplementary material S1. We stated that all information would be handled confidentially and no identifying information from any protocol would be published.

The last author (BP) first sent out the survey by postal service in October 2015 to all departments of anaesthesiology in the Netherlands. A second round was sent out via email in July 2016 to all clinics that did not respond initially. The first author (AH) contacted all remaining clinics by telephone in September 2016. In January 2017, having read all protocols and surveys, we contacted clinics and requested additional information whenever information on a subject was insufficient to complete our data collection sheet. In February 2017, data collection stopped and all data were extracted for analysis.

We used a standardised data collection sheet to collect information about the protocol or the reported standard of care from the questionnaires. The data collection sheet was constructed by the first two authors (AH and JH), data extraction was completed first by AH and checked by JH. Conflicts were resolved by discussion between authors. All data points on the collection sheet are summarised in Table 1. Data were gathered in an electronic database using using SPSS (version 24), and GraphPad Prism 7 was used for graphical representation of the results.

Table 1. Summary of data extraction
General information
Response to request, protocol used, protocol sent, completed questionnaire
Authors of protocol
Distinction between DM patients, mention of type 1 DM, Distinction between operations
Preoperative
Standard preoperative actions, laboratory measurements, planning of surgery
Withholding OAD, long-acting, short acting and mixed insulin, insulin pumps on day before and of surgery.
Glucose measurements
Frequency before, during and after surgery measurement interval after glucose or insulin interventions, method of measurement, potassium measurements.
Glucose control
Target range glucose.
Glucose, insulin and potassium infusion used, respective starting doses, route of administration.
Insulin dosing dependence on TDD insulin, used thresholds.
Actions in case of hypoglycaemia and hyperglycaemia, respective doses of glucose and insulin.
Miscellaneous
Additional information of interest.

Results

Out of the 80 hospitals in the Netherlands, 72 responded to our request (response rate: 90%). In 63 of these 72 hospitals a protocol for peri-operative treatment of patients with DM was used, 55 of the hospitals did sent us their protocol, the remaining 17 responded via the questionnaire. Fourteen of the hospitals that sent us their protocol also completed the questionnaire. Protocols were written mostly by anaesthetists (13%), internists (21%), or a combination (30%). We summarised all information in a non-identifiable database, available upon request from the authors. Below we report our most relevant data only.

Preoperative actions

A patient with known DM presenting for surgery would be referred for internal medicine consultation in 19 hospitals (27%). We summarised prescribed pre-operative laboratory measurements for all DM patients in Table 2.

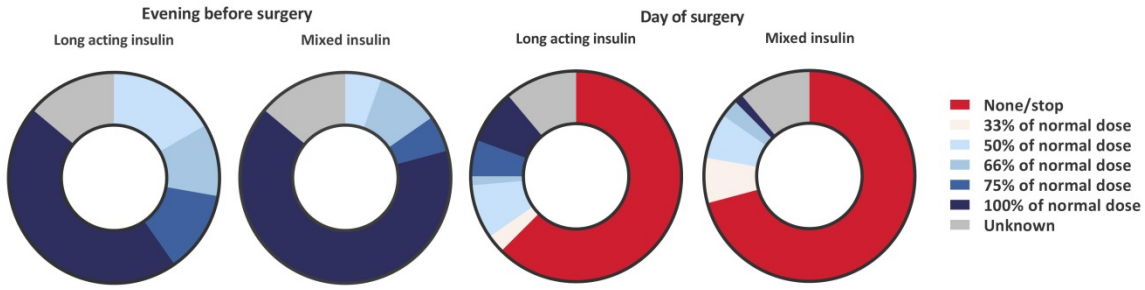
Table 2. Protocolised preoperative laboratory measurements

	Number of hospitals	%
None	26	32,5
Glucose	2	2,5
HbA1c	6	7,5
Glucose + HbA1c	6	7,5
Glucose + creatinine	2	2,5
Glucose + HbA1c + creatinine	3	3,8
Glucose + HbA1c + creatinine + potassium	8	10,0
Creatinine + potassium	3	3,8
Unknown	16	20,0
Total	72	100

These were combined with an electrocardiogram in 7 hospitals (10%). Non-insulin anti-diabetes medication was almost universally withheld on the day of surgery (66/72, 92%). However, metformin formed an exception in many protocols. The stop moment for metformin differed from that of other non-insulin anti-diabetes medication in 17 hospitals (17/72, 25%). In two of these hospitals, metformin was continued during the entire peri-operative period (2/72, 3%). The other hospitals advocated to withhold metformin for at least 8 h (1/72, 1%), 24 h (5/72, 7%) 48 h (4/72, 6%), or 72 h (1/72, 1%) before surgery.

In most hospitals, policy on insulin administration was differentiated for short-acting, long-acting, and mixed insulin preparations. The prescribed dosages on the evening before surgery and on the morning of surgery are shown in Figure 1.

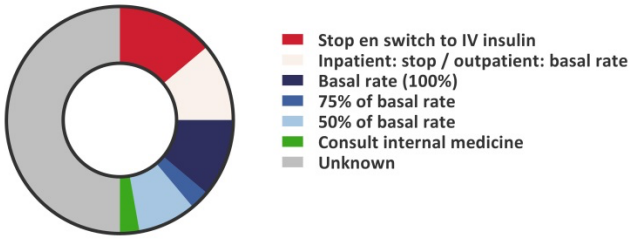
Figure 1. Percentage of regular dose of insulin prescribed before surgery



On both time points, the reduction of long-acting and mixed insulin showed considerable variation between clinics.

Half (36, 50%) of the responding hospitals mentioned insulin pumps in their protocols. These pumps were continued on the day before surgery in most hospitals (32, 89%). Policy on the day of surgery, was more variable and is summarised in Figure 2.

Figure 2. Prescribed actions regarding subcutaneous insulin pumps before surgery



Diabetes mellitus type 1

Seventeen of the 55 protocols that we received made mention of DM type 1 (31%). On the day of surgery, many hospitals withhold long-acting insulin. Often, a preoperative glucose-insulin infusion was started instead. However, in 10 of the hospitals a full stop of long acting insulin was combined with not starting insulin infusion peri-operatively. None of these 10 hospitals made specific mention of DM1.

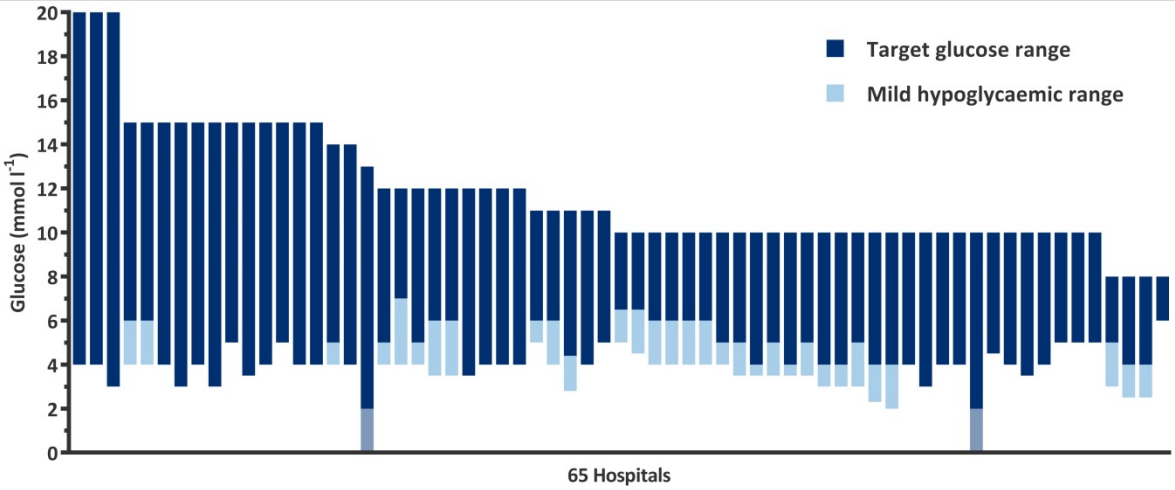
Measuring glucose

Except for 10 cases in which no explicit statement was retrieved, all 62 remaining hospitals started glucose measurements before surgery. Intraoperatively, glucose measurement frequency varied from every hour to once every six hours. The median prescribed interval was 2 h (22 hospitals). In many hospitals the prescribed interval increased for the postoperative period, with a median of 6 h (19 hospitals), while 17 hospitals still prescribed 2-hourly measurements in the postoperative period. Additional glucose measurements after glucose or insulin adjustments (for hypoglycaemia and hyperglycaemia, respectively) were prescribed in 34 hospitals. After insulin adjustments, the median interval was one hour (18 hospitals), after glucose administration for hypoglycaemia this was either 30 minutes (10 hospitals) or 15 minutes (13 hospitals). In addition to glucose, 21 hospitals (29%) mentioned measuring potassium, either regularly or when instigating insulin treatment.

Glucose targets

We retrieved information on peri-operative glucose targets from 65 hospitals. Some hospitals defined a mild and stricter lower glucose target, these are represented together with their upper glucose targets in Figure 3.

Figure 3. Peri-operative glycaemic targets

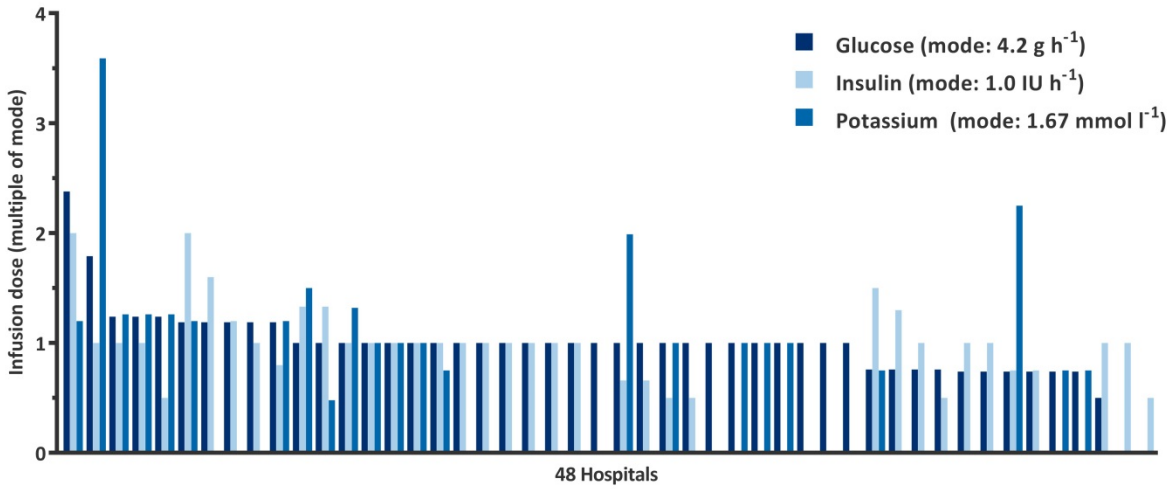


Glucose, insulin (potassium) administration

In 51 of the responding hospitals (71%), patients were started on a glucose drip in the morning before surgery, doses ranged from 2.1 – 10 g h^{-1} with a mode of 4.2 g h^{-1} (corresponding to 1.5 L of glucose 5% in 24 h). In 48 (67%) hospitals, patients received a continuous insulin infusion before start of surgery, with a starting dose between 0.5 – 3 IU h^{-1}, with a mode of 1.0 IU h^{-1}. In 23 hospitals (32%) a

potassium infusion was added, with a dose between 0.8 – 6 mmol h^{-1} and a mode of 1.67 mmol h^{-1}. In Figure 4, we plotted for each hospital the dose of glucose, insulin, and potassium, with dose expressed as multiples of the respective mode.

Figure 4. Intraoperative continuous glucose, insulin, and potassium dose prescribed

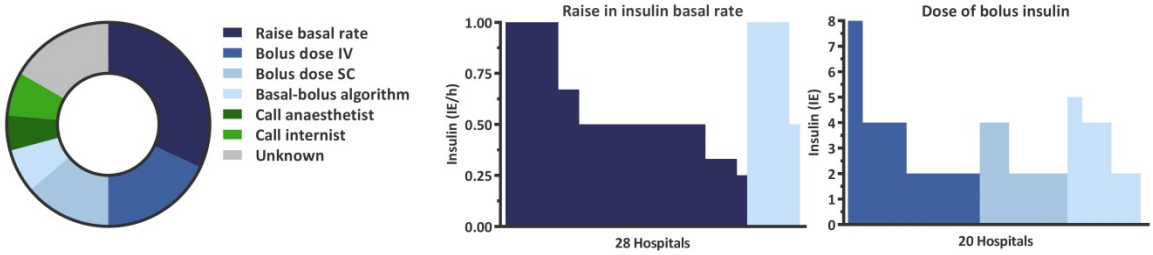


The prescribed starting dose of intraoperative insulin infusion was dependent on the total daily dose (TDD) of insulin in 23 hospitals. In three hospitals, the insulin dose was a function of the TDD (e.g. 1/8 of TDD insulin added to bag of glucose 5% given over 8 h). In the remaining twenty hospitals, the starting rate of insulin infusion was set according to the TDD of insulin, using thresholds (e.g. below 50 IU TDD, the starting rate was 1.0 IU h^{-1} and above 2.0 IU h^{-1}). This threshold ranged between 20 – 100 IU with a mode of 50 IU per day.

Hyperglycaemia

In case of hyperglycaemia additional insulin was administered in the majority of hospitals, however, no specific actions were described in 12 hospitals (17%). We visualised the first prescribed action in case of hyperglycaemia in Figure 5, together with the initial insulin dose.

Figure 5. Treatment of hyperglycaemia



Hypoglycaemia

In 59 hospitals, any action in case of hypoglycaemia was defined (82%). In 46 hospitals, treatment of hypoglycaemia was different for 'mild' and 'severe' hypoglycaemia, with thresholds for this distinction differing between hospitals. Prescribed actions in case of low glucose measurements are summarised in Figure 6. In 33 hospitals, a dose of glucose to be administered intravenously was defined, with a spread of 4 – 25 g.

Consensus in practice

We attempted to summarise to what degree we could find agreement in practice. To this end, we formulated a statement that reflected >50% agreement in peri-operative diabetes care, see Table 3.

Figure 6. Treatment of hypoglycaemia

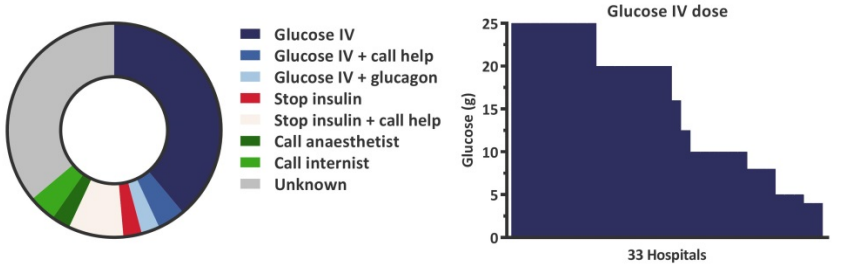


Table 3. Elements with general consensus (practice in >50% of hospitals)
General information
Have protocol in place for peri-operative treatment of patients with DM
Make distinction in DM patients according to insulin
Preoperative
Plan patients using insulin in the morning to minimise fasting
Withhold OAD on the day of surgery
Continue patient's insulin on day before surgery (50-100% of regular dose)
Stop patient's own insulin on day of surgery
Obtain a glucose measurement before start of surgery
Glucose measurements
Measure glucose once every 1 – 3 h
Glucose control
Maintain glucose between 4 – 10 mmol l^{-1}
Administer a continuous glucose and insulin infusion (no agreement on dose)
Miscellaneous
Addition of potassium is no standard requirement

Discussion

The results of this survey show that most hospitals in the Netherlands delivering anaesthesia care have a protocol in place for the treatment of patients with DM. The content of these protocols, however, varies considerably. Adherence to a peri-operative glucose protocol has been reported to be low.[14,15] It is therefore conceivable that actual care differs from what is reported here and it seems likely that the variability in practice is substantial. It remains a matter of debate whether practice should be more uniform. In the absence of solid evidence from clinical trials it is hard to make strong recommendations on many of the practices we described. However, some findings are worth discussing.

We found that only 31% of the protocols explicitly mentioned type 1 diabetes mellitus (DM1). This group is known to be more susceptible to dysregulation in the peri-operative period and always needs some insulin administration to prevent keto-acidosis (DKA).[16] Some hospitals that do not mention DM1, withhold subcutaneous insulin without starting an insulin infusion, hence putting these patients at risk for DKA.

Non-insulin anti-diabetes medication are almost universally withheld on the day of surgery (66/72 hospitals, 92%), with metformin stopped even earlier in 15 hospitals. Although the risk of hypoglycaemia is low, metformin is usually withheld peri-operatively, because of the perceived risk of metformin-associated lactic acidosis.[3,7,17] However, since a Cochrane review[18] showed no increased risk of lactic acidosis in patients treated with metformin, guidelines are moving towards continuing metformin peri-operatively.[5,6] These guidelines from Australia and the UK are not reflected in Dutch practice. Although the risk of lactic acidosis is likely to be low, no advantage of continuing metformin has been demonstrated either.[19] Despite some significant outliers, there is also some consensus between hospitals on peri-operative glucose targets. The modal range we found was between 4 – 10 mmol l^{-1}, which is in line with the guidelines from the American Diabetes Association.[20] However, this also remains subject to debate with recent studies advocating lower targets peri-operatively.[21]

The European Society of Anaesthesiology has no guideline on peri-operative management of DM. Hence, the most relevant guide to practice for all hospitals included in this survey was the protocol by the Dutch Society of Anaesthesiology. This guideline is part of a broader guideline on in-hospital care for DM patients written by the Dutch Society of Internal Medicine.[7] Unsurprisingly, in view of the available literature, compliance with this national guideline seems poor. To exemplify, we compared some of the recommendations from this guideline with the findings of our survey. It states that a preoperative HbA1c has to be known, within 3 months of surgery. However, we observed that only 28% of hospitals performed standard HbA1c measurements. Nearly all hospitals (except for two) withhold metformin before surgery and 85% (63 hospitals) restarted all diabetes medication with resumption of oral intake. While the first complies with this Dutch guideline, on the latter it recommends withholding metformin until ascertaining the absence of lactic acidosis, hemodynamic instability, fever, fluid losses, and kidney function deterioration. On intraoperative insulin dosing, the only recommendation made is to have an algorithm in place in case of continuous insulin infusion. Although not very specific, all hospitals seem to comply with this recommendation.

Wider applicability of this study is limited by the inclusion of only Dutch hospitals, however, with a response rate of >90% it gives a good representation of practice within a single country with an advanced health care system. Furthermore, we wanted to investigate the extent of variability in practice, which is likely even greater internationally. As mentioned above, adherence to these protocols might be low. Nonetheless, we consider the data from this survey to be a valuable proxy of actual care.

In conclusion, we found great variability in practice of peri-operative care for patients with DM. This was expected, and likely reflects the diversity of data on this topic. A European guideline could support

uniformity of care for these patients and guide physicians through the abundance of conflicting literature.

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Two

Comparison of perioperative glucose regulation in patients with type 1 versus type 2 diabetes mellitus: a retrospective cross-sectional study

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Abstract

Background

Most perioperative diabetes mellitus (DM) guidelines do not distinguish between patients with type 1 (DM1) and type 2 (DM2). We hypothesised that similar treatment of DM1 and DM2 patients leads to differences in their perioperative glucose control.

Methods

We performed a retrospective cross-sectional study, of all DM patients undergoing surgery between May 2013 and November 2015 in a Dutch university hospital. We compared DM1 with DM2 patients, treated according to the same perioperative glucose protocol. Our primary outcome was the incidence of hyperglycaemia (glucose ≥10 mmol l^{-1}). Secondary outcomes were short-term glycaemic control (glucose before surgery and peak glucose perioperatively), long-term glycaemic control (HbA1c in 90 days before and after surgery) and the incidence of hypoglycaemia (glucose <4 mmol l^{-1}).

Results

We included 2,259 patients with DM, 216 (10%) of which had DM1. The calculated incidences in our population were 7/1000 patients with DM1 and 69/1000 patients with DM2. Compared to those with DM2, patients with DM1 were younger, had a lower BMI, a higher glucose concentration before surgery, and a higher perioperative peak glucose concentration (11.0 [8.2–14.7] vs. 9.4 [7.7–11.7], p<0.001). The incidence of the primary endpoint, perioperative hyperglycaemia, was significantly higher in DM1 compared to DM2 patients (63% vs. 43%, p<0.001). Hypoglycaemia occurred more often in the DM1 (7.1% vs. 1.3%, p<0.001).

Conclusion

Providing similar perioperative treatment to patients with DM1 and DM2 is associated with poorer short-term and long-term glycaemic control in DM1 throughout the perioperative period, as well as an increased risk of hypoglycaemia.

Introduction

Anaesthetists encounter patients with diabetes mellitus (DM) on a daily basis. The majority of these patients are diagnosed with DM type 2 (DM2), while approximately 5-10% have the auto-immune, type 1 variety of this disease (DM1).[1] For the moment, most perioperative DM guidelines and literature recommendations do not distinguish between DM1 and DM2[2,3] and simply provide advice on the patient with DM or on in-hospital hyperglycaemia. However, in regards to pathophysiology and outpatient diabetes treatment, patients with DM1 differ significantly from those with DM2.[4] Therefore it is surprising that the diseases are lumped together given the complexity of the perioperative period. With DM1 usually requiring more specialised outpatient care as compared to DM2, we would also expect this patient group to be more prone to glucose dysregulation in the perioperative period. This is relevant, because perioperative hyperglycaemia is associated with increased postoperative morbidity[5–7].

We studied short-term and long-term perioperative glucose control in a large cohort of patients undergoing anaesthesia, comparing DM1 with DM2 patients, treated according to the same clinical protocol. Our hypothesis was that similar perioperative treatment of DM1 and DM2 would show differences in perioperative glucose control. First, we compared glucose control in these groups, and secondly, we analysed DM1 as a risk factor for perioperative hyperglycaemia.

Methods

Reporting is in accordance with the STROBE statement on reporting cross-sectional retrospective studies.

Design and setting

All data in this single-centre, cross-sectional cohort study were collected in a database of all electronic anaesthesia care records in the Academic Medical Center in Amsterdam, the Netherlands. Clinical data for every patient receiving procedural sedation, regional or general anaesthesia were retrieved from a digital patient data management system (MetaVision; iMDsoft, Tel Aviv, Israel). All clinical and laboratory data were extracted for analysis after de-identification. The minimal pre-operative dataset that had to be completed for all patients undergoing elective procedures included the presence and type of DM. The medical ethics committee in our institution waived ethical approval and informed consent for this study because of the anonymously collected data. (Decision MEC-AMC: W17_118#17.137).

Glucose regulation protocol

The clinical protocol for perioperative glucose regulation in our institution did not distinguish between DM1 and DM2. A bolus correction schedule was used in the perioperative period with a glucose target range between 4.0 – 10.0 mmol l^{-1}. In addition, glucose-lowering oral anti-diabetics were stopped on the morning of surgery, long-acting insulin was reduced by 25% the night before surgery, short-acting insulin was stopped on the morning of surgery, and no additional background infusion of glucose with insulin was required for patients treated with oral anti-diabetic agents only. For patients taking insulin, $1/8^{th}$ of the total daily insulin dose was added to 500 ml glucose 5% (without potassium) and set to infuse over eight hours. We reported previously in more detail on the effectiveness and adherence to this clinical protocol for patients with DM in our centre.[8] Our protocol is available in full as online-only supplementary material S1.

Cohort and data collection

Relevant data were extracted for the period May 2013 to November 2015. Start date of inclusion was set May 1^{st} because a new protocol for patients with DM was introduced. This ensured that all patients in this database were treated according to the same protocol. The final date of inclusion was set because our institution changed its patient data management system and data export to our electronic database was insufficiently consistent after this date. Inclusion criteria were a first procedure for any individual patient in the database, documented DM, and ≥18 years of age. To be included in the final cohort, a dataset containing at least age, sex, date of surgery and type of diabetes had to be available. Also, records with a duration of surgery <30 minutes were excluded because of likely insignificant surgical stress. Extracted data included patient characteristics, time and date of arrival to and departure from the operating theatre and recovery room, medical history, surgical specialty, type of anaesthesia, medication used, and selected laboratory values (glucose, HbA1c and serum creatinine).

Laboratory measurements

Glucose measurements were either from point-of-care fingerprick (Statstrip, Nova Biomedical, Waltham, MA, USA) or blood gas analysis (Rapidlab 1200, Bayer Healthcare, Tarrytown, NY, USA). For each patient, the pre-operative glucose was defined as either the last glucose measurement on the day of surgery (but before start of surgery) or, if missing, a fasting glucose measurement on the day before surgery.

All glucose measurements during surgery and up to discharge from the recovery ward were extracted. Pre-operative HbA1c values were extracted if measured within 90 days before operation and postoperative HbA1c values within 90 days after operation. Serum creatinine values were extracted if measured within six months before operation.

Outcome measures

Our primary outcome was the incidence of hyperglycaemia (glucose value of ≥10 mmol l^{-1}) in the perioperative period, defined as from start of surgery until three hours after surgery or until discharge from the recovery ward (whichever came first). Secondary outcome measures were short-term glucose control, defined as fasting glucose before surgery and the highest perioperative peak glucose value, long-term glucose control, as measured by the HbA1c value before and after surgery, and the incidence of mild (any glucose value <4.0 mmol l^{-1}) or severe (≤2.5 mmol l^{-1}) hypoglycaemia during and after surgery. These cut-offs were chosen in accordance with the perioperative glucose regulation protocol in our centre. As a marker of glucose variability, the mean average glucose (MAG) change[9] was calculated from start of surgery until discharge from the recovery ward. The MAG is calculated by summation of the absolute differences between consecutive measurements, divided by the time between the first and the last measurement. MAG change was chosen because it is the measure of glucose variability with the strongest relation to complications.[10]

Statistical analysis

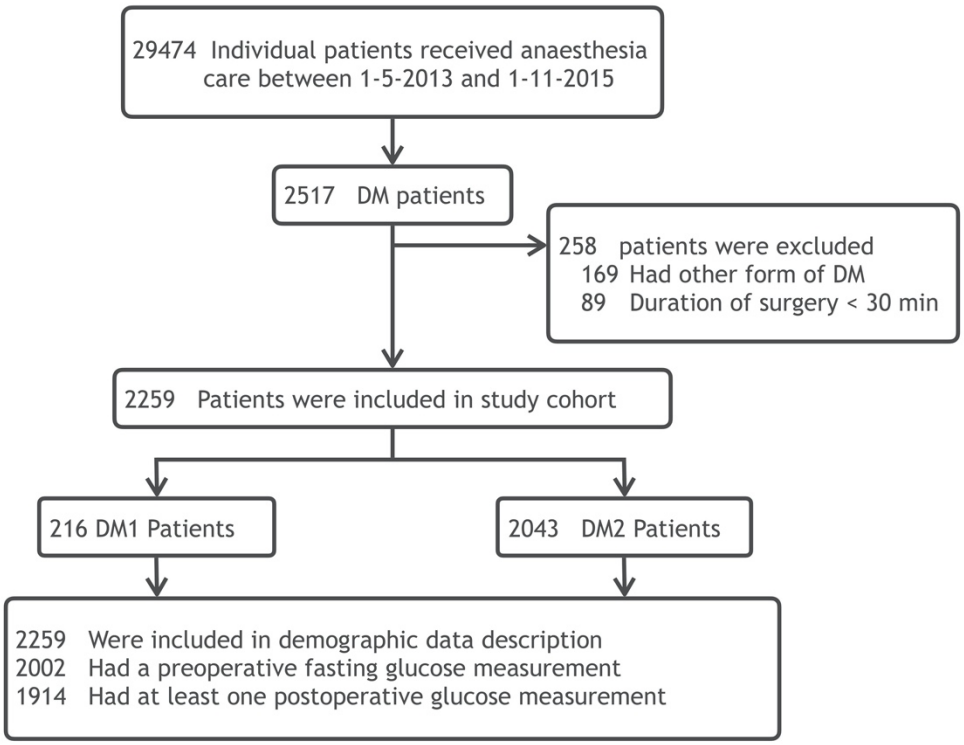
Continuous data are presented as mean (±SD) or median (IQR), and were compared using Student's *t*-test or the Mann-Whitney rank-sum test, when appropriate. We plotted all data to assess the normality of distribution and used Levene's test to assess the equality of variances. Categorical data are presented as percentages and were compared using the χ^2 test.

We assessed the association between perioperative hyperglycaemia and type of DM, pre-operative glucose concentration, duration of surgery and dexamethasone administration with univariate logistic regression. These are reported as unadjusted odds ratios (with 95% CI) for perioperative hyperglycaemia. These factors were chosen due to their clinical relevance and before analysis of our data. All significant predictors were to be entered in a multivariate logistic regression analysis to calculate adjusted odds ratios (with 95% CI) for perioperative hyperglycaemia, but only if a ratio of 10:1 cases with any one outcome per predictor was maintained. Based on clinical relevance we also adjusted for age, sex and BMI. All statistical analyses were performed in SPSS version 24 (SPSS Inc., Chicago, IL, USA).

Results

During the study period, we identified 29,474 unique patients with an anaesthesia health record, of which 2,517 patients had diabetes. After exclusion of patients with another form of diabetes than type 1 or 2, and duration of surgery <30 minutes, we included 2,259 patients in the final analyses (Flow-chart, Figure 1). Of these, 216 (10%) had DM1 and 2,043 (90%) had DM2. Thus, calculated incidences in our population were 7/1,000 DM1 patients and 69/1,000 DM2 patients, respectively.

Figure 1. Flow Diagram of study population.



DM1: diabetes mellitus type 1, DM2: diabetes mellitus type 2.

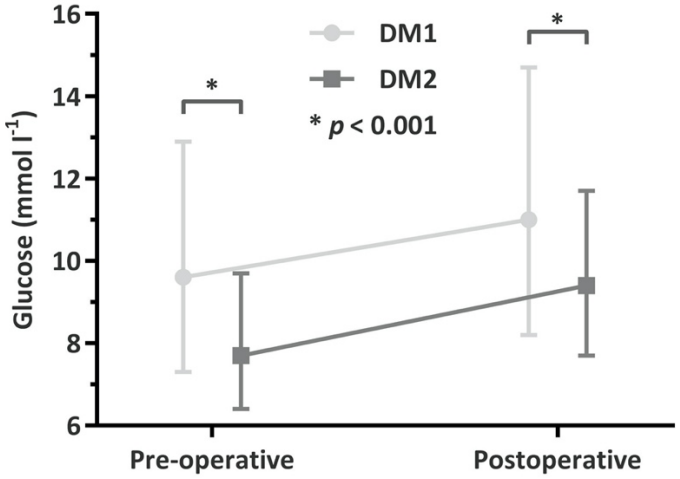
Table 1 lists the characteristics of the whole study population and of the groups with DM1 or DM2. There were considerable differences in age, weight, BMI, components of medical history, type of surgery and duration of the procedure.

Table 1. Patient characteristics.

	N	All	Type 1 DM	Type 2 DM	*p* value
		(n=2259)	(n=216)	(n=2043)	
Sex (female)	2259	999 44.2%	108 50.0%	891 43.6%	0.072~
Age (y)	2259	65 ± 12.7	54 ± 16.4	66 ± 11.7	< 0.001*
Weight (kg)	2178	84 ± 18.2	78 ± 16.9	85 ± 18.3	< 0.001*
Height (cm)	2117	171 ± 10.1	171 ± 11.2	171 ± 10.0	0.78*
BMI (kg m^{-2})	2108	29 ± 5.9	27 ± 5.6	29 ± 5.9	< 0.001*
ASA II	2231	1186 53.2%	127 58.8%	1059 51.8%	< 0.001~
ASA III	2231	1006 45.1%	74 34.3%	932 45.6%	< 0.001~
Alcohol abuse	2259	554 24.5%	171 79.2%	509 24.9%	0.19~
Smoking	2259	453 20.1%	45 20.8%	402 19.7%	0.17~
GFR (mL/min/1.73 m2)	1664	77.6 ± 59.9	96.8 ± 179.8	75.9 ± 32.5	0.18*
METs	2259	6	7	6	0.97^
		4 - 7	3 - 7	4 - 7	
Case Duration (min)	2259	140	113	143	0.001^
		81 - 247	69 - 201	84 - 250	
Recovery duration (min)	1640	211	196	213	0.48^
		136 - 383	135 - 330	136 - 391	
ANAESTHESIA	2259				0.68~
General		1847 82%	183 85%	1664 81%	
Regional		56 2%	5 2%	51 2%	
Gen + Reg		159 7%	13 6%	146 7%	
SURGERY	2259				< 0.001~
General		539 24%	55 25%	484 24%	
Cardiac		313 14%	13 6%	300 15%	
Ophthalmic		216 10%	31 14%	185 9%	
Other		1191 53%	117 54%	1074 53%	
Received Dexamethasone	2259	582 25.8%	53 24.5%	529 25.9%	0.67~

BMI: Body Mass Index, METs: Metabolic Equivalent of Task, GFR: Glomerular Filtration Rate. MDRD: Modification of Diet in Renal Disease formula ASA: American Society of Anesthesiologists physical status classification. Statistical tests DM1 vs. DM2; * unpaired Student´s t-test ^ Mann-Whitney U test, ~Chi square test.

Figure 2. Median (fasting) glucose concentrations and IQR before and after surgery — but before discharge from recovery ward.

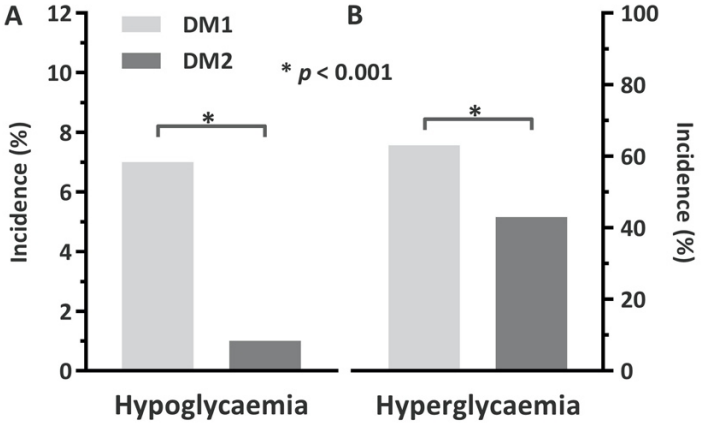


DM1: diabetes mellitus type 1, DM2: diabetes mellitus type 2.

Of all 2,259 patients, 2,002 (89%) had a pre-operative glucose measurement and 1,914 (85%) had their glucose measured at least once in the perioperative period. The mean number of glucose measurements per case was 3.4 (±2.5). The median glucose in the whole cohort was 7.8 (6.5 – 9.8) pre-operatively and increased to 9.5 (7.7 – 11.9) after surgery. The mean increase was 1.55 mmol l^{-1} (±3.3), 95% CI: 1.40 – 1.71, p < 0.001, which was similar in the DM1 and DM2 cohort (1.1 (±3.9) vs. 1.6 (±3.2), p = 0.15), Figure 2.

Glucose values before, during and after surgery were significantly higher in the DM1 cohort for all time periods. Table 2 displays the differences in glucose values, HbA1c, and the incidence of hypoglycaemia and hyperglycaemia for the entire cohort as well as the DM1 and DM2 patients separately. Our main outcome, the median peak glucose after surgery was significantly higher in DM1 patients than DM2 (11 [8.5 – 14.7] vs. 9.4 [7.7 – 11.7], difference [95% CI] = 1.6 [0.99 – 2.21], p < 0.001). Median pre-operative HbA1c was also higher in DM1 patients compared to DM2; 66 (55 – 76) vs. 54 (47 – 64) mmol mol^{-1}, difference 12 mmol mol^{-1}, 95% CI: 7 – 17, p < 0.001. Hypoglycaemia (glucose < 4 mmol l^{-1}) occurred in 35 patients (1.5%), and more often in the DM1 group (13, 7.1%) than in the DM2 group (22, 1.3%), p < 0.001, Figure 3. A severe hypoglycaemic event with a glucose measurement ≤2.5 mmol l^{-1} occurred in 7 patients (0.4%), also predominantly in DM1 patients (4 (2.1%) vs. 3 DM2 patients (0.2%) in DM2).

Figure 3. Glucose control during or after surgery, until discharge from the recovery ward.
A Incidence of any hypoglycaemic event (glucose < 4 mmol l^{-1})
B Incidence of any hyperglycaemic event (glucose ≥10 mmol l^{-1})



DM1: diabetes mellitus type 1, DM2: diabetes mellitus type 2.

Table 2. Perioperative glucose values, incidence of hypo- and hyperglycaemia, and HbA1c values.										
		All			Type 1 DM			Type 2 DM		*p* value
Pre-operative	**N**	**2259**		**N**	**216**		**N**	**2043**		
HbA1c (mmol mol^{-1})	822	55 (47 - 66)		87	66 (55 - 76)		735	54 (47 - 64)		< 0.001*
Glucose (mmol l^{-1})	2002	7.8 (6.5 - 9.8)		166	9.6 (7.3 - 12.9)		1836	7.7 (6.4 - 9.7)		< 0.001*
Perioperative										
Peak glucose (mmol l^{-1})	1914	9.5 (7.8 - 11.9)		183	11.0 (8.2 - 14.7)		1731	9.4 (7.7 - 11.7)		< 0.001*
Hyperglycaemia (≥10 mmol l^{-1})	1914	862	45%	183	116	63%	1731	746	43%	< 0.001^
Mild hypoglycaemia (<4 mmol l^{-1})	1914	35	2%	183	13	7%	1731	22	1%	0.002^
Severe hypoglycaemia (<2.3 mmol l^{-1})	1914	7	0%	183	4	2%	1731	3	0%	< 0.001~
Postoperative										
HbA1c (mmol mol^{-1})	248	54 (45 - 64)		34	60 (50 - 69)		214	53 (44 - 63)		0.042*

All values are medians with (IQR) or numbers with (%). *Mann-Whitney U test, ^Chi-square test, ~Fisher's Exact test

Glucose variability, calculated as the MAG, was significantly higher in the DM1 group, median (IQR) 0.92 mmol l^{-1} h^{-1} (0.43 – 1.66) compared to 0.53 mmol l^{-1} h^{-1} (0.27 – 0.86) in the DM2 group (p < 0.001).

The results of univariate logistic regression for our proposed predictors of hyperglycaemia is presented in Table 3. Total daily dose of insulin was not a significant predictor of hyperglycaemia. DM1, higher pre-operative HbA1c, higher pre-operative glucose, intraoperative dexamethasone and longer duration of surgery all had increased odds ratios for perioperative hyperglycaemia.

Table 3. Univariate analysis of odds ratios for perioperative hyperglycaemia (glucose ≥10 mmol l^{-1})			
	Odds Ratio	**95% CI**	***p* value**
Diabetes mellitus type 1	2.29	1.67 - 3.13	<0.001
Total daily dose of insulin (IE)	1.00	0.99 - 1.00	0.989
Pre-operative HbA1c (mmol mol^{-1})	1.04	1.03 - 1.05	<0.001
Pre-operative glucose (mmol l^{-1})	1.42	1.36 - 1.48	<0.001
Received dexamethasone	2.02	1.64 - 2.48	<0.001
Duration of surgery (h)	1.20	1.15 - 1.25	<0.001

Total daily dose of insulin was not entered in our multivariate regression because it was not a significant univariate predictor. Because of missing values (64%), pre-operative HbA1c was also not entered. The results of our multivariate logistic regression analysis are presented in Table 4. After adjusting for age, sex, BMI, and the following factors; DM1, a higher fasting glucose pre-operatively, a longer duration of surgery, and receiving dexamethasone carried independently higher odds ratios of hyperglycaemia at any time in the perioperative period.

Table 4. Multivariate analysis of odds ratios for perioperative hyperglycaemia (glucose ≥10 mmol l^{-1})			
	Adjusted Odds Ratio*	**95% CI**	***p* value**
Diabetes mellitus type 1	1.89	1.20 - 3.00	0.006
Pre-operative glucose (mmol l^{-1})	1.46	1.39 - 1.54	<0.001

Received dexamethasone	2.69	2.08	-	3.48	<0.001
Duration of surgery (h)	1.28	1.21	-	1.35	<0.001

*Adjusted for age, sex, BMI, DM type, pre-operative glucose, duration of surgery, dexamethasone administration.
Model statistics: selected cases: 1658 (73% of all 2259 cases) Chi-square: 489, degrees of freedom: 7, *p* value: <0.001, Cox & Snell R^2: 0.26, Nagelkerke R^2: 0.34

Discussion

In this retrospective cross-sectional study, we found that using the same clinical protocol for glucose treatment, DM1 patients have poorer short-term and long-term perioperative glucose control as compared to patients with DM2. This includes a higher incidence of hyperglycaemia and hypoglycaemia, as well as increased glucose variability and higher HbA1c values. The prevalence of diabetes in this study is higher than previously reported for the Netherlands in the general population.[11] This might be explained by a higher proportion of elderly people in our population, sicker patients in our tertiary care centre, and because patients with DM are more likely to undergo surgery.[12] The prevalence of DM1 is estimated to represent between 5-10% of all DM patients, which is in line with our findings.[13,14]

The perioperative glucose control in our study is comparable to other studies. A recently published prospective analysis of DM2 patients undergoing major surgery in six Dutch hospitals[15] reported a comparable pre-operative and postoperative mean value of 8.2 mmol l^{-1} and 9.1 mmol l^{-1}, respectively, compared to 7.8 and 9.5 in our study. The incidence of hyperglycaemia (defined as glucose >10 mmol l^{-1}) in their population was 33% (45% in our study). A retrospective analysis of 18,278 patients undergoing gastrointestinal surgery in the United States also showed an incidence of hyperglycaemia (defined as glucose >10 mmol l^{-1}) of 29%.[16] The long-term glucose control (i.e. HbA1c) of DM1 patients in our cohort is in line with international reports as well.[17] The HbA1c values of the DM2 patients are in line with those reported in the "RABBIT 2 surgery" trial.[18]

While current guidelines[6,7] recommend targeting glucose values <10 mmol l^{-1}, a recent meta-analysis of 15 randomised controlled trials showed a benefit regarding the incidence of surgical site infections by even stricter glucose control (<8.3 mmol l^{-1}).[5] In addition, the previously mentioned RABBIT-2 trial showed that lowering mean postoperative glucose from 9.7 to 8.7 mmol/l using a basal-bolus regimen for DM2 patients reduced the number of postoperative complications.[18] With over 60% of DM1 patients having at least one glucose value above 10 mmol l^{-1} in our study, these patients deserve more attention with respect to their glucose control.

In our cohort, DM1 patients not only had more hyperglycaemic events and higher mean glucose values in the perioperative period, they also had a higher incidence of hypoglycaemia perioperatively. Hypoglycaemia is associated with worse outcomes, such as cardiovascular events as well as all cause and ICU mortality.[19,20] Although the causal relation is not evident,[19] we feel this still deserves attention since patients in the perioperative period are more vulnerable to hypoglycaemia due to the masking of hypoglycaemic symptoms by anaesthetics. Case reports show that during anaesthesia the only symptom of severe hypoglycaemia may be diaphoresis, while vital signs remain normal.[21,22]

Of note, while DM1 patients had a lower proportion of ASA III scores and a shorter duration of surgery, they still had an increased risk of hyperglycaemia as compared to DM2. Next to having DM1, higher pre-operative glucose was also a significant independent predictor of postoperative hyperglycaemia. It seems that patients presenting with worse glucose control before surgery have a higher risk of postoperative hyperglycaemia, i.e. "worse in, worse out", which increases the risk of complications.[5,23] The same is true for the longer term: patients with DM1 have higher HbA1c values, both before and after surgery.

Limitations

Limitations of this study include the single centre nature and retrospective design. Although all data were generated for a clinical purpose, they were collected in a prospective database with the intent of research. While it is a single centre study our results are in line with findings in other centres, as described above. Another inherent limitation of database research is the validity of the data. However, both the presence of DM and the distinction between types of DM had to be consciously made during the pre-operative consultation and was conditional to complete pre-assessment. In addition, the proportion of patients with DM1 and DM2 was in line with other international reports. A final concern

was missing data, e.g. HbA1c was unknown for 64% of cases. Although this was a significant predictor for perioperative hyperglycaemia we could not enter this in our multivariate regression analysis.

Conclusion

Also in the perioperative period, DM1 and DM2 are evidently distinct diseases. DM1 patients have poorer short-term and long-term glycaemic control in the perioperative period and thus have an increased risk of both hypoglycaemia and hyperglycaemia. This warrants investigation of diabetes-type-specific protocols for perioperative glucose treatment and postoperative follow-up. The presence of patients with DM1 in the operating theatre deserves more attention by both clinicians and researchers.

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Three

Perioperative continuation of metformin does not improve glycemic control in patients with type 2 diabetes; a randomized controlled trial

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Diabetes, Obesity and Metabolism 2017; 20 (3): 749-752

Abstract

Objective

Historically, metformin was withheld before surgery in patients with type 2 diabetes mellitus in fear of metformin associated lactic acidosis (MALA). Risk of MALA is low and guidelines are moving towards continuation of metformin. However, there are sparse data on the effects of continuation of metformin on perioperative glucose control. Our goal was to investigate the effect of perioperative continuation versus withholding metformin on glycemic control, plasma lactate levels and postoperative outcomes.

Research Design and Methods

We performed a single-blind multicenter RCT in type 2 diabetes mellitus patients scheduled for elective non-cardiac surgery, allocating patients to a continuation of metformin (MF+) or withholding metformin (MF–) group. Patients in the MF+ group used their usual dose of metformin on the morning of surgery. Patients in the MF– group stopped taking metformin the day before surgery. Main outcome parameters were the differences in perioperative plasma glucose and lactate levels.

Results

We randomized 70 patients (37 MF+ group and 33 MF– group) with type 2 diabetes mellitus. Pre- and postoperative glucose levels were similar between groups (postoperative plasma glucose 148 mg dl^{-1} in both groups, p=0.95). Although preoperative lactate levels were slightly higher in the MF+ group compared to the MF– group (1.5 vs. 1.2 mmol l^{-1}, p=0.02), the postoperative lactate levels were not significantly different (1.2 vs. 1.0 mmol l^{-1}, p=0.18).

Conclusions

Continuation of metformin during elective non-cardiac surgery does not improve glucose control or raise lactate levels to a clinically relevant degree.

Introduction

Metformin is the first line oral glucose lowering agent for patients with type 2 diabetes mellitus and it has been shown to lower diabetes related morbidity and mortality.[1] Metformin associated lactic acidosis (MALA) is a very rare, albeit severe, adverse reaction caused by hepatic gluconeogenesis and inhibition of mitochondrial respiration.[2] The clinical relevance of MALA remains a matter of debate. A Cochrane review of 347 studies showed no increased risk of lactic acidosis in patients treated with metformin.[3] While many guidelines, including our national Dutch guideline, still recommend withholding metformin preoperatively,[4-6] guidelines from the UK and Australia are moving towards continuing metformin, at least for patients without chronic renal failure undergoing minor surgery.[7,8] However, there are no data on the possible benefit on glycemic control after perioperative continuation of metformin. Potentially, perioperative hyperglycemia could be prevented by both lowering preoperative blood glucose concentrations as well as reducing the impact of stress hyperglycemia by metformin. This is relevant since lowering postoperative blood glucose concentrations in patients with type 2 diabetes decreased postoperative complications in the general surgical population.[9] To test the hypothesis that continuing metformin perioperatively would lower pre- and postoperative glucose concentrations without causing a significant increase in plasma lactate, we randomized patients with type 2 diabetes to either continuation or withholding their metformin in the 24 hours before surgery.

Research Design and Methods

This report is written in accordance with the revised recommendations of the CONSORT group for reporting randomized trials.[10]

Study design

This was a randomized two center, single blind parallel, clinical trial, with a 1:1 randomization, conducted in the Netherlands. The study was approved by the regional research ethics committee of the Academic Medical Centre Amsterdam (ref: NL51964.018.15) and was registered in the Nederlands Trial Register before start of enrolment (ref: NTR5254). The study was conducted in accordance with the most recent version of the Declaration of Helsinki and good clinical practice guidelines.

Participants and setting

We screened patients scheduled for elective non-cardiac surgery at the Academic Medical Center (AMC) and the Medical Center (MC) Slotervaart in Amsterdam (a tertiary and secondary teaching hospital, respectively) between July 2015 and March 2016. Inclusion criteria were age between 18 and 80 years, planned for non-cardiac surgery, and a history of type 2 diabetes and daily metformin use for at least three months. Exclusion criteria were insulin use, day case surgery, expected surgery duration < 45 minutes, perioperative corticosteroid treatment, planned postoperative intensive care stay, and based on history; renal failure, severe liver disease, alcohol abuse, pregnancy or breast-feeding. Eligible subjects were contacted at least 24 hours before their preoperative consultation at the anesthesia department. Written informed consent was obtained before inclusion.

Randomization and intervention

Patients were randomized 24-72 hours before surgery by an independent researcher. Randomization was performed using sequentially numbered, sealed, opaque envelopes and block randomization. Block sizes varied between two and ten and were generated by a random even number generator. Randomization was stratified for low (≤1000 mg) or high (>1000 mg) total daily metformin dose. The independent researcher contacted the patients to provide instructions regarding their treatment group. The randomization list remained inaccessible to the researchers who were responsible for data collection and analyses until completion of the trial. Patients were either randomized to continuation of metformin (MF+) or withholding metformin (MF–) perioperatively. Patients in the MF– group were instructed to withhold their metformin dose 24 hours before surgery. In the MF+ group, patients were instructed to continue their usual dose of metformin, including on the morning of surgery.

Measurements and anesthetic management

Type of anesthesia and medication used was left to the discretion of the anesthesiologist except for perioperative corticosteroid treatment, which was avoided. Fasting plasma glucose and lactate were measured on the day of surgery, two hours after the end of surgery and on the first postoperative day, by blood gas analysis (ABL90 FLEX analyzer, Radiometer, Brønshøj, Denmark). Hyperglycemia was corrected using a sliding scale insulin algorithm, see table S1 in the supplementary online-only material. After 30 days, all patients were interviewed by telephone call and medical charts were reviewed to assess postoperative complications and length of hospital stay.

Outcome measures

The primary outcome was the between-group difference in mean glucose concentration two hours postoperatively. This measure was chosen because glucose concentration reaches its maximum around two hours after surgery while decreasing in consecutive days.(11,12)
Secondary outcomes were the difference in fasting glucose before and at day 1 after surgery, lactate levels before, two hours and one day after surgery, amount of insulin administered during surgery,

occurrence of mild (<72 mg dl^{-1}) and severe hypoglycemia (<41 mg dl^{-1}), length of hospital stay and number of complications within 30 days after surgery.

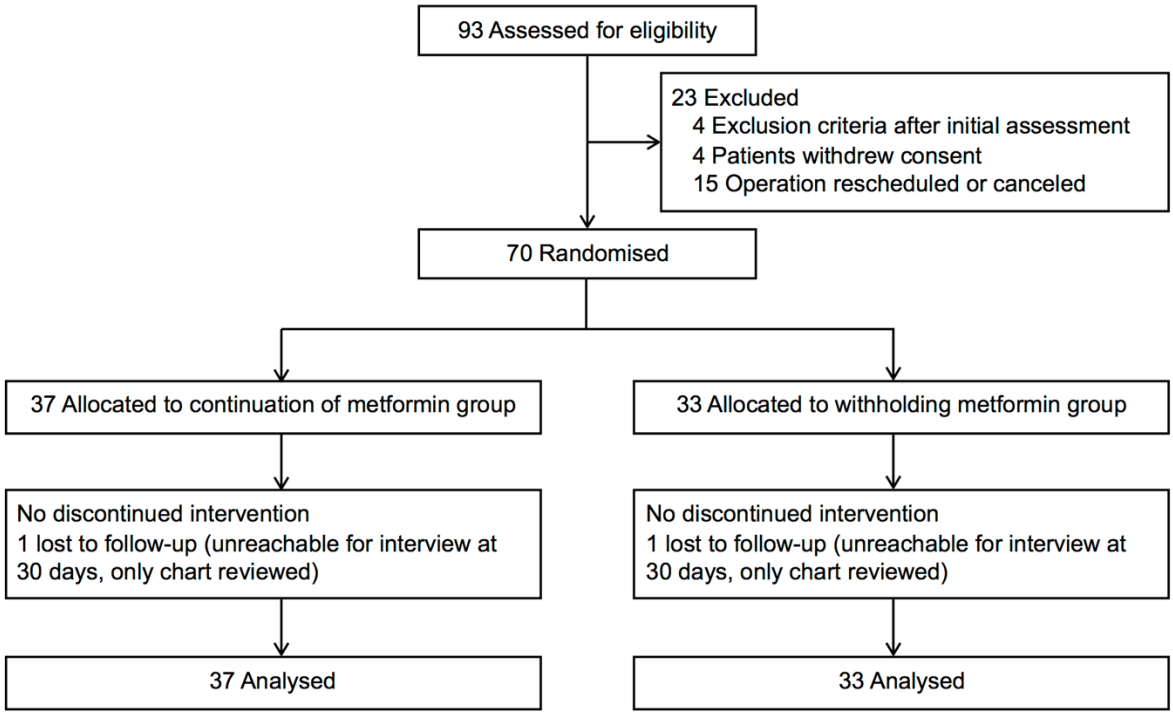
Sample size and statistical analysis

With a reported postoperative glucose of 180 mg dl^{-1} and a standard deviation of 40 mg dl^{-1},(9) a minimum group size of 34 was needed to be able to detect a difference in blood glucose concentration of 27 mg dl^{-1} with a power of 80% and a significance level of 5%. Dropouts were to be replaced. Analyses were based on the intention-to-treat principle, using SPSS (IBM SPSS Statistics 23, Armonk, NY, USA). Between group differences in plasma glucose, lactate and length of hospital stay were compared using a student *t*-test or Mann-Whitney U test, respectively, depending on the distribution of data. Equality of variance was tested using Levene's test. Normality was assessed by comparison of histogram with normal distribution plots and tested using the Shapiro-Wilk test. Differences in postoperative complications within 30 days after surgery were assessed using a χ^2 test.

Results

From July 2015 to March 2016, 93 patients were assessed for eligibility. Of them, 23 were excluded before randomization: four withdrew their consent; four did not meet inclusion criteria at full assessment; and 15 had their operation rescheduled without awareness of researchers responsible for randomization. Of the remaining 70 subjects, 37 patients were randomly allocated to the metformin MF+ group and 33 patients to the MF– group, Figure 1.

Figure 1. Flow Diagram of study population.



All patients reported compliance with the intervention. Seven patients received dexamethasone intraoperatively despite the study protocol: four patients (10.8%) in the MF+ group, three patients (9.1%) in the MF– group. These patients were included in the intention-to-treat analysis. One patient in each group could not be contacted by telephone call for assessment of postoperative complications after 30 days and therefore only a chart review could be performed in these cases.
Baseline characteristics are displayed in Table 1 and were comparable between groups, including type 2 diabetes duration and HbA1c level before surgery. Most of the participating patients were enrolled in the MC Slotervaart (87.1%), and nearly half of the patients had laparoscopic gastric bypass surgery (45.7%).

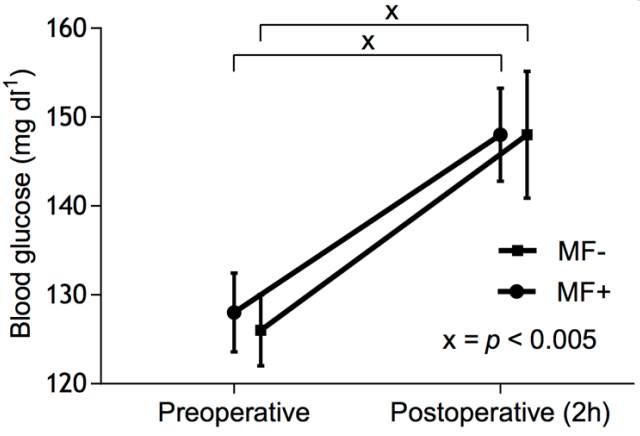
Table 1. Baseline characteristics of the patients.

	MF+, N=37	MF-, N=33
Age (years)	59 (11)	59 (11)
Female sex	19 (51%)	20 (60%)
Caucasian	35 (95%)	29 (88%)
Other	2 (5%)	4 (12%)
BMI (kg m^{-2})	33.5 (7.4)	33.8 (6.8)
Surgery duration (min)	64 (36)	67 (42)
History of type 2 diabetes (years)	7.3 (5.4)	4.9 (3.6)
Metformin dose (mg)	1464 (786)	1325 (752)
Other anti-hyperglycemic agents	11 (30%)	10 (30%)
Sulfonylurea	11 (30%)	10 (30%)
GLP-1-R agonist	3 (8%)	1 (3%)
HbA1c (%)	6.6 (0.8)	6.3 (0.9)
HbA1c (mmol mol^{-1})	49 (9)	45 (10)
ASA II	20 (54%)	21 (64%)
ASA III	17 (46%)	12 (36%)
MC Slotervaart	33 (89%)	28 (85%)
AMC	4 (11%)	5 (15%)
Anesthesia		
General	32 (87%)	31 (94%)
Spinal	5 (13%)	2 (6%)

MF+ = continuation of metformin MF– = withholding metformin. Data are presented as number (%) or mean (SD). GLP-1-R = Glucagon like peptide 1 receptor. ASA = American Society of Anesthesiologists physical status classification system.

The outcome measures are given in Table 2. There was no difference in mean (±SD) postoperative blood glucose levels two hours after surgery, (148 ± 32 (MF+) vs. 148 ± 41 mg dl^{-1} (MF–), p=0.95 [difference, 95% CI 0.0 (-1.0 – 0.9 mg dl^{-1}]). Glucose increased significantly in both groups during surgery; MF+ group (mean before surgery 128 ± 27 mg dl^{-1} vs. 148 ± 3.2 mg dl^{-1} after surgery, p=0.004), MF– group (126 ± 23 vs. 148 ± 41 mg dl^{-1}, p=0.002), Figure 1. Only 8 patients received insulin in the study period for a glucose concentration >180 mg dl^{-1} (4 patients in either group), median total insulin dose was zero units in both groups (range between 0 and 16 IU).

Figure 2. Glucose concentrations before and after surgery



MF+ = continuation of metformin MF– = withholding metformin.

The preoperative median lactate levels were significantly higher in the MF+ group than the MF– group (1.5 (1.2 – 1.8) vs. 1.2 (1.0 – 1.5) mmol l^{-1}, p= 0.02). After surgery, the difference between groups was not significant (1.2 (0.9 – 1.6) vs. 1.0 (0.8 – 1.4) mmol l^{-1}, p= 0.18). The highest measured lactate after surgery was 3.7 mmol l^{-1} which occurred in the MF– group, the maximum in the MF+ group was 2.3 mmol l^{-1}. Only one patient (MF+ group) suffered a mild hypoglycemia (blood glucose of 68 mg dl^{-1}) 30 minutes before surgery and was treated with 250 mg glucose intravenously. Finally, there was no between group difference with regard to length of hospital stay or postoperative complications. The number of complications are listed in Table 2, a detailed list is accessible in Table S2 in the supplementary online-only material.

Table 2. Postoperative glucose, lactate, hospital stay and complications.

	MF+, N=37	MF-, N=33	Difference & 95% CI	*p*-value
Blood glucose (mg dl^{-1})				
Preoperative	128 (27)	126 (23)	3.6 (-9 – 16)	0.60*
Postoperative, 2 hours	148 (32)	148 (41)	0.0 (-18 – 16)	
Postoperative, 1 day	135 (29)	135 (25)	0.0 (-14 – 14)	0.95*
				0.96*
Hypoglycemia (glucose < 72 mg dl^{-1})	1 (3%)	0 (0%)	2% (-2.5% – 8%)	0.34†
Hyperglycemia (glucose > 180 mg dl^{-1})	9 (24%)	9 (27%)	-3% (-23% – 18%)	0.78‡
Lactate (mmol l^{-1})				
Preoperative	1.5 (1.2–1.8)	1.2 (1.0–1.5)	-0.3 (-0.6 – 0.0)	0.02§
Postoperative, 2 hours	1.2 (0.9–1.6)	1.0 (0.8–1.4)	-0.2 (-0.5 – 0.1)	0.18§
Hospital stay (days)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.0 (-0.5 – 0.5)	0.83§
Postoperative complications	4 (11%)	3 (9%)	2% (-12% – 16%)	0.81‡

MF+ = continuation of metformin MF– = withholding metformin. Data are presented as number (%), mean (SD) or median (IQR). *p*-values are from * = student *t*-test, † = Fisher's Exact test, ‡ = χ^2 test, § = Mann-Whitney U test.

A per protocol analysis excluding all cases where the patient received glucocorticoids (7 cases) or/and the operating time was less than 45 minutes (21 cases) yielded similar results for all outcomes.

Discussion

This is the first prospective RCT comparing the effect of perioperative continuation versus withholding metformin on glycemic control and plasma lactate in surgical patients with type 2 diabetes. We observed that continuing metformin had no effect on perioperative glycemic control. In addition, the hyperglycemic response to the stress of surgery was comparable in both groups. Only a clinically non-relevant increase in plasma lactate was observed. This study was not powered to find a difference in length of hospital or incidence of postoperative complications, which were secondary outcomes.

Only few studies have been performed reporting on the initiation of metformin in the perioperative period.[13,14] El Messaoudi and coworkers started metformin in patients without type 2 diabetes before cardiac surgery.[13] Postoperative glucose levels were not reported in this study, but there was no occurrence of lactic acidosis in either treatment group perioperatively. Baradari and colleagues demonstrated that postoperative administration of metformin reduced blood glucose concentration after cardiac surgery in type 2 diabetes patients and reduced insulin need, without occurrence of lactic acidosis.[14]

In our study, preoperative median lactate levels were mildly but significantly raised in the MF+ group (from 1.2 to 1.5 mmol l^{-1}). During surgery, lactate decreased in the MF+ group and there was no significant difference of lactate levels between groups after surgery. Moreover, these differences can be regarded as clinically irrelevant (0.3 mmol l^{-1} before surgery and 0.2 mmol l^{-1} after surgery) and no extremes in lactate levels were measured (maximum 3.7 mmol l^{-1} in the MF– group). This is in accordance with the abovementioned studies[13,14] and the Cochrane analysis(3) that found no increased risk of lactic acidosis in type 2 diabetes patients treated with metformin.[3]

This study has several limitations. First, we studied a relatively healthy patient population, with few major surgeries, which might have contributed to the lack of effect of our intervention. However, our in- and exclusion criteria were based on the literature and manufacturer's instructions. Mean (±SD) operation time was 66 (±39) minutes, despite these short operating times, we did observe a significant increase in glucose concentrations from pre- to postoperatively in the vast majority of patients. However, we cannot extrapolate our findings to scenarios of increased lactate production or decreased metabolism, such as hypovolemic shock, low flow states, longer duration of surgery, hepatic and renal failure, anemia, and cardiac failure.

Another exclusion criterion was glucocorticoid treatment perioperatively. However, seven patients received dexamethasone for postoperative nausea and vomiting prophylaxis. Nonetheless, a per protocol analysis yielded similar results for all outcomes.

We found a between group difference in postoperative glucose of 0 mg dl^{-1} with a 95% CI of -18 – 16 mg dl^{-1} in this study. Therefore, subsequent confirmatory studies with larger sample size could potentially find glucose differences up to 18 mg dl^{-1}, the clinical relevance of which can be discussed.

As stated before, guidelines on perioperative management of type 2 diabetes patients are moving towards continuing metformin.[7,8] This may prevent medication errors when restarting metformin postoperatively.[15] If, however, other medication is discontinued during surgery as well, this potential advantage might be limited. Moreover, the theoretically expected beneficial effect on glycemic control could not be confirmed in the present study. And although very rare, MALA is a potentially fatal complication with a mortality of 50%.[16]

In conclusion, this is the first study on continuation of metformin during elective non-cardiac surgery and it shows no improvement in glucose control after continuation of metformin. An associated small, but significant increase in plasma lactate when continuing metformin is not deemed clinically relevant. As such, the decision to continue or withhold metformin during surgery should not be based on its glucose lowering potential in the perioperative period.

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Part II

Glucagon-Like Peptide-1 in the perioperative period

Four

Systematic review of incretin therapy during peri-operative and intensive care

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Critical Care 2018; 22 (1): 1-12

Abstract

Background

Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are incretin hormones. By lowering blood glucose in a glucose-dependent manner, incretin-based therapies represent a novel and promising intervention to treat hyperglycaemia in hospital settings. We performed a systematic review of the literature for all current applications of incretin-based therapies in the peri-operative and critical care setting.

Methods

We searched MEDLINE, the Cochrane Library, and EMBASE databases for all randomised controlled trials using exogenous glucagon-like peptide 1 (GLP-1), GLP-1 receptor agonists, exogenous glucose-dependent insulinotropic polypeptide (GIP), and dipeptidyl peptidase–IV inhibitors in the setting of adult peri-operative care or intensive care. We defined no comparator treatment. Outcomes of interest included blood glucose, frequency of hypoglycaemia and insulin administration.

Results

Of the 1190 articles identified during the initial literature search, 38 fulfilled criteria for full text review and 19 single-centre studies were subsequently included in the qualitative review. Of the 18 studies reporting glycaemic control, improvement was reported in 15, defined as lower glucose concentrations in 12 and as reduced insulin administration (with similar glucose concentrations) in 3 studies. Due to heterogeneity, meta-analysis was only possible for the outcome of hypoglycaemia. This revealed an incidence of 7.4% in those receiving incretin-based therapies and 6.8% in comparator groups ($p = 0.94$).

Conclusions

In small single-centre studies, incretin-based therapies lowered blood glucose, and reduced insulin administration without increasing the incidence of hypoglycaemia.

Registration:

PROSPERO: CRD42017071926

Introduction

Hyperglycaemia occurs frequently in the peri-operative period and during critical illness even in patients without a history of diabetes mellitus. [1–3] Usual management of hyperglycaemia in these settings primarily involves intravenous infusions of insulin with the dose titrated according to intermittent measurement of blood glucose.[4] This strategy is somewhat complicated, labour intensive and increases the risk of hypoglycaemia and glycaemic variability, which are both associated with adverse outcome.[3,5–10]

The incretin effect is the physiological phenomenon observed following the ingestion of glucose, which results in endogenous insulin secretion almost two-fold greater than after a comparable intravenous glucose load.[11] This process is attributed to the enterohormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) that have insulinotropic and glucagonostatic properties.[12] The insulinotropic response is glucose-dependent, meaning that even when GLP-1 and GIP are administered in pharmacological doses there is negligible risk of hypoglycaemia.[12]

GLP-1 and GIP are rapidly metabolised by the enzyme di-peptidyl peptidase 4 (DPP-IV).[12] Accordingly, incretin-based therapies necessitate a continuous infusion of either exogenous GLP-1 or GIP, administration of a DPP-IV resistant receptor agonist (GLP-1 receptor agonists, first-in-class drug: exenatide), or a DPP-IV antagonist that increases endogenous GLP-1 and GIP concentrations (first-in-class drug: sitagliptin). [12] All currently available and applicable drugs are named in additional file 1.

GLP-1 receptor agonists and DPP-IV inhibitors are now established therapies for the management of patients with type 2 diabetes (T2DM).[13] The efficacy and safety-profile of incretin-based therapies have fostered enthusiasm to use these agents as adjuncts or alternatives to insulin for glycaemic control in the operating room and intensive care unit (ICU). The purpose of this systematic review was to evaluate the safety and efficacy of incretin therapies for glucose control in the operating room and ICU.

Methods

This systematic review was prospectively registered it in the PROSPERO Database (PROSPERO: CRD42017071926) and conducted according to the PRISMA guidelines.[14]

Eligibility criteria

Studies eligible for inclusion were prospective randomised controlled trials utilising an incretin-based therapy in the operating room and/or the ICU. Studies from any language and without publication date restriction were considered. Paediatric, animal and observational studies were excluded.

Search strategy

We performed an unrestricted electronic database search of MEDLINE, the Cochrane Library and the EMBASE databases from their inception to 13 February, 2018. Our search included terms to specify the intervention (incretin therapy), setting (peri-operative and ICU care) and study type (prospective randomised controlled trials). Searches included synonyms and combinations of the following terms: “operating room”, “OR”, “peri-operative period”, “ICU”, “critical care”, “incretin therapy”, “GLP-1”, “GIP” and “DPP-IV inhibitor” as well as generic names of the currently marketed forms of these medications. Our complete search terms and methodology are available as additional material (see additional file 1) and accessible via PROSPERO. Reference lists of retrieved papers were also reviewed for potentially eligible studies not captured in the primary search. We defined no specific comparator for any intervention.

Study selection

After deletion of duplicate studies, two investigators (AH, MP) screened all titles and abstracts using Rayyan.[15] Relevant studies were then evaluated in full text for eligibility with any conflicts resolved by a third investigator (JH). The authors of conference abstracts and published protocols without subsequent full-texts were contacted to request the data and/or manuscript.

Risk of bias assessment

Two authors independently assessed the quality of the research methodology of all randomised controlled trials using the Cochrane Collaboration’s Risk of Bias Tool.[16]

Data extraction

We extracted data including study characteristics (author, publication year, country, design, funding source and sample size), setting (operating room, intensive care unit, post cardiac surgery) patient characteristics (demographics) and intervention and comparator parameters (incretin therapy, route, dose and duration, as well as additional treatments). We did not predefine primary outcomes in this scoping exploratory systematic review; all reported outcomes were recorded and summarised if reported across multiple studies. Due to the expected heterogeneity of interventions, comparators, settings, and outcomes, we did not plan a meta-analysis of outcomes. Due to the frequency with which hypoglycaemia was reported across studies we decided to retrospectively perform a meta-analysis on this outcome. This was not feasible for all other outcomes.

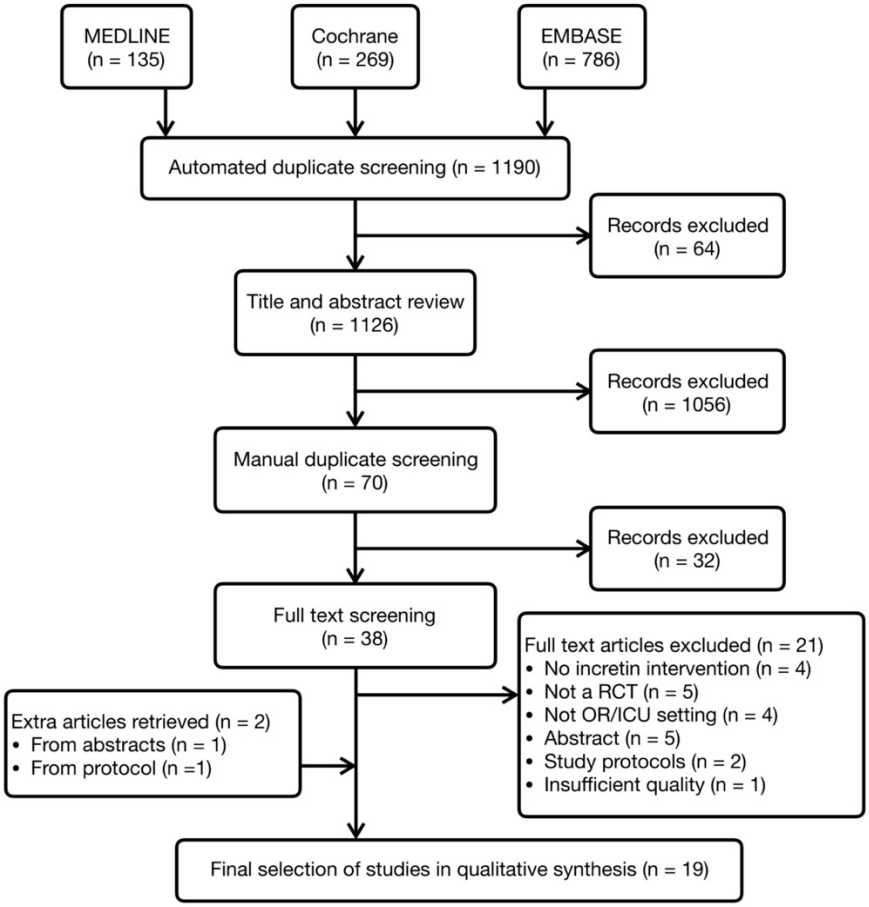
Statistical analysis

For data extraction and meta-analysis, we used Review Manager version 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). We used a random effects model because of expected clinical heterogeneity between trials. Results of the meta-analysis was expressed as Mantel-Haenszel odds ratios, with 95% confidence intervals, because of the dichotomous outcome. As markers for inter-trial heterogeneity we used τ^2, χ^2 and I^2 statistics.

Results

Our search yielded 1126 citations and after elimination of duplicates, abstracts and full texts, 19 studies were included in this systematic review (Figure 1).

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.



ICU Intensive care unit, OR Operating room, RCT Randomised controlled trial Risk.

Study characteristics

Characteristics of the included studies are summarised in Table 1, including setting of care, duration, type and dose of intervention, and reported outcomes.[17-34] In total, 1410 patients participated in these studies, of which 988 were known to have T2DM. All studies recruited patients in a single centre. Comparator groups included placebo or combinations of intravenous or subcutaneous insulin.

Table 1. Study characteristics.

Author, year	Participants, setting, n	DM, %, n	Intervention duration	Intervention, dose, n	Comparator, n	Standard glycaemic therapy	Outcome parameters
Besch 2017[19]	CABG, OR+ICU n = 104	21% n = 22	48 h	Exenatide IV 25 ng/min n = 53	Standard glycaemic therapy n = 51	Continuous insulin IV + bolus regimen	Glycaemia *Insulin administration, complications, LoS*
Brackbill 2012[20]	CABG, ward, n = 62	100% n = 62	4 d	Sitagliptin PO 100mg q.d. n = 30	Placebo n = 32	Basal bolus insulin SC regimen	Glycaemia *LoS*
Deane 2009[21]	Mechanically ventilated, ICU n = 7	0% n = 0	240 min	GLP-1 IV 1.2 pmol/kg/min n = 7	Placebo n = 7	None	Glycaemia *Insulinaemia, Glucagon, GLP-1*
Deane 2010[22]	Mechanically ventilated, ICU n = 25	0% n = 0	360 min	GLP-1 IV 1.2 pmol/kg/min n = 25	Placebo n = 25	None	Glycaemia *Gastric emptying, glucose absorption, Insulinaemia, Glucagon*
Deane 2011[23]	Mechanically ventilated, ICU n = 11	100% n = 11	240 min	GLP-1 IV 1.2 pmol/kg/min n = 11	Placebo n = 11	None	Glycaemia *Insulinaemia, C-peptide, glucagon, FFA*
Galiatsatos 2014[24]	Surgical/Burn, ICU n = 18	50% n = 9	72 h	GLP-1 IV 1.5 pmol/kg/min n = 9	Saline n = 9	Intensive insulin treatment protocol	Glycaemia *Insulin administration, glucagon, C-peptide, CV-medication*
Garg 2017[35]	In hospital, ward (74% surgical) n = 66	100% n = 66	5 d	Saxagliptin PO 5 mg q.d. n = 33	Basal bolus insulin SC regimen n = 33	Corrective insulin bolus regimen	Glycaemia *Insulin administration, Treatment failure, LoS*
Holmberg 2014[25]	CABG, OR n = 62	19% n = 12	390 min	Exenatide IV 43 ng/min n = 21	RIPC n = 20 Placebo n = 21	Unknown	Cardiac enzymes *Complications, LoS*
Kar 2015[26]	Mechanically ventilated, ICU n = 20	0% n = 0	300 min	GIP IV 4 pmol/kg/min n = 20	Placebo n = 20	None	Glycaemia *Gastric emptying, glucose absorption, insulinaemia*
Kohl 2014[27]	CABG, OR n = 77	14% n = 11	72 h	GLP-1 IV 1.5 pmol/kg/min n = 37	Placebo n = 40	Continuous insulin IV + bolus regimen	Glycaemia *Insulinaemia, glucagon, GLP-1, cortisol, FFA.*
Lee 2013[28]	Mechanically ventilated, ICU n = 20	0% n = 0	300 min	GIP IV 4 pmol/kg/min n = 20	Standard glycaemic therapy n = 20	GLP-1 IV 1.2 pmol/kg/min (300 min)	Glycaemia *Insulinaemia, glucagon, GLP-1, GIP,*

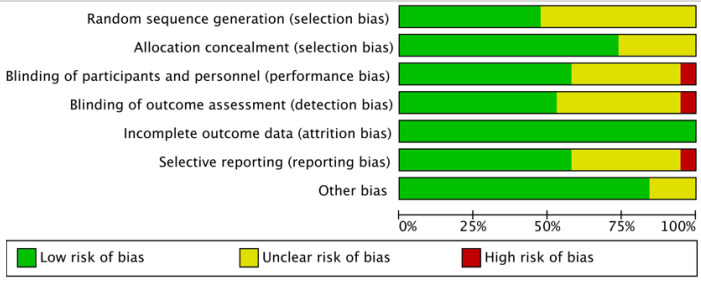
Table 1. Study characteristics.

Author, year	Participants, setting, n	DM, %, n	Intervention duration	Intervention, dose, n	Comparator, n	Standard glycaemic therapy	Outcome parameters
Lips 2017[17]	CABG, OR n = 38 n = 26	68%	72 h	Exenatide IV 20 ng/min n = 19	Placebo n = 19	Intensive insulin treatment protocol	Glycaemia *Echocardiography, CV medications, complications*
Meier 2004[29]	Major surgery, ward n = 8 n = 8	100%	8 h	GLP-1 IV 1.2 pmol/kg/min n = 8	Placebo n = 8	None	Glycaemia *Insulinaemia, C-peptide, glucagon, GLP-1*
Miller 2017[30]	Mechanically ventilated, ICU n = 12 n = 0	0%	270 min	GLP-1 IV 1.2 pmol/kg/min n = 12	Placebo n = 12	None	Glycaemia *Glucose absorption*
Mussig 2008[31]	CABG, ICU n = 20 n = 20	100%	12 h	GLP-1 IV 3.6 pmol/kg/min n = 10	Continuous Insulin IV n = 10	Corrective insulin bolus regimen	Glycaemia *Insulin administration, haemodynamics*
Pasquel 2017[32]	In hospital, ward (16% surgical) n = 277 n = 277	100%	10 d	Sitagliptin PO 100 mg q.d. n = 138	Bolus insulin regimen n = 139	Basal (glargine) insulin regimen	Glycaemia *Insulin administration, complications, treatment failure*
Polderman 2018[18]	Surgical, OR n = 150 n = 150	100%	2 d	Liraglutide SC 0.6 mg + 1.2 mg n = 44	GIK infusion n = 53 Bolus insulin algorithm n = 53	Bolus insulin treatment algorithm	Glycaemia *Insulin administration, Potassium, nausea, complications*
Sokos 2007[34]	CABG, OR n = 20 n = 5	25%	60 h	GLP-1 IV 1.5 pmol/kg/min n = 10	Standard insulin therapy n = 10	Standard insulin therapy	Glycaemia *LVEF, haemodynamics*
Umpierrez 2014[33]	In hospital, ward (45% surgical) n = 90 n = 90	100%	10 d	Sitagliptin PO 100 mg q.d. n = 27 Sitagliptin + basal insulin, n = 29	Basal-bolus insulin regimen n = 26	Correction bolus insulin regimen	Glycaemia *Insulin administration, complications, treatment failure*

b.i.d.= twice a day, CABG= Coronary Artery Bypass Grafting, CV= Cardiovascular, d= days DM= diabetes mellitus, FFA= free fatty acids, GIK= glucose-insulin-potassium infusion, GIP= gastric inhibitory polypeptide, GLP-1= Glucagon-like peptide-1, h= hours ICU= Intensive Care Unit, IV= intravenously, LVEF = left ventricular ejection fraction, LoS= Length of Stay, min= minutes, OR= Operating Room, PO= per os, q.d.= once a day, RIPC= Remote ischaemic preconditioning, SC= subcutaneous. All secondary outcomes are in italics.

Risk of bias

Figure 2. Review authors' judgements about each risk-of-bias item presented as percentages across all included studies.



A summary of the risk of bias in the included studies is presented in Figures 2 and 3. Randomisation sequence generation was often briefly described and therefore assessed as unclear. Allocation concealment carried a low risk of bias in most studies and was only scored as unclear if it remained unmentioned in the manuscript. Most trials were blinded and adequately described as such. In some trials the intervention was not blinded; however, if the primary outcome was a measurable physiological variable (e.g. glucose), a low risk of bias was ascribed. Only one trial was deemed to have a high risk of bias due to both open-label administration of study drug and an outcome measure (insulin administration) that has the capacity to be influenced by the knowledge of treatment allocation.[19] With limited numbers of patients per study and short follow-up periods for the main outcome parameters, attrition bias was deemed low in all studies. As most studies reported similar outcomes (Table 1) the risk of selective reporting between studies was considered low. The majority of studies had registered protocols demonstrating consistent reporting of outcomes, and in only one case there was a discrepancy between reported and registered outcomes.[24] Other potential sources of bias identified were an early termination due to slow enrolment,[18] deviation from baseline reporting for some outcomes[22] and one study published as a letter to the editor with consequently brief reporting and unclear identification of sources of bias.[31]

Efficacy of intervention

A measurement of glycaemic control was reported as the primary outcome in 17 out of 19 included studies. We summarised all primary outcomes in Table 2.

Table 2. Summary of main outcomes of included studies

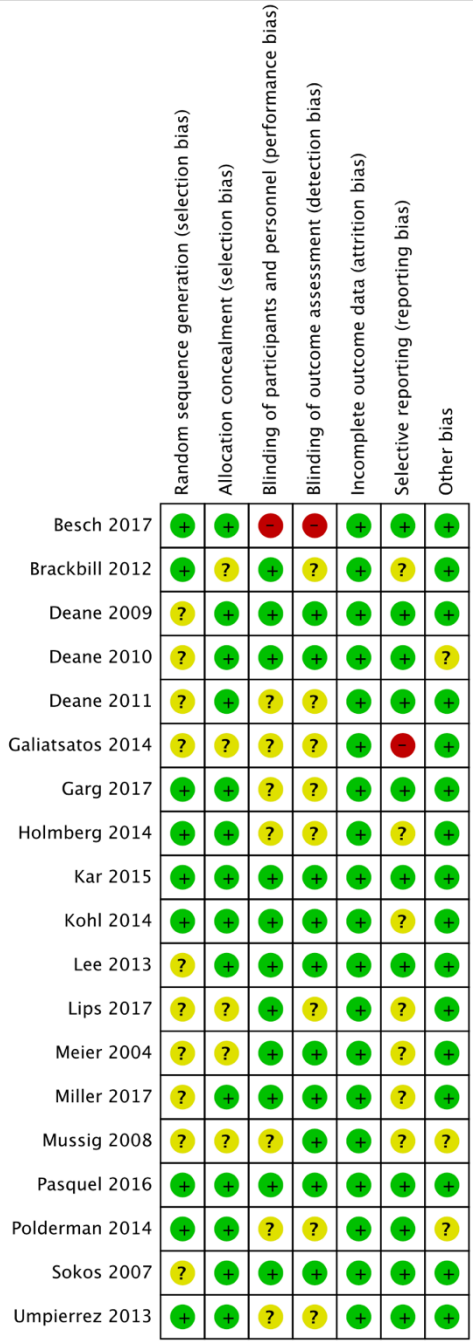
Author, year	Main outcome	Result
Meier, 2004[29]	GLP-1 IV lowered mean glucose levels	+
Sokos, 2007[34]	GLP-1 IV reduced peri-operative glucose levels	+
Mussig, 2008[31]	GLP-1 IV reduced insulin administration with comparable glycaemic control	+
Deane, 2009[21]	GLP-1 IV lowered mean post-prandial glucose levels	+
Deane, 2010[22]	GLP-1 IV lowered mean post-prandial glucose levels	+
Deane, 2011[23]	GLP-1 IV lowered mean post-prandial glucose levels	+
Galiatsatos, 2014[24]	GLP-1 IV did not lower mean glucose levels	-
Kohl, 2014[27]	GLP-1 IV lowered mean glucose levels	+
Miller, 2017[30]	GLP-1 IV reduced intestinal glucose absorption	+
Kar, 2015[26]	GIP IV did not lower mean glucose levels	-
Lee, 2013[28]	GIP IV did not lower mean glucose levels	-
Polderman, 2018[18]	Liraglutide SC reduced postoperative glucose levels	+
Holmberg, 2014[25]	Exenatide IV did not lower postoperative cardiac enzymes	-
Besch, 2017[19]	Exenatide IV did not increase number of patients that spend >50% in target range	-
Lips, 2017[17]	Exenatide IV did not improve left ventricular ejection fraction	-
Garg, 2017[35]	Saxagliptin PO resulted in similar glucose levels compared to basal-bolus insulin	+
Pasquel, 2017[32]	Sitagliptin PO or bolus insulin, as adjunct to basal insulin, resulted in similar glucose levels	+
Umpierrez, 2014[33]	Sitagliptin PO resulted in similar glucose levels compared to basal-bolus insulin	-
Brackbill, 2012[20]	Sitagliptin PO did not lower the mean postoperative glucose levels	-

+ = study positive for primary outcome, - = study negative for primary outcome

Intra-operative glucose lowering

A number of studies assessed the effect of GLP-1 receptor stimulation as an adjunct to standard insulin therapy during cardiac surgery. The first of these randomised 20 patients to a continuous intravenous infusion of GLP-1 (1.5 pmol kg^{-1} min^{-1}) or placebo, commencing 12 hours pre-operatively and continuing for 48 hours postoperatively. GLP-1 resulted in lower mean glucose in the pre- and peri-operative periods with nearly half the insulin administered to achieve comparable glycaemic control in the post-operative periods.[34] In 77 patients undergoing elective cardiac surgery, using the same dose of intravenous GLP-1 infused intra-operatively, Kohl and colleagues reported that mean blood glucose values were 0.68 mmol l^{-1} lower for subjects receiving GLP-1 compared to those receiving placebo (95% CI: 0.13 – 1.22 mmol l^{-1}, P = 0.015).[27] Lips and colleagues randomised 38 patients with decreased left ventricular function undergoing coronary artery bypass grafting (CABG) to a 72-hour infusion of intravenous exenatide (20 ng min^{-1}) or placebo as an adjuvant to standard insulin therapy.[17] Patients receiving exenatide demonstrated lower peri-operative mean blood glucose (6.4 ± 0.5 vs. 7.3 ± 0.8 mmol/L; P < .001) and a greater percentage of time in the target range of 4.5 – 6.5 mmol/L (54.8% ± 14.5% vs. 38.6% ± 14.4%; P = .001). In a similar study of 104 patients undergoing elective CABG, Besch and colleagues did not observe a statistical difference in the glycaemic outcome of interest (time in target range) between intravenous exenatide (25 ng min^{-1}) and placebo, however, exenatide was insulin sparing with a longer time to commencement of insulin and significantly less insulin administered.[19] Polderman and colleagues compared pre- and intraoperative subcutaneous liraglutide (0.6 mg + 1.2 mg) (a GLP-1 receptor agonist) with an intravenous glucose-insulin-potassium infusion and an insulin bolus regimen.[18] Median plasma glucose one hour postoperatively was lower in the liraglutide group (6.6 mmol l^{-1}) compared to both the continuous insulin infusion (7.5 mmol l^{-1}) and insulin bolus (7.6 mmol l^{-1}) groups (P = 0.015). In this study, liraglutide showed an insulin sparing effect, with fewer episodes of insulin administration and reduced total insulin administration.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Green: low risk of bias; yellow: unclear risk of bias; red: high risk of bias

Postoperative glucose lowering

In their vanguard study, Meier and colleagues randomised eight patients with T2DM who had undergone major surgery within the preceding week, to eight-hour infusions of intravenous GLP-1 (1.2 pmol kg^{-1} min^{-1}) and placebo in a cross-over fashion.[29] GLP-1 'normalised' blood glucose (fasting <7 mmol/L) in the cohort within 150 minutes whereas patients remained hyperglycaemic (>8 mmol/L) in the control arm.[29] In a further study of post-operative glycaemic control in T2DM, Müssig and colleagues randomised patients to GLP-1 (3.6 pmol kg^{-1} min^{-1}) or standard intravenous insulin in the 12 hours following CABG.[31] Glycaemic control was comparable between groups, however the GLP-1 cohort had significantly less insulin administered during the first 6 hours following surgery.[31]

Studies assessing the efficacy of the oral DPP-IV inhibitor sitagliptin for post-operative glycaemic control in patients with T2DM have reported varied results. In the study by Brackbill and colleagues the post-CABG addition of sitagliptin (100 mg once daily) to standard subcutaneous basal insulin and regular oral hypoglycaemic agents did not result in any difference in glycaemia or insulin administration.[20] Two related studies on the ward, one[33] a pilot preceding a larger trial,[32] which included both medical and surgical patients (Table 1) assessed sitagliptin (100 mg once daily) as an adjunct to a basal insulin when compared to a standard basal-bolus insulin regimen. The primary outcome of the larger trial was non-inferiority of mean blood glucose. Sitagliptin group was non-inferior to standard care and was associated with less total daily insulin requirement (24 ± 16 units vs. 34 ± 20 units per day; P <0.001).[32] Garg and colleagues compared the oral DPP-IV inhibitor saxagliptin (5 mg once daily) with basal-bolus insulin in a non-critically ill population of hospitalised patients with T2DM, predominantly in the post-operative period.[35] Saxagliptin was non-inferior to basal-bolus insulin for glycaemic control as determined by the daily mean blood glucose (primary outcome) with saxagliptin treatment causing less glycaemic variability.[35]

Intensive care unit

Deane and colleagues have assessed continuous intravenous infusions of GLP-1 in a series of cross-over trials in heterogeneous cohorts of mechanically ventilated patients.[21-23,30] At a dose of 1.2 pmol kg^{-1} min^{-1} infused over 270 to 330 minutes, GLP-1 reduced the glycaemic response to small intestinal nutrient delivery in patients with T2DM[23] and to intra-gastric and small intestinal nutrient delivery in patients not known to have T2DM.[21,22,30] Enteral nutrient stimulated hyperglycaemia was attenuated but not suppressed completely at this dose, with the glucose lowering effect more prominent in those patients without a history of diabetes. This group also evaluated the glycaemic effect of intravenous infusions of GIP during intragastric and small intestinal nutrient administration in mechanically ventilated patients and, in contrast to the profound glucose lowering effect of GIP in health, they reported no glucose lowering effect when GIP was given as stand-alone therapy or added to GLP-1.[26,28] Galiatsatos and colleagues compared an extended intravenous GLP-1 infusion (1.5 pmol kg^{-1} min^{-1} for 72 hours) with placebo as an adjunct to intensive insulin therapy in critically ill surgical patients. They reported no difference in mean blood glucose or insulin use between groups, but substantially less glycaemic variability (given by the co-efficient of variation of mean glucose) in the GLP-1 cohort.[24]

Hypoglycaemia

Data regarding hypoglycaemia are summarised in Table 3. The threshold to diagnose moderate hypoglycaemia ranged from <2.8 to <4.0 mmol/L. The incidence of moderate hypoglycaemia in the incretin arm varied from zero to 17%, except for one outlier with a reported incidence of 36% (8/23 patients).[25] In the latter trial intravenous exenatide was infused at double the dose of subsequent trials and it is unclear whether insulin was concurrently administered.[25] Meta-analysis revealed no difference in incidence of hypoglycaemia (incretin-based therapy: 36/484 (7.4%) vs. comparator: 36/540 (6.7%), P = .96). Of note, incretin-based therapies were administered with insulin in 10 out of the 14 studies reporting hypoglycaemia (Table 1).

Non-glycaemic effects

Due to the heterogeneity of definitions and infrequency of reporting of non-glycaemic end-points, quantitative analysis of these data was not possible.

Plasma insulin and glucagon concentrations were reported in eight studies.[21-28] GLP-1 was reported to increase plasma insulin levels[23,29] or insulin/glucose ratios[21,22] in enterally fed critically ill and post-operative patients. However, this insulinotropic effect was not observed in studies that sampled blood intra-operatively in fasted patients.[27,34]

The effect of GLP-1 on glucagon concentration was similarly heterogeneous, with several studies reporting a glucagonostatic effect[24,29,34] and others reporting no difference.[21,22,27]

The addition of GIP to a GLP-1 regimen in critically ill patients did not have an additional insulinotropic effect[28] and GIP as a sole agent was not shown to have an effect on plasma insulin or glucagon concentrations in critically ill patient.[26]
In the critically ill, GLP-1 slows gastric emptying when emptying is relatively normal, but appears to have minimal effect when emptying is already delayed,[22] whereas GIP appears to have no effect on gastric motility.[26] Similarly, GLP-1 delayed enteral glucose absorption, even when nutrient was delivered directly into the small intestine,[23,30] whereas GIP had no effect.[26]
Five studies compared the cardiovascular effects of GLP-1 or a GLP-1 receptor agonist with placebo.[17,24,25,31,34] In these studies there were no differences in cardiac enzymes,[17,25] echocardiographic measurements of left ventricular function,[17,34] haemodynamic parameters (heart rate, mean arterial pressure, pulmonary artery diastolic pressure)[31,34] or vasoactive medication requirement.[17,24,25,31]
There was no difference in the incidence of post-operative nausea and vomiting in studies comparing placebo with intravenous exenatide,[19] oral sitagliptin,[32] and subcutaneous liraglutide.[18] However, pre-operative nausea was more common when subcutaneous liraglutide was administered the night before surgery (13% vs. 0%, P = 0.007, n = 150).[18]
Incretin-based therapies have not been reported to increase post-operative complications or serious adverse events.[17-19,25,32]

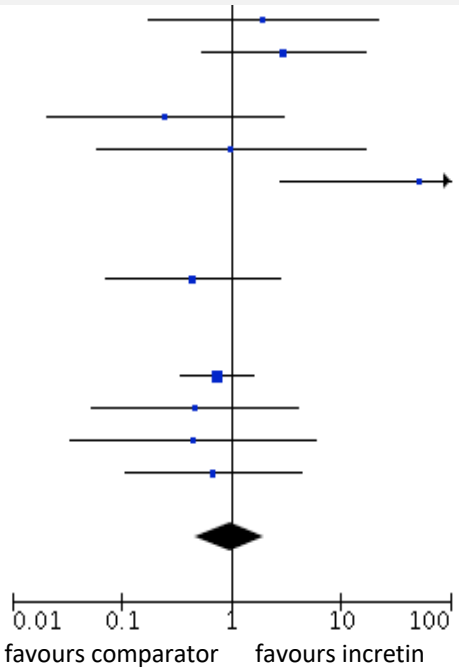
Diabetes mellitus

Eight studies were performed exclusively in patients with T2DM,[18,20,23,29,31-33,35] five studies in patients without T2DM[21,22,26,28,30] and a further six studies in mixed cohorts of patients with and without T2DM (Table 1).[17,19,24,25,27,34] None of the studies recruiting mixed populations reported subgroup analyses according to diabetic status. Due to the heterogeneity of interventions and outcome, it was not possible to draw meaningful conclusions on the effects of incretins in patients with T2DM compared to those without.

Table 3. Analysis of hypoglycaemia incidence in reported studies.

Author, year	Threshold for definition of hypoglycaemia	Incretin n	Incretin group	Comparator n	Comparator group	Weight	Odds Ratio M-H, Random, 95% CI	*p* value	Odds Ratio M-H, Random, 95% CI
Besch, 2017[19]	3.3 mmol l^{-1}	2	53	1	51	8.1%	1.96 [0.17, 22.32]	.58	
Brackbill, 2012[20]	3.3 mmol l^{-1}	5	30	2	32	12.9%	3.00 [0.54, 16.81]	.06	
Deane, 2010[22]	3.0 mmol l^{-1}	0	25	0	25		Not estimable	1	
Galiatsatos, 2014[24]	2.8 mmol l^{-1}	1	9	3	9	7.8%	0.25 [0.02, 3.04]	.58	
Garg, 2017[35]	3.9 mmol l^{-1}	1	33	1	33	5.7%	1.00 [0.06, 16.69]	1	
Holmberg, 2014[25]	4.0 mmol l^{-1}	8	21	0	41	6.1%	52.26 [2.83, 966.6]	.003	
Kar, 2015[26]	Not stated	0	24	0	24		Not estimable	1	
Kohl, 2014[27]	3.8 mmol l^{-1}	0	37	0	40		Not estimable	1	
Lips, 2017[17]	3.3 mmol l^{-1}	2	19	4	19	11.9%	0.44 [0.07, 2.76]	.12	
Meier, 2004[29]	4.0 mmol l^{-1}	0	8	0	8		Not estimable	1	
Mussig, 2008[31]	Not stated	0	10	0	10		Not estimable	1	
Pasquel, 2017[33]	3.9 mmol l^{-1}	13	138	17	139	24.7%	0.75 [0.35, 1.60]	.45	
Polderman, 2018[18]	4.0 mmol l^{-1}	1	44	5	106	9.5%	0.47 [0.05, 4.14]	.26	
Sokos, 2007[34]	3.3 mmol l^{-1}	1	10	2	10	7.4%	0.44 [0.03, 5.88]	.39	
Umpierrez, 2014[33]	3.9 mmol l^{-1}	3	56	2	26	11.8%	0.68 [0.11, 4.33]	.86	
Total (95% CI)			484		540	100%	0.97 [0.47, 2.02]	.94	
Total events		37		37					

Heterogeneity: $Tau^2 = 0.39$ $Chi^2 = 12.94$, df = 9 ($p = 0.17$); $I^2 = 30\%$
Test for overall effect: Z = 0.08 ($p = 0.94$)



Discussion

We systematically reviewed all randomised controlled trials of incretin-based interventions performed in the operating room and/or ICU setting and identified 19 studies, which included 1410 patients. Most studies reported a reduction in blood glucose or glycaemic variability when incretin-based therapies were used as a sole agent and/or a decrease in insulin administration when used as adjuvant therapy. Incretin-based therapies did not significantly reduce the incidence of hypoglycaemia. Incretin-based therapies did appear to attenuate glycaemic variability, although the latter was infrequently reported.

A number of studies attempted to delineate mechanisms underlying glucose-lowering in this cohort. The recognised insulinotropic effect of GLP-1 was consistently demonstrated in enterally-fed patients, whereas glucagonostasis was less reliably reported. In small single-centre studies, exogenous GLP-1 slowed gastric emptying in the setting of normal gastric motility and delayed intestinal glucose absorption, both of which likely contribute to attenuating nutrient stimulated hyperglycaemia.[22,30]

While compliance with GLP-1 receptor agonists is relatively good in ambulant patients with T2DM, the primary reason for discontinuation of therapy is gastro-intestinal discomfort, particularly nausea and vomiting.[36,37] Critically ill and post-operative patients are at increased risk of nausea and vomiting, and it is therefore somewhat surprising that only three of the studies reported on this side effect. Notwithstanding the relatively small number of patients studied, it is reassuring that incretin therapy did not appear to further increase the risk of post-operative nausea and vomiting.

Large trials in ambulant patients with T2DM have reported beneficial cardiovascular effects with GLP-1 receptor agonists.[38-40] This signal is supported by preliminary animal and observational human data identifying potential cardio-protective properties of incretin-based therapies.[41,42] This provides a persuasive rationale for the use of GLP-1 in the setting of cardiac surgery. In murine models, GLP-1 reduced ischaemia-induced myocardial injury[41] and in patients with heart failure, administration of GLP-1 was associated with improvements in left ventricular function, myocardial oxygen uptake and distance during a 6-minute walking test.[42] On the other hand, the most recent trial in patients with diabetes and heart failure observed no difference in time to death or rehospitalisation for heart failure.[43] None of the studies included in this review reported any differences in acute indices of cardiac performance between incretin-based therapies and control.

Strengths and limitations

Strengths of this systematic review include the structured search, complete retrieval of the identified research and validated methods in accordance with the PRISMA statement. However, there are some limitations. We found marked clinical heterogeneity between the studies including the dose and type of incretin therapy and duration of intervention, ranging from four hours to ten days. In addition, there were substantial differences in the glycaemic control strategies of the control arms ranging from blinded placebo to open-label intravenous insulin. The broad scope of this review revealed a marked heterogeneity in the populations studied which included patients undergoing elective cardiac surgery, ward surgical patients and mechanically ventilated critically ill patients. Furthermore, there were trials exclusively performed in patients with pre-existing diabetes whereas in other trials patients with pre-existing diabetes were excluded, and still others included both groups of patients. Inferences should therefore be circumspect as it is increasingly recognized that

hyperglycaemia does not represent the same insult to all patients and may be modified by patient's pre-morbid glycaemic control.[44] It should be noted, however, that the majority of included patients were diagnosed with DM. While all of the studies assessed 'glycaemic control', there was substantial variation in the outcomes reported such that meta-analysis was only possible on the variable of hypoglycaemia. Finally, most studies were small single-centre trials and thus underpowered to detect differences in clinical and patient-centred outcomes and safety endpoints.

Future directions

Taken together, these data signal the potential for incretin-based therapies, particularly GLP-1-based regimens, as effective glucose-lowering agents with a relatively low incidence of hypoglycaemia. However, due to the limitations of the original studies, it is not possible to draw definitive conclusions regarding the role for incretin therapies in the operating room and ICU. Future studies are required to determine (i) the population most likely to benefit (ii) optimal dosing regimens, including the role for combination therapy with insulin (iii) and finally clinical efficacy and safety outcomes.

Conclusion

Incretin-based therapies represent a promising novel approach to glucose control in the peri-operative period and during critical illness, with a low risk of hypoglycaemia. Further studies with larger sample sizes[45] are required to determine the optimal agent and dosing regimen and effects on patient-centred outcomes.

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Five

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

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BMJ Open 2018; 8 (6): 1-6

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 Center (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.

Registration

This trial has been registered with the European Union Drug Regulating Authorities Clinical Trials database (2017-000043-40) and the Nederlands Trial Register (NTR6323). Last amendment of protocol: version 8.0 January 2018.

Background

Perioperatively, the incidence of hyperglycaemia (glucose >8 mmol l^{-1}) 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^{-1} reduced complications in randomised controlled trials in patients with and without diabetes mellitus.[1,4] However, stricter glucose control is also complicated by increasing incidence of hypoglycaemia.[5,6]

For this reason, the American Diabetes Association currently recommends a perioperative glucose target range of 4.4 – 10 mmol l^{-1}.[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 entero-endocrine 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 anti-hyperglycaemic 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 once daily dosage this therapy is not only safer (preventing hypoglycaemia) but also a considerably less time consuming for perioperative care-givers.

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; 95% CI: 0.40 – 1.25 mmol l^{-1}) and a higher percentage of time spent in glucose target range, compared to placebo.[13] A continuous intravenous GLP-1 infusion during cardiac surgery also lowered glucose levels by 0.8 – 0.9 mmol l^{-1}, as compared to 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 to continuous or bolus insulin regimens.[15] While the American Diabetes Association currently recommends a upper glucose target limit of 10 mmol l^{-1} perioperatively, recent trials indicated benefit of a moderate glycaemic control below < 8 mmol l^{-1}.[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^{-1} in the intraoperative period.

Methods/Design

The manuscript was written in accordance with the SPIRIT guideline on reporting of intervention trial protocols.[17]

Trial design

The study is a multi-centre 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 in- 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^{-1} 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^{-1} 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 NYHA class IV
- Serum-creatinine ≥ 133 µmol l^{-1} for males and ≥ 115 µmol l^{-1} for females
- 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
- Female of child-bearing potential who is pregnant, breast-feeding or intend to become pregnant or is not using adequate contraceptive methods

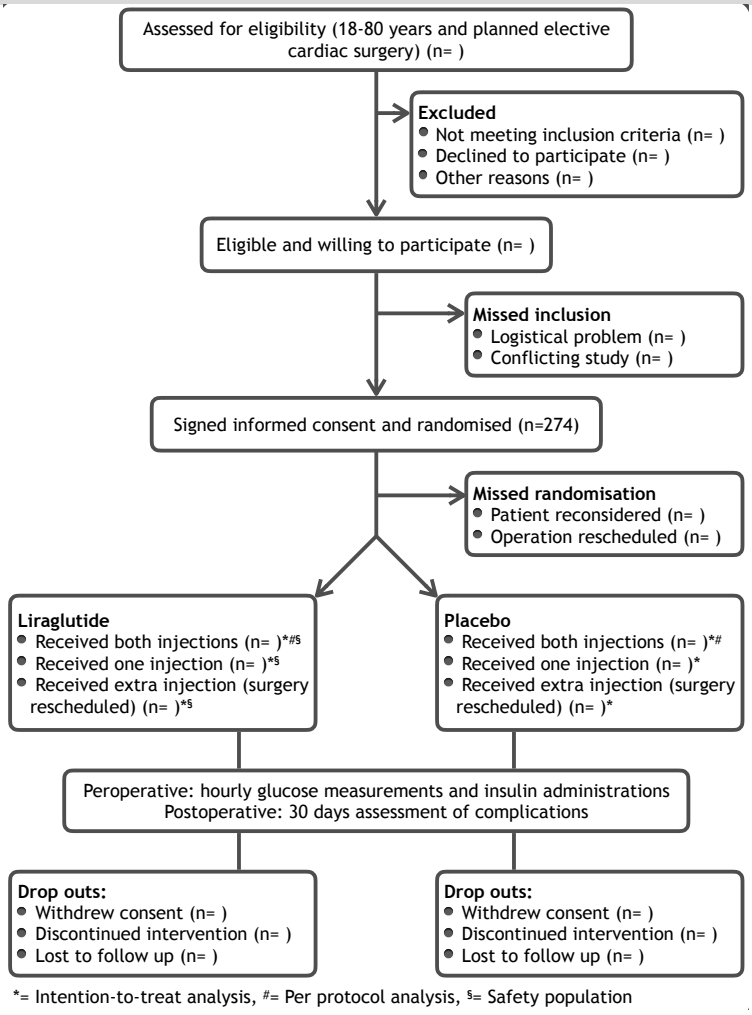
Researchers will screen all patients presenting for elective cardiac surgery, patients will be contacted and informed in case of eligibility.

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 (BMI), medical history, medication use and American Society of Anesthesiologists (ASA) 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 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.

Figure 1. Consolidated Standards of Reporting Trials flow diagram.



*= Intention-to-treat analysis, #= Per protocol analysis, §= Safety population

Surgical and anaesthetic details will be recorded. It is common practice to administer prophylactic 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 presence of all complications listed in Table 1, until 30 days after surgery. For the CONSORT 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]

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 global MI taskforce
		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 non-cardiovascular mortality
		Re-operation	Unplanned surgical intervention
		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; UTI = urinary tract infection; CDC = Center for Disease Control and Prevention; RBC: Red Blood Cell; ICU: Intensive Care Unit; LoS: Length of Stay; SAE: Serious Adverse Event.			

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 diabetes mellitus type 2.

Allocation concealment and blinding

Randomisation will be performed at the local pharmacy department, distant from patient wards, the OR, or offices for health care 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 (SUSAR). 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 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 induction of anaesthesia and every 60 minutes 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^{-1} 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^{-1}.[15]

Laboratory measurements

A creatinine measurement within six months of the day of surgery will be recorded or determined if not present in the health records. Blood for HbA1c and fasting glucose determination will be sampled before induction of anaesthesia. Glucose will be measured every hour after the first measurement with an acceptable range of 15 minutes 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 induction of anaesthesia.

Table 2: Glucose correction study algorithm.

Blood glucose (mmol l^{-1})	1st insulin bolus	2nd insulin bolus if glucose increases	3rd insulin bolus if glucose increases
< 4 *	-	-	-
4 – 8	-	-	-
8 – 9	2 IU	4 IU	6 IU
9 – 10	3 IU	5 IU	7 IU
10 – 11	4 IU	8 IU	12 IU
11 – 12	5 IU	9 IU	13 IU
12 – 13	6 IU	12 IU	18 IU
13 – 14	7 IU	13 IU	19 IU
14 – 15	8 IU	15 IU	20 IU
15 – 16	9 IU	16 IU	21 IU
>16**	10 IU	17 IU	22 IU

* Glucose is 2.3 – 4 mmol l^{-1}, give 4 g glucose IV. Glucose <2.3 mmol l^{-1}: give 50 g glucose IV. In both cases, measure again after 10 min and consult research physician.
** Consult research physician.

Postoperative complications

Delirium is marked present on any day the CAM-ICU score[20] 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 pre-set 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^{-1}) events, the number of mild (<4 mmol l^{-1}), and severe (<2.3 mmol l^{-1}) hypoglycaemic events, proportion of patients with postoperative nausea and vomiting (PONV), and four composites of complications (listed in Table 1).

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 exact test, based on an intention-to-treat analysis. Based on the data of the 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}.[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% (2-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, 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 sub-analysis 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 sub-analysis according to preoperative diagnosis of DM2. All analyses will be done using SPSS (IBM, version 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 thirty inclusions or after one 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

Ethical approval and registration

This study protocol has been approved by the medical ethics committee of the AMC in Amsterdam and by the Central Committee on Research Involving Human Subjects (CCMO) as the Dutch competent authority. The study protocol is in adherence with the Declaration of Helsinki and the guideline of Good Clinical Practice.
Written informed consent will be obtained by trained study personnel, all subjects will receive a written patient information letter and informed consent form (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.
This trial has been registered with the European Union Drug Regulating Authorities Clinical Trials database (2017-000043-40) and the Nederlands Trial Register (NTR6323).

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 Academic Medical Center 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 upon 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.

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Six

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

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Diabetes, Obesity and Metabolism 2020; 22 (4): 557-565

Abstract

Aims

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

Materials and methods

In this randomised, blinded, placebo-controlled, parallel-group, balanced (1:1), multicentre randomised, superiority trial, adult patients undergoing cardiac surgery in four Dutch tertiary hospitals were randomised 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 above 8·0 mmol/L in the operating theatre. Research pharmacists used centralised, stratified, variable-block, randomisation software. Patients, care providers, and study personnel were blinded to treatment allocation.

Results

Between June 2017 and August 2018, 278 patients were randomised 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 to 80 (61%) patients in the placebo group, absolute difference: 18% (95% CI 5·9–30·0, p=0·003). Dose and 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 to placebo, reduces insulin requirements while improving perioperative glycemic control during cardiac surgery.

Registration

trialregister.nl Identifier: NTR6323

Introduction

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

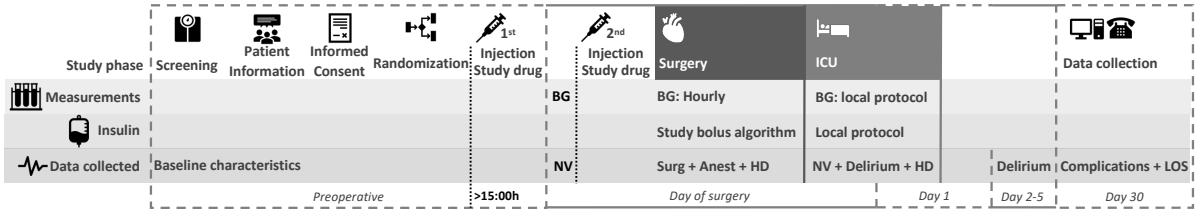
Glucagon-like peptide 1 (GLP-1), stimulates insulin release and suppresses glucagon secretion in a glucose-dependent manner, thereby reducing BG concentrations without increasing the risk of hypoglycemia.[8] GLP-1 receptor agonists (GLP-1 RA) are an established therapy for type 2 diabetes mellitus and 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] Their main side effect, gastrointestinal intolerance, could, however, be problematic in this setting. In a recent systematic review, we found only small single-center trials studying incretin-based therapies in the perioperative period.[9] Therefore, we performed a multicenter randomized trial to evaluate the efficacy of a GLP-1 RA 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 glycemic control during surgery.

Materials and methods

Study design

We performed a multicenter, triple-blind, placebo-controlled, parallel-group, phase 3, randomized superiority clinical trial in four Dutch tertiary care centers. Participating hospitals were Amsterdam UMC (Amsterdam), Amphia (Breda), Catharina Hospital (Eindhoven), and OLVG (Amsterdam). The study protocol was approved by the medical ethics committee of the Amsterdam UMC (registration number: 2017_012) 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 1) 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. We wrote this paper following the CONSORT recommendations for reporting of randomized trials.[11] The study workflow is summarized in figure 1.

Figure 1. Workflow patients through the study.



BG=blood glucose, NV=nausea and vomiting, HD=hemodynamics, LOS=Length of stay.

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, GLP-1 RAs, 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.

Randomization and masking

Research pharmacists coordinated 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 center 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 liraglutide-placebo with solvents and water for injections, visually identical, equal in

appearance and weight, and provided by Novo Nordisk), to trained research personnel, responsible for the administration of the study medication. All patients, care providers, and study personnel were thus blinded to treatment allocation.

Procedures

Patients received a first subcutaneous injection with liraglutide 0.6 mg (Novo Nordisk A/S, Bagsvaerd, Denmark) 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). 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 anesthesia unless the patient reported a nausea score above four preoperatively. Researchers measured BG hourly, starting just before induction of anesthesia and until transfer to the intensive care unit (ICU). BG concentrations were measured in arterial blood samples by point-of-care blood gas analysis equipment. Insulin was administered as intravenous bolus injections according to a previously published algorithm, with a BG target range between 4.0–8.0 mmol/L (appendix).[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 centers had a nurse-driven glycemic control protocol in place employing continuous insulin infusions to achieve BG levels below 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.

Outcomes

The primary endpoint was the difference between groups for any insulin given to control BG below 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, the number of insulin administrations, the mean intraoperative BG concentration, number of hyperglycemic events (BG >11.0 mmol/L), the number of mild (BG <4.0 mmol/L) or severe (<2.3 mmol/L) hypoglycemic 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 bacteremia, and urinary tract infection and 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.

Statistical analysis

Based on the glycemic 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] Drop-outs due to 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 (IQR) 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% CIs. Normality of distributions was assessed visually with histograms, Q-Q plots, and the Shapiro-Wilk test. A *P* value of less than 0.05 was considered significant. Statistical analyses were performed using SPSS (IBM version 24).

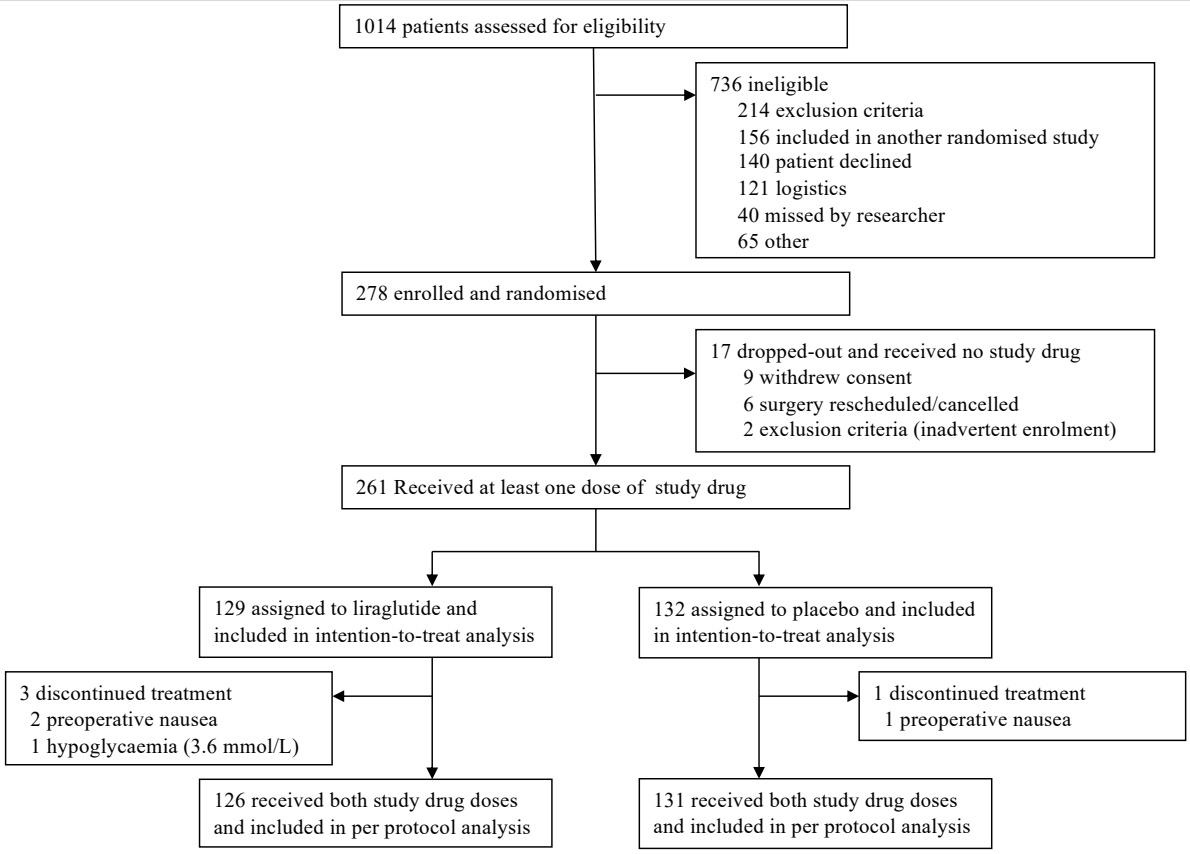
Role of the funding source

The funder of the study 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.

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 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: 3, placebo: 1), 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.

Figure 2.CONSORT flowchart of patients in the study.



Baseline variables

Patients were well balanced between groups, as we observed no notable differences in baseline characteristics between the two groups (table 1; appendix). The mean 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, 6 (2%) of whom used insulin. The mean GHb 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

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, No. (%)	211 (81)	105 (81)	106 (80)
Ethnic origin, No. (%)			
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, No. (%)			
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)
GHb, mean (SD), %	5.8 (0.8)	5.8 (0.9)	5.8 (0.8)
GHb, mean (SD), mmol/mol	40 (8.9)	40 (9.7)	40 (8.1)
ASA score, No. (%)			
II	36 (14)	22 (17)	14 (11)
III	189 (72)	94 (73)	95 (72)
IV	36 (14)	13 (10)	23 (17)
Smoker past year, No. (%)	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, No. (%)			
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 anesthesia, No. (%)			
Propofol	16 (6)	8 (6)	8 (6)
Sevoflurane	245 (94)	121 (94)	124 (94)

There were no significant differences between the two treatment groups for any of the baseline characteristics. Continuous variables were compared with t tests or Mann-Whitney U tests, and categorical variables compared with χ^2 test. ASA=American society of anesthesiologists, CABG=Coronary artery bypass surgery, GHb=Glycated Hemoglobin.

was 1.27% (0.89–1.97), and the mean duration of surgery was 222 min (165–293), resulting in a median of 5 (4–6) intraoperative BG measurements per patient.

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*=.003). In the liraglutide group, the total intraoperative insulin doses and number of insulin administrations were lower compared to 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*=.54]), nor was the median total dose of insulin administered (liraglutide 0 IU (0–20) vs. placebo 0 IU (0-22), *P*=.63).

Table 2. Insulin therapy, glycemic control, nausea and vomiting, and postoperative complications.

	Liraglutide 129	Placebo 132	Absolute Difference	95% CI	*p*-value*
Insulin therapy					
Any insulin administered, No. (%)	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
Glycemic control					
Intraoperative					
Mean blood glucose, mean (SD)	6.3 (1.1)	7.0 (1.1)	0.66	(0.39–0.93)	<0.001
Hyperglycemia (>11 mmol/L), No. (%)	7 (5)	5 (4)	-2%	(-7%–3%)	0.57
Hypoglycemia mild (2.3-4 mmol/L), No. (%)	3 (2)	2 (2)	-1%	(-4%–3%)	0.68
Hypoglycemia severe (<2.3 mmol/L), No. (%)	1 (1)	1 (1)	0%	(-2%–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
Hyperglycemia (>11 mmol/L), No. (%)	42 (33)	50 (38)	5%	(-7%–18%)	0.36
Hypoglycemia mild (2.3-4 mmol/L), No. (%)	0 (0)	0 (0)	-	-	-
Hypoglycemia severe (<2.3 mmol/L), No. (%)	0 (0)	0 (0)	-	-	-
Nausea and Vomiting, No. (%)					
Preoperative	4 (3)	1 (1)	-2%	(-6%–1%)	0.21
Postoperative	33 (26)	27 (20)	-5%	(-15%–6%)	0.37
Hemodynamics, mean (SD)					
Heart rate preoperative (beats/min)	77 (16)	68 (17)	-10	(-13– -5.5)	<0.001
Heart rate postoperative (beats/min)	78 (13)	72 (18)	-6	(-9.8– -2.1)	0.003
Heart rate ICU 1h postop (beats/min)	81 (12)	73 (13)	-8	(-11– -4.6)	<0.001
Mean arterial pressure preoperative (mmHg)	92 (18)	88 (20)	-4	(-9– 0.39)	0.07
Mean arterial pressure postoperative (mmHg)	71 (13)	67 (15)	-4	(7.6– -0.77)	0.02
Mean arterial pressure ICU 1h postop (mmHg)	77 (16)	77 (13)	0	(-3.9– 3.2)	0.85
Complications, No. (%)					
Composite endpoint cardiac	53 (41)	58 (44)	3%	(-9%–15%)	0.64
Composite endpoint infectious	12 (9)	11 (8)	-1%	(-8%–6%)	0.78
Composite endpoint other	23 (18)	28 (21)	3%	(-6%–13%)	0.49
Any complications	68 (53)	76 (58)	5%	(-7%–17%)	0.43
Delirium (ICU + Ward)	4 (3)	10 (8)	4%	(-1%–10%)	0.17
Delirium (CAM-ICU only)	2 (2)	7 (5)	4%	(-1%–8%)	0.17

*** *P* values represent comparisons among the treatment groups, - =not applicable. ICU=intensive care unit, CAM-ICU=confusion assessment method for the intensive care unit.**

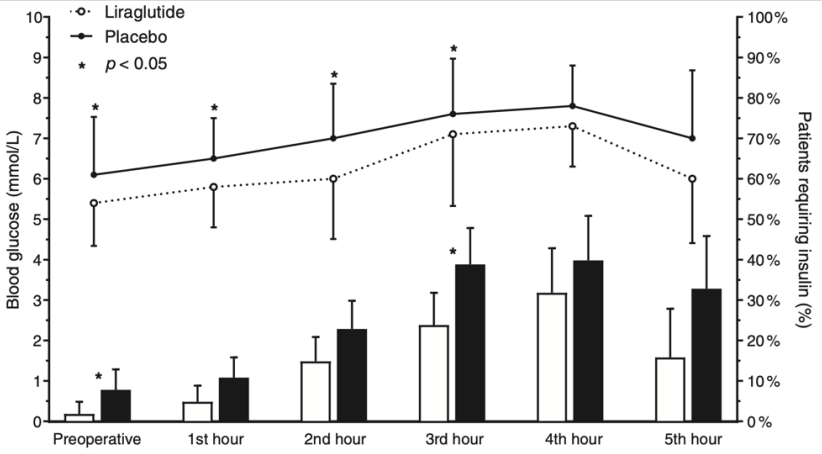
Glycemic control

The incidence of BG measurements above 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 hypoglycemia (BG <4.0 mmol/L) with 4 (3%)
patients in the liraglutide group vs. 3 (2%) patients in the placebo group (*P*=.72). Hyperglycemia (BG >11.0 mmol/L) and mild or severe hypoglycemia (between 4.0–2.3 or <2.3 mmol/L, respectively) all occurred with an incidence of 5% or less, and rates did not differ between groups (table 2). In the first 24 postoperative hours, mean BG concentrations rose to 9.0 (1.4) mmol/L, while remaining 0.49 mmol/L lower in the liraglutide group (95% CI 0.15–0.84, p<0.0001).

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 to placebo, whereas the mean arterial pressures were comparable. Lengths of ICU or hospital stay were not different between groups, nor was 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: 3, placebo: 2) and eight with a cerebrovascular accident (liraglutide: 4, placebo: 4). Other significant complications included postoperative cardiac stunning and postoperative hypoperfusion syndrome (appendix table 3). The per-protocol analysis revealed similar results as the intention-to-treat analysis for all outcomes (appendix table 2).

Figure 3.Mean intraoperative blood glucose concentrations and incidence of hyperglycemia requiring insulin administration.



Blood glucose concentrations during surgery (mean (SD), lines, top of figure) and incidence of blood glucose above 8 mmol/L (% [95% CI], bars, bottom of the figure).

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 table 2). Nonetheless, 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 centers, 164 patients (63%) received intraoperative corticosteroids, 81 of these patients had been allocated to liraglutide and 83 to placebo. Patients receiving corticosteroids were administered a median dose of 0.95 mg/kg (0.49–1.02) dexamethasone. Compared to patients not receiving any corticosteroids, insulin requirements and BG concentrations were higher in patients having corticosteroid injection during surgery (appendix table 2). 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 versus more complex procedures) nor the type of anesthesia ($p_{interaction}$= 0.072 for propofol versus sevoflurane maintenance of anesthesia).

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 hypoglycemia. We observed no differences in adverse outcomes such as hyperglycemia, nausea and vomiting, length of hospital or ICU stay, or postoperative complications.

The first trials studying a continuous infusion of GLP-1 in cardiac surgery patients all found either lower BG concentrations or fewer insulin requirements with comparable glycemic control.[14–16] While three trials studied a GLP-1 RA in cardiac surgery,[17–19] all used the short-acting GLP-1 RA 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, including 104 patients, showed no difference in the number of patients requiring any insulin, total insulin dose, nor glycemic control, although this study used a slightly higher dose of exenatide.[17] A trial comparing exenatide once-weekly to liraglutide once-daily in type 2 diabetes mellitus patients found liraglutide to be more effective for improvement of glycemic 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 four to six week.[20] In a systematic review, 18 out of 19 trials studying a GLP-1RA in the perioperative or ICU setting, found either improved glycemic control or reduced insulin requirements.[9] A previous trial from our own group in a non-cardiac surgery population showed improved glycemic 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 hypoglycemia, so far there were no alternatives to insulin for the treatment of perioperative hyperglycemia.[2] With hyperglycemia and hypoglycemia 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 non-insulin alternatives for in-hospital glycemic control.[7,9,24] Our trial shows that liraglutide is indeed an effective alternative to insulin for the treatment of hyperglycemia induced by the stress of cardiac surgery. Reassuringly, the lower BG attained in the liraglutide group was not accompanied by a higher hypoglycemia rate. This is in line with a meta-analysis of perioperative and intensive care trials, studying incretin therapies.[9]

Liraglutide is DPP-4 resistant GLP-1 analogue that stimulates insulin and inhibits glucagon secretion, thereby reducing BG levels.[8] GLP-1 also acts on other organs such as the liver, fat, and muscle tissue stimulating glucose uptake and glycogen synthesis.[8] GLP-1 also has a direct effect on the heart. GLP-1 receptors have been found in the sinus node, increasing heart rate, as also observed in our study.[8] In addition, various studies have postulated cardioprotective properties of GLP-1 therapy such as, reducing ischemia-reperfusion injury, reducing infarction size, and improving ischemic 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, glycemic control in the placebo group was also quite good, with a mean intraoperative BG of 7.0 mmol/L, and only four percent of patients experiencing hyperglycemia above 11.0 mmol/L. Most likely, the glycemic 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 glycemic control.[4,22] Considering the relatively modest contrast in glycemic 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 GLP-1RAs.[8] The American Diabetes Association highlighted this as a potential concern for the in-hospital use of GLP-1 RAs.[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 to 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 anesthesia.[21] The emetic effects of anesthesia 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*=.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 centers in our trial. We, therefore, stratified our randomization per center. Consistent with the literature, we observed higher BG concentrations in the patients treated with corticosteroids.[30] The efficacy of liraglutide was nonetheless comparable, whether patients received intraoperative corticosteroids or not.

Limitations

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 GLP-1 RA therapy, such as a history of pancreatitis. Finally, in this trial liraglutide was administered preoperatively only, and while the duration of action is 24 hours,[8] a considerable rise in BG was still observed postoperatively. While we found a statistically significant difference in glycemic control, a greater difference is likely required to result in further reductions in postoperative complications, for which our trial was not powered. Hence, higher doses, more potent, or longer-acting preparations could further improve glycemic control postoperatively.

To summarize, liraglutide reduced insulin requirements and improved glycemic control, without an increase in hypoglycemia. These effects should be viewed in combination to appreciate the potential of GLP-1 RAs to safely improve perioperative care, in a healthcare provider- and patient-friendly way. This multicenter trial validates previous smaller studies and provides support for the use of liraglutide in the perioperative setting. We expect future in-hospital glycemic control studies to focus on the potential of GLP-1 RAs to reduce complications.

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Seven

Effects of Liraglutide on Myocardial Function After Cardiac Surgery: A Secondary Analysis of the Randomised Controlled GLOBE Trial

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Abstract

Introduction

Previous studies demonstrated the cardioprotective properties of glucagon-like peptide-1 receptor agonists in patients with diabetes or cardiac disease. We investigated whether preoperative subcutaneous liraglutide improves myocardial function after cardiac surgery.

Methods

We performed a pre-planned secondary analysis of adult patients undergoing cardiac surgery included in the GLOBE trial. Patients were randomised to receive 0.6 mg subcutaneous liraglutide on the evening before surgery and 1.2 mg after induction of anaesthesia, or matching placebo. Perioperative echocardiographic assessments, haemodynamic parameters, doses of vasoactive inotropic support and postoperative measurements of troponin, Creatine Kinase-MB (CK-MB), creatinine and lactate were compared between groups.

Results

The study population consisted of the entire intention-to-treat cohort of the GLOBE trial. In this study, 129 patients received liraglutide and 132 patients placebo. Baseline characteristics were comparable between groups. Postoperatively, 170 (65%) patients underwent echocardiography. In the liraglutide group, more patients had a normal left ventricular systolic function (68%, 59 patients) compared to placebo (53%, 44 patients), difference = 15%, 95%CI = 0–30, P=.049. Assessment of the right ventricle revealed no difference in function.

Conclusions

Patients receiving short-term preoperative liraglutide treatment better maintained normal myocardial function after cardiac surgery. This study warrants further evaluation of the potential beneficial effects of GLP-1 receptor agonists in cardiac surgery patients.

Registration

trialregister.nl Identifier: NTR6323

Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1RA) improve perioperative glucose regulation, without increasing the incidence of hypoglycaemia compared to insulin.[1] In addition, various cardioprotective mechanisms have been attributed to GLP-1RAs. We recently reported that two preoperative subcutaneous injections of liraglutide (a long-acting GLP-1RA) improved glycaemic control during cardiac surgery (GLOBE trial).[2] In this secondary analysis of the GLOBE trial, we aimed to evaluate the effect of liraglutide on postoperative cardiac function through analysis of postoperative echocardiography, haemodynamic parameters, and routinely collected biomarkers of cardiac injury.

GLP-1 has been reported to increase myocardial metabolic efficiency of glucose usage, reduce systemic and pulmonary vascular resistance and activate ischaemic preconditioning pathways.[3–5] However, these mechanisms have mainly been demonstrated in animal studies, while there are only a few physiological studies in humans.[6] Some indications of positive GLP-1 mediated effects on cardiac function were observed in clinical studies, showing an improved left ventricular function and reduced infarct size after ischaemic injury in GLP-1 treated subjects.[7–9] These results were mainly seen in patients with coronary artery disease undergoing dobutamine stress testing or percutaneous coronary interventions for acute myocardial infarction and were assessed at a limited interval after the intervention (up to 72 hours).[6] More recently, longer-term treatment with liraglutide was shown to reduce the incidence of major cardiovascular complications in high-risk patients with type 2 diabetes mellitus.[10,11]

From the dataset of a recently reported multicentre, randomised, placebo-controlled, trial, wherein we administered a long-acting GLP-1 receptor agonist, liraglutide, to patients undergoing cardiac surgery, we here report a pre-planned secondary analysis of indicators of cardiac function collected in routine clinical care. Based on the aforementioned studies, we hypothesised that liraglutide, compared to placebo, improves postoperative cardiac function.

Materials and Methods

Study design

This study is a secondary analysis of the GLOBE trial, a multicentre, triple-blind, placebo-controlled, parallel-group, phase 3, randomised superiority clinical trial which ran in four Dutch tertiary care centres. The primary hypothesis of the GLOBE trial was that the preoperative administration of liraglutide reduces the number of patients requiring insulin for glycaemic control during cardiac surgery. The trial was registered with www.trialregister.nl, number NTR6323. The study protocol was approved by the medical ethics committee of the Amsterdam UMC (registration number: 2017_012) before initiation of the trial. The detailed study protocol is available open access,[12] and the primary results of the GLOBE trial have recently been published.[2] The relevant methodology concerning this cardiac analysis is described below. We wrote this paper in adherence to the CONSORT recommendations for reporting of randomised trials.[13]

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, GLP-1 RAs, 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 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 had to provide written informed consent before any trial-related procedures.

Randomisation and masking

At each institution, central research pharmacists allocated patients after on-line randomisation through an electronic data management system. Randomisation was balanced (1:1), with variable random blocks of four, six, or eight patients, and stratified per centre and type 2 diabetes mellitus. The research pharmacy distributed study medication in visually identical pen-injectors, equal in appearance and weight (provided by Novo Nordisk) directly to trained research personnel, responsible for the administration of the study medication. All patients, care providers, and study personnel were thus blinded to treatment allocation.

Procedures

Patients received a first subcutaneous injection with liraglutide 0.6 mg (Novo Nordisk A/S, Bagsvaerd, Denmark) or placebo on the evening before surgery (after 15:00 h) and a second dose of 1.2 mg or placebo was given after the induction of anaesthesia. Starting with the induction of anaesthesia and lasting until transfer to the intensive care unit (ICU), researchers measured blood glucose concentrations every hour; an intravenous insulin bolus injection algorithm was used for targeting intra-operative blood glucose concentrations between 4.0–8.0 mmol/L.[12] After transfer to the ICU, study interventions stopped, and further treatment, including blood glucose management, was left to the discretion of the ICU physician.

Data collection and outcomes.

Baseline characteristics, comorbidities, perioperative haemodynamic data and glycaemic control were recorded per study protocol as reported previously.[2] Echocardiography was performed as part of routine perioperative care by the treating cardiologist. We collected transthoracic echocardiographic assessments before, and up to thirty days after surgery. In case of multiple investigations, we recorded the assessment closest to the day of surgery. We recorded qualitative assessment (categorised as normal, or mildly, moderately or severely reduced function) of right and left ventricular function as noted by the echocardiographer. We recorded heart rate, heart rhythm and mean arterial pressure from the continuous recordings stored in the patient electronic health records from the start of surgery until 24 hours after surgery, or discharge of the patients from the ICU, whichever occurred first. Data were recorded at predefined time-points; at start of surgery, end of surgery, and 1, 6, 12, and 18 hours thereafter. Noted measurements were the means of the three values before, at, and after the respective time points. From the ICU electronic health records, we also noted the total dose of norepinephrine, dobutamine, milrinone, and amiodarone administered in the first 48 postoperative hours. In all participating centres, as part of routine clinical care, either Creatine Kinase-MB (CK-MB) or Troponin T levels were recorded postoperatively until two consecutive measurements showed a decline in these markers of cardiac injury. Hence, periods between these measurements varied, and we, therefore, analysed peak postoperative values in the first 24 hours. We also noted lactate levels in this period, and creatinine measurements obtained up to five days after surgery.

Statistical analysis

The sample size was defined by the number of patients included in the intention to treat analysis of the GLOBE trial.[2] 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 (IQR) 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 the respective 95% CIs. Normality of distributions was assessed visually with histograms, Q-Q plots, and the Shapiro-Wilk test. All statistical tests were 2-sided, and a *P* value of less than 0.05 was considered significant. Statistical analyses were performed using SPSS (IBM version 26).

Role of the funding source

The funder of the study 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.

Results

The cohort of patients consists of all 261 patients included in the primary intention-to-treat analysis of the GLOBE trial. Of these, 129 patients were allocated to the liraglutide group and 132 to the placebo group. Baseline characteristics were well balanced and are summarised in Table 1. In this trial we observed that patients treated with liraglutide required less insulin for glycaemic control during surgery, compared to placebo, and also had lower glucose concentrations during surgery and ICU admittance.[2]

Table1. Baseline characteristics of the intention-to-treat population.

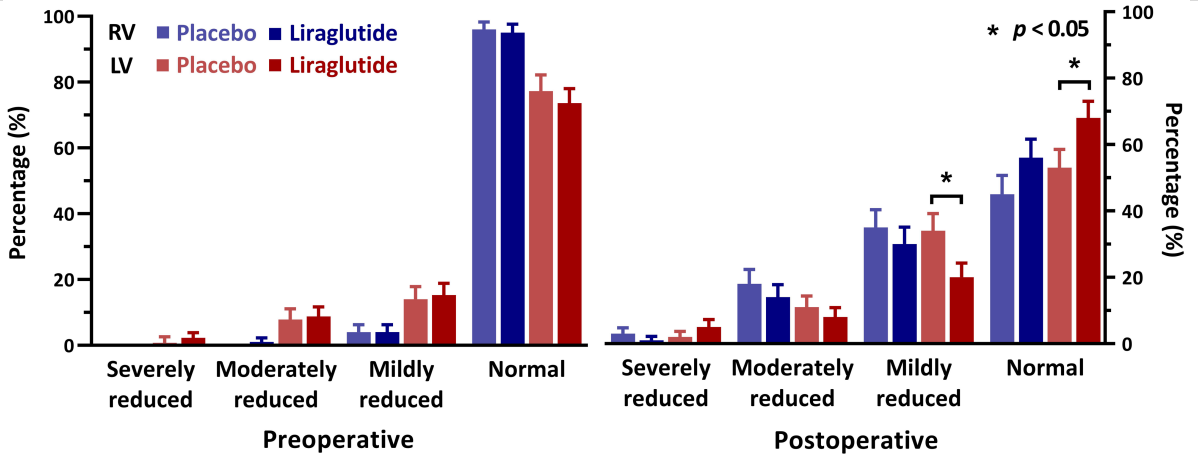
	All 261	Liraglutide 129	Placebo 132
Age, mean (SD), years	65.0 (10.9)	64.6 (11.2)	65.3 (10.7)
Male sex, No. (%)	211 (81)	105 (81)	106 (80)
ASA score III, No. (%)	189 (72)	94 (73)	95 (72)
Smoker past year, No. (%)	54 (21)	26 (20)	28 (21)
Hypertension, No. (%)	111 (43)	57 (44)	54 (43)
BMI, mean (SD), kg/m^2	27.5 (4.2)	27.3 (4.0)	27.7 (4.4)
Diabetes mellitus type 2, No. (%)	42 (16)	21 (16)	21 (16)
Creatinine clearance, mean (SD), ml/min	80.4 (16.6)	80.6 (17.0)	80.2 (16.2)
Glycated hemoglobin, mean (SD), mmol/mol	40 (8.9)	40 (9.7)	40 (8.1)
EuroSCORE II, median (IQR), %	1.27 (0.89–1.97)	1.22 (0.84–1.93)	1.34 (0.90–2.05)
Left ventricular function < 50%, No. (%)	64 (25)	34 (26)	30 (23)
Type of surgery, No. (%)			
CABG-only procedure	92 (35)	46 (36)	46 (35)
Single non-CABG procedure	102 (39)	52 (40)	50 (38)
Combined procedures	67 (26)	31 (24)	36 (27)
Duration of surgery, median (IQR), min	222 (165–293)	222 (162–276)	219 (169–308)
Type of anaesthesia maintenance, No. (%)			
Propofol	16 (6)	8 (6)	8 (6)
Sevoflurane	245 (94)	121 (94)	124 (94)

There were no significant differences between the two treatment groups for any of the baseline characteristics. ASA=American Society of Anesthesiologists, CABG=Coronary artery bypass surgery.

Echocardiography

Preoperative echocardiographic assessment of left ventricular function was reported for all included patients; however, postoperatively echocardiography was available in only 65% (170) of patients. Echocardiography was performed at a median of 4 days (IQR 3-5) after surgery. Baseline characteristics of the cohorts with and without an available echocardiographic assessment revealed no significant differences, except for the type of surgery; patients without postoperative echocardiography underwent coronary artery bypass graft surgery (CABG)-only procedures in 77% of cases, while this procedure-type comprised only 20% of the cohort that had an echocardiography postoperatively (Supplementary Material). Assessment of right and left ventricular function preoperatively and within 30 days after surgery are visualised in figure 1. While left ventricular systolic function was comparable between groups preoperatively, we observed a higher rate of patients with a normal left ventricular systolic function in the liraglutide group compared to the placebo group (liraglutide: 59 patients (68%) vs placebo: 44 patients (53%), difference = 15% (95% CI 0–30, *P*=.049)). We observed no difference in right ventricular function.

Figure 1. Echocardiographic assessment of cardiac function before and after surgery.

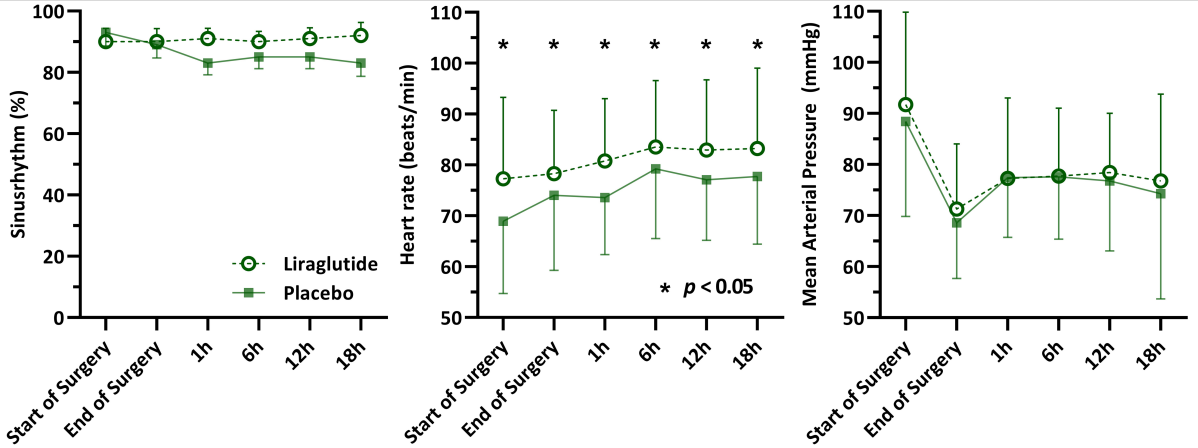


RV=right ventricle, LV=left ventricle.

Haemodynamics

Continuous measurement of heart rate, heart rhythm, and mean arterial pressure from the start of surgery for up to 18 hours after surgery were available for 81% (212) of patients (figure 2). Mean postoperative heart rate was significantly higher in the liraglutide group, with a heart rate of 83 (±11) beats/min compared to 77 (±11) in the placebo group, (difference=6; 95% CI 3–8, *P*<.001). There was no difference in mean arterial pressure at any of the time points. At every postoperative time point, most patients had sinus rhythm (>83%) without statistically significant differences between the groups (figure 2). On the ICU, 74% (192) of patients received norepinephrine, 7% (19) dobutamine, and 7% (18) milrinone. The number of patients receiving vasoactive/inotropic support and the respective doses of different drugs did not differ between groups (Supplementary Material).

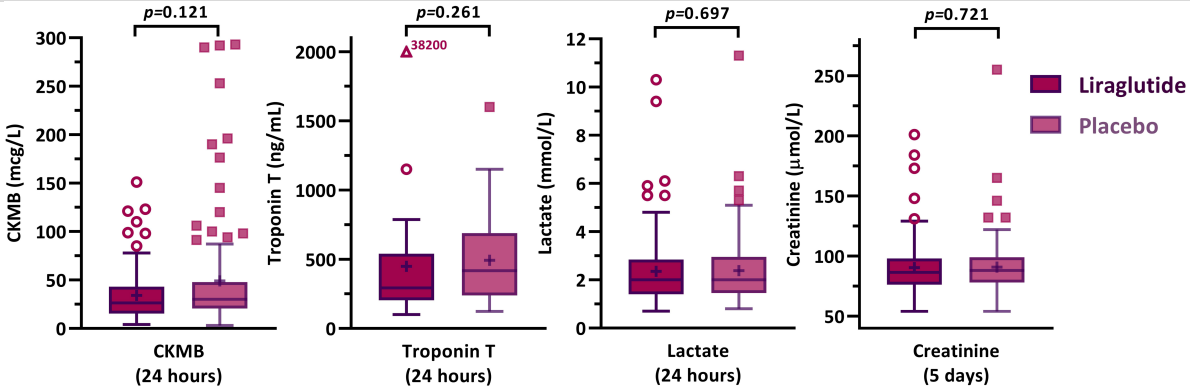
Figure 2. Perioperative haemodynamic measurements.



Biomarkers

To monitor postoperative myocardial ischaemia, one of the four involved centres used troponin measurements (48 patients) while the other three centres measured CK-MB postoperatively (213 patients). Peak values of both markers revealed no significant differences between the liraglutide and placebo group (figure 3). Likewise, we found no between-group difference in peak and mean lactate and creatinine levels (Supplementary Material).

Figure 3. Postoperatively measured biomarkers, peak concentrations.



Discussion

This analysis of cardiac outcomes of a randomised controlled trial suggests that liraglutide might better preserve myocardial function after cardiac surgery. Echocardiographic assessments revealed that more patients had a normal left ventricular systolic function when treated preoperatively with liraglutide, compared to patients in the placebo group in which more patients had a reduced cardiac function postoperatively. In addition, we observed an increased heart rate in liraglutide treated patients, but no differences in mean arterial pressure. Other markers of short-term cardiac function such as vasoactive/inotropic support or levels of biomarkers seemed unaffected by pre-operative liraglutide treatment.

Studies on GLP-1 induced cardioprotection are limited, and all used different combinations of patient populations (with variability in cardiovascular health), incretin interventions (with differing GLP-1 receptor agonistic mechanisms) and cardiac outcome (using various imaging techniques and biomarkers).[6] Our current study differs from previous studies on most of these aspects. Many previous studies analysed patients with ischaemia-induced cardiac injury after percutaneous coronary interventions. GLP-1 infusion improved LV ejection fraction determined by echocardiography following successful percutaneous coronary intervention (PCI),[7] and it reduced left ventricular dysfunction after balloon occlusion.[8] In a later study, a six-hour exenatide infusion after PCI reduced infarct size on cardiac magnetic resonance imaging.[14] Also, twice daily exenatide (a GLP-1 receptor agonist) for 72 hours reduced infarct size on cardiac magnetic resonance imaging and cardiac biomarker release.[15] However, both studies observed no functional differences in echocardiography.[14,15] While we did find a better echocardiographic function in the liraglutide group, compared to placebo, our population consisted of patients undergoing cardiac surgery, in which the release of biomarkers is caused mostly by direct surgical injury to the cardiac muscle, contrasted by ischaemia-induced release during PCI. In addition, biomarker release varies according to the magnitude and number of surgical interventions. Based on the measurement of biomarkers of cardiac injury, we detected no evidence of cardioprotection in our study. Unfortunately, other techniques used before, such as cardiac magnetic resonance imaging, were unavailable in our patient population due to the reliance on routine clinical diagnostics for the outcome of this sub-study.

Another difference with previous studies is the type of GLP-1 RA studied. While we performed the first randomised trial using liraglutide in patients undergoing cardiac surgery,[2] Besch et al. randomised patients undergoing CABG to either a continuous exenatide infusion or insulin for glycaemic control.[16] Similar to our present study, the authors performed an analysis of cardiac outcomes and found no difference in postoperative troponin levels nor in the incidence of reduced LV ejection fraction between treatment and control groups.[17] Of note, the primary outcome of this trial (time spent within the glycaemic target range) also did not reach a significant difference between groups.[16] In contrast, liraglutide proved effective in improving glycaemic control during cardiac surgery in our patient population,[2] and the current analysis also reveals a signal of improved cardiac outcomes.

Indications of beneficial effects on cardiac outcomes are not only based on preclinical data and the aforementioned studies of ischaemia-induced cardiac injury. Currently, indications of GLP-1 mediated cardioprotection are reinforced by the results from large cardiovascular outcome trials in patients with diabetes mellitus. In the LEADER trial, patients with diabetes mellitus randomised to receive liraglutide had lower rates of major adverse cardiovascular events, including cardiovascular death, compared to placebo.[10] Similarly, dulaglutide, another

long-acting GLP-1 RA, reduced the composite incidence of myocardial infarction, stroke and cardiovascular death.[11] Haemodynamically, both trials observed an increase in heart rate and a reduction in mean arterial pressure in the intervention group. In the present study, the most statistically robust findings were also the higher heart rates observed in the liraglutide group. This effect has been consistently demonstrated in previous studies,[16–19] and GLP-1 receptors have been found in the sinoatrial node.[10,20,21] Some authors have found GLP-1 RAs to induce vasodilation and microvascular recruitment, resulting in lower systemic vascular resistance[21] as well as an atrial natriuretic peptide-mediated reduction of systolic and diastolic blood pressures.[4] Although we found no differences in mean arterial pressure (with a concurrent increase in heart rate in the liraglutide group), the available data are insufficient to infer whether this is due to a reduction in systemic vascular resistance, cardiac preload or contractility.

Limitations

This study has some limitations: it is a secondary analysis of a randomised clinical trial. As such, results should be interpreted cautiously and only as supportive evidence of the hypothesis that GLP-1RA might improve cardiovascular outcomes after cardiac surgery. Secondly, outcomes were collected from echocardiographic, haemodynamic and laboratory data coming from routine clinical care, and therefore some parameters suffered from missing data. Specifically, follow-up of valve surgery more often included echocardiography, compared to CABG-only procedures. However, the cohorts of patients with and without postoperative echocardiography had comparable baseline characteristics. Thus, we deemed it unlikely that a significant bias influenced the decision of whether or not postoperative echocardiography was performed. Furthermore, while an echocardiographic study was performed in most patients postoperatively, only qualitative assessments of cardiac function were consistently reported, and more quantitative measurements were not available.
In conclusion, liraglutide administered before cardiac surgery modestly improved postoperative cardiac function. It altered immediate haemodynamics (increased heart rate) and better preserved left ventricular function on echocardiography at postoperative follow-up. This warrants further investigation of liraglutide in larger trials of cardiac surgery patients with a primary focus on postoperative cardiovascular outcomes.

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Eight

Preoperative considerations of new long-acting Glucagon-Like Peptide-1 Receptor Agonists in type 2 diabetes mellitus

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Abstract

Recently, long-acting once-weekly preparations of Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have come to the market. These drugs are used as a second-line treatment option in patients with diabetes mellitus type 2. GLP-1 RAs reduce hyperglycaemia by stimulating insulin secretion and reducing glucagon concentrations in a glucose-dependent matter. In addition, during the first months of treatment they reduce gastric emptying, while the inhibitory effect on food intake due to stimulation of satiety mechanisms in the Central Nervous System (CNS) seem to be a more chronic effect. Both these effects also contribute to the glucose-lowering efficacy of GLP-1 RAs. Clinical studies in diabetic patients have shown a beneficial safety profile for these drugs regarding glucose homeostasis, while they additionally reduce major cardiovascular events in high-risk patients. Furthermore, perioperative studies applying long-acting GLP-1 RAs showed better glycaemic control compared to placebo or standard care with insulin in the perioperative period without a higher risk for developing hypoglycaemia. Side effects, most frequently gastro-intestinal of nature, are mostly mild and diminish over time. Historically, all non-insulin glucose lowering medications are stopped on the day of surgery. However, stopping these once weekly preparations would require stopping the respective medication several weeks preoperatively. This is not only impractical but would also lead to inadequate glycaemic control for a prolonged period. Furthermore, in light of the current evidence continuation of these drugs is likely a safe practice, with regard to glycaemic control and the initial side effect of reduced gastric emptying. We would therefore recommend our colleagues to continue all GLP-1 RAs during the perioperative period.

Introduction

The current preoperative recommendation for the use of non-insulin glucose-lowering treatment is to withhold this medication on the day of surgery.[1,2] The reasons are variable for different preparations and involve the risk of hypoglycaemia, lactic acidosis, and keto-acidosis. Until recently, all the drugs involved had short half-lives, they were taken once or multiple times daily, and washed-out within one day. This enabled the one-size-fits-all recommendation, that is now well-known and well-adhered to.[3] However, recently advances in diabetes treatment include once-weekly preparations of long-acting glucagon-like peptide-1 receptor agonists (GLP-1 RAs). This prompts anaesthesiologists to reconsider their current practice of stopping anti-diabetic medication. We believe that the benefits of perioperative continuation outweigh the risk of withholding these medications, and therefore propose a non-withholding policy for all GLP-1 RAs.

Glucagon-Like Peptide-1 Receptor Agonists

Endogenous GLP-1 is a gut-derived incretin hormone that reduces glycaemia by stimulating insulin production and secretion in pancreatic beta cells and reducing glucagon secretion in alpha cells. In addition, GLP-1 inhibits gastric emptying, and reduces appetite and food intake which contribute to glucose lowering.[4,5] Importantly, the pancreatic effects of GLP-1 only operate during hyperglycaemia, making the risk for hypoglycaemia extremely low.[4] Endogenous GLP-1 has a half-life of several minutes and is rapidly broken down in the body by di-peptidylpeptidase-4 (DPP-4). The first generation of GLP-1 RAs (e.g. exenatide, lixisenatide) was designed to resist DPP-4-breakdown and could be administered once-daily.[5] Second generation GLP-1 RAs (e.g. liraglutide, dulaglutide) have a higher protein-binding thereby reducing their renal clearance, and further prolonging their half-life.[5] In the last decade, GLP-1 RAs came to the market as a second-line treatment option for type 2 diabetes

mellitus.[4] Besides established efficacy in improving glucose control, enthusiasm for these medications increased with the findings of large cardiovascular outcome trials (CVOT).[6–11]

Cardiovascular outcomes in diabetes mellitus type 2

The long-term CVOTs with GLP-1 RAs were designed to prove cardiovascular safety. All CVOTs confirmed that GLP-1 RAs are safe and did not increase the long-term risk of major cardiovascular adverse events (MACE).[12] What was even more important from these early studies is that several studies actually showed a reduction in risk of MACE with GLP-1 RAs compared to standard treatment. The most important findings from these trials are summarised in Table 1.

Table 1. Overview of currently available GLP-1 RAs with most relevant characteristics and trial findings.

	Duration of action		Effectiveness		Reference
Drug	**Half life**	**Dosing frequency**	**HbA1c lowering mmol mol^{-1}**	**Major Adverse Cardiovascular Events**	**Cardiovascular Outcome Trial**
Lixisenatide	2.5 hours	Daily 10-20 mcg	3 (2 – 3)	Non-inferior to placebo (HR=1.02, 95% CI=0.89–1.17, P=0.81*)	ELIXA[8]
Exenatide	3 hours	Twice daily 5-10 mcg / Weekly 2 mg**	8 (7 – 8)	Non-inferior to placebo (HR=0.91, 95% CI=0.83–1.00, P=0.06*)	EXSCEL[11]
Liraglutide	12.5 hours	Daily 1.8 mg	5 (4 – 5)	Superior to placebo (HR=0.87, 95% CI=0.78–0.97, P=0.01*)	LEADER[9]
Albiglutide	5 days	Weekly 30-50 mg	8 (7 – 8)	Superior to placebo (HR=0.78, 95% CI=0.68–0.90, P=0.006*)	HARMONY[12]
Dulaglutide	5 days	Weekly 1.5 mg	7 (6 – 7)	Superior to placebo (HR=0.88, 95% CI=0.79–0.99, P=0.026*)	REWIND[13]
Semaglutide	7 days	Weekly 0.5-1.0 mg	11 (10 – 12)	Superior to placebo (HR=0.74, 95% CI=0.58–0.95, P=0.02*)	SUSTAIN-6[10]

*for superiority, ** originally a once-daily formulation, now available as prolonged release injection for once-weekly.

Cardiovascular effects

The observed cardioprotective effects of GLP-1 RAs have resulted in extensive research on their effects on cardiovascular physiology, with many postulated mechanisms.[13] The most consistently reported finding is the expression of GLP-1 receptors in the sinoatrial node.[12] Although this explains the increased heart rate found in all studies administering GLP-1 RAs, it is unlikely to be the explanation for any of the cardioprotective properties.[12,14] So far, cardioprotective mechanisms are poorly understood. Animal studies showed increases in myocardial metabolic efficiency of glucose usage, lower vascular resistances in pulmonary and systemic circulations and activation of ischaemic preconditioning pathways.[13,14] In humans, the relevance of these findings remains unclear, despite some promising results of improved left ventricular function and reduced infarct size after ischaemic injury in GLP-1 RA treated subjects.[15,16] What remains, however, are the findings from major CVOTs (Table 1) that found clear cardiovascular benefits with reduced rates of myocardial infarction, stroke and revascularisation procedures. [7,8,10,11]

Gastro-intestinal side-effects

The most commonly reported side-effects of GLP-1 RAs are gastro-intestinal, such as nausea, vomiting and diarrhoea.[4] In the SUSTAIN trial, 52% of patients reported gastro-intestinal side-effects in those receiving semaglutide compared to 35% in the placebo group, resulting in discontinuation of medication in 14% and 8% of patients, respectively.[17]
Nausea and vomiting are explained by direct central effects of GLP-1 as well as delayed gastric emptying. Both effects decrease over time with ongoing treatment, due to tolerance and tachyphylaxis.[5,18–22] After eight weeks of treatment with liraglutide (a long-acting GLP-1 RA), gastric emptying returned to near baseline values.[21] Of note, contrasting effects have been found with shorter acting GLP-1 RAs that retained delayed gastric emptying over time.[21] Although associated with reduced oral intake and a beneficial loss of weight in overweight and obese patients, these effects might worry anaesthesiologists, for the theoretically increased risk of aspiration. However, although commonly reported by patients, these symptoms are mostly mild in nature, are rarely a reason for discontinuation of therapy, and seem to decrease over time with ongoing treatment.[4,23–25] While gastrointestinal side-effects occurred commonly in the large CVOTs, most were reported in the first weeks after initiation and they only lead to discontinuation of treatment in 1-3% of cases.[7,8] On the ICU, GLP-1 was also found to decrease gastric motility, although its effect was minimal when gastric emptying was already delayed.[26] In patients with diabetes, gastroparesis is already a known complication that requires attention and appropriate action by the anaesthesiologist. Postoperatively, gastrointestinal upset remains a common concern for the anaesthesiologists. Despite the fact that surprisingly few perioperative studies recorded this outcome,[27] it is reassuring that GLP-1 RAs do not appear to further increase the risk of post-operative nausea and vomiting (PONV).[28–30] We performed two randomized trials studying preoperative liraglutide administration, including over 400 patients. In both trials, the liraglutide intervention group did not report significantly higher rates of nausea or vomiting, compared to non-GLP-1 groups, neither before nor after surgery.

GLP-1 in perioperative care

Recently, several studies investigated different GLP-1 RAs in the perioperative period, showing its efficacy in improving glycaemic control.[27] The first two studies used a continuous infusion of GLP-1 during Coronary Artery Bypass Grafting (CABG) which resulted in lower perioperative glucose levels.[31,32] A continuous exenatide (first generation, short acting GLP-1 RA) infusion during CABG also reduced blood glucose levels and insulin requirements, during and after surgery.[30,33] Liraglutide (second generation, longer acting GLP-1 RA) administered before surgery was effective in lowering glucose and insulin requirements in cardiac surgery as well as in patients undergoing non-cardiac surgery.[28,34] Although not appropriately powered, none of these studies observed a difference in adverse effects or complications. Meta-analysis of perioperative studies revealed no increased incidence of hypoglycaemia for perioperative GLP-1 RAs usage.[27]

Perioperative recommendations

The use of GLP-1 RAs in patients with diabetes mellitus is growing. As a result, anaesthesiologists will increasingly encounter patients using these medications. With the introduction of the newer long-acting GLP-1 RAs, taken once-weekly, the advice to stop these medications preoperatively needs to be reconsidered. Firstly, to stop long-acting GLP-1 RAs before surgery would be impractical. Discontinuation would require stopping ≥1 weeks in advance, affecting glycaemic control for a similar period. As patients are often seen only

shortly before surgery, this policy could lead to unnecessary postponement of surgery. In addition, worse preoperative glycaemic control is associated with a higher risk of postoperative complications.[35,36] Secondly, continuation of GLP-1 RAs perioperatively is likely a safe practice. GLP-1 improves glycaemic control by reducing the incidence of hyperglycaemia without increasing hypoglycaemia. Few side-effects have been reported and most are mild. While anaesthesiologists should be aware of the theoretical side-effects such as delayed gastric emptying and possible nausea and vomiting, GLP-1 RAs can be considered safe and effective in the perioperative period. So, although shorter-acting preparations could be withheld, we recommend our colleagues to continue all GLP-1 RAs during the perioperative period.

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Conclusion

Thesis summary and future perspectives

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This thesis focussed on the treatment of glucose in patients in the perioperative period. In Part I, we discussed current perioperative treatment and the influence of the type of diabetes. We also discussed the use of metformin as a preoperative treatment strategy for optimising perioperative glucose levels. Part II revolves around the use of glucagon-like peptide-1 for the treatment of stress hyperglycaemia, in patients with as well as without diabetes mellitus.

Part I

Chapter 1 provides a summary of the current treatment of patients with diabetes in the perioperative period in Dutch hospitals as it was reported by consultant anaesthesiologists in a survey. As the evidence behind perioperative recommendations for treatment of patients with diabetes is contradictory and scarce, it confirmed our suspicion that the reported practice in Dutch hospitals is highly variable with regard to treatment goals (such as glucose targets) and treatment modes (dose and way of insulin administration).

Chapter 2 explores the difference in glucose control before and after surgery between patients with type 1 and type 2 diabetes. First of all, we found that patients with type 1 diabetes had worse preoperative glycaemic control compared to patients with type 2 diabetes. Secondly, we observed that, while both cohorts were treated according to the same perioperative protocol, also in the postoperative period, patients with type 1 diabetes had worse glycaemic control, including higher incidences of hyperglycaemia as well as hypoglycaemia.

Chapter 3 studied the perioperative effect of metformin continuation before surgery. Most patients with type 2 diabetes take metformin as a first-line anti-hyperglycaemic agent. Preoperatively this is traditionally withheld due to concerns of metformin associated lactic acidosis. As clinical evidence shows the risk of lactic acidosis to be negligible, perioperative continuation of metformin is now considered safe by many. We hypothesised that continuation would have the benefit of improving perioperative glycaemic control. Surprisingly this was not the case in our randomised controlled trial, that showed similar perioperative glucose concentrations. Although the sample size was too small for conclusions on safety, lactic levels were also low and comparable in both groups.

Part II

Chapter 4 introduces the main subject of Part II, namely glucagon-like peptide-1 based treatment in the perioperative period. In this chapter we performed a systematic search and review of the literature, and summarize all studies using a form of incretin treatment in patients requiring intensive or perioperative care. We found that compared to placebo or standard care with insulin, incretin treatment improved glycaemic control. It reduced insulin requirements and lowered glucose concentrations without an increase in the incidence of hypoglycaemia. Although the involved studies were mostly small, it is reassuring that we observed no difference in complications such as nausea, vomiting, or more serious adverse effects.

In Chapter 5 we introduce our hypothesis and methodology behind the GLOBE trial, a study comparing the efficacy of liraglutide, a GLP-1 receptor agonist, to placebo in controlling perioperative glucose concentrations. We hypothesised that preoperative administration of

liraglutide would reduce intraoperative insulin administration, when guided by a protocolised insulin bolus algorithm.

The main results of this trial are reported in Chapter 6. Our hypothesis was confirmed with a clear difference between the intervention and placebo group for the primary outcome. Our secondary outcomes related to intra-operative and postoperative glucose concentrations also showed significant improvements in glycaemic control for the liraglutide group. Other secondary outcomes related to postoperative complications revealed no significant differences.

From physiological studies and large cardiovascular outcome trials in type 2 diabetes patients came evidence of cardioprotective effects associated with GLP-1 treatment. For this reason, we analysed postoperative outcomes related to cardiac function in a secondary analysis of the GLOBE trial in Chapter 7. In the patients who had a postoperative echocardiography, we found a higher percentage of patients with a normal left ventricular function in those that received liraglutide compared to the placebo. This finding from a sub-study of our primary trial should be viewed as hypothesis generating and further investigation into the perioperative cardioprotective properties of GLP-1 is required.

In recent years, longer-acting preparations, that are administered once-weekly, have been developed and are increasingly used by patients. In Chapter 8, we discuss this new medication-subclass, arguing, in line with the rest of Part II, that these medications are effective alternatives to insulin for treatment of glucose control in the perioperative period. We also, discuss various safety concerns and conclude that it is most pragmatic to continue GLP-1 RAs in those patients already taking these.

Future prospects

Since the development of the first non-insulin antihyperglycaemic medication, many different types of medication have been used for the treatment of type 2 diabetes mellitus. Currently a plethora of medications, most of which being discussed in this thesis, are regularly used in clinical practice. When considering a reduction of diabetes-related complications, two classes seem more effective than most, the SGLT2-inhibitors and GLP-1 receptor agonists. In perioperative medicine these are likewise promising, although most research so far has been done with GLP-1 based therapies.

The appeal of replacing or complementing insulin with GLP-1 in the perioperative period, is a long-acting, stable form of glucose control, without increasing the risk of hypoglycaemia. An idea that sounds nice in theory, but needs to be confirmed in practice, before changing clinical care. As we observed in Chapter 4 and 5 that the idea is at least efficacious in clinical practice, the next step should be to study significantly larger sample sizes. Based on the correlation between glucose dysregulation and postoperative complications such as infection, I hypothesise that an improvement of glycaemic control with GLP-1 will reduce those postoperative complications.

My arguments for this hypothesis are various. First of all, reflecting back on Part I, we observed that clinical practice is highly variable. Just in the Netherlands, between hospitals, not only the way in which glucose is controlled varies, but also to what degree and intensity. The labour-intensive aspect of measuring, treating and checking glucose further contributes

to inter-physician variation in adherence to any glycaemic control protocol. Therefore, the mere simplicity of a once-daily or even once-weekly administration that can be prescribed to all at risk of stress-hyperglycaemia, could reduce perioperative hyperglycaemia. Secondly, the pharmacodynamic mechanism of GLP-1 reduces the risk of hypoglycaemia, which is besides hyperglycaemia, also independently associated with postoperative complications. Lastly, GLP-1 has been hypothesised to possess various glycaemia-independent organ-protective properties. The reduced incidence of myocardial infraction and cardiac death, as well as less progression of chronic renal insufficiency, indicate possible cardio-reno-protection. Especially in a higher-risk population, based on medical history as well as type of surgery, postoperative myocardial infarction and acute kidney injury, are among the most common complications.

So, to follow-up on the research of this thesis, a larger clinical trial powered on a reduction of complications is needed to prove that GLP-1-based therapy can improve perioperative care in a meaningful way. Alas, such a study is no simple undertaking and would require overcoming several significant obstacles. Today, research in clinical practice is more costly than ever before and a large trial requires more funding than what is commonly obtained in the field of anaesthesiology. Furthermore, the period available to the anaesthesiologist for exerting any control over a patient, is traditionally limited to the time of surgery. These mere few hours are unlikely sufficient to have any significant effect on relevant outcomes. This is a dual challenge. On the one hand it prevents us from having any lasting impact, while on the other hand, we should accept the challenge and expand our (time) zone of influence. By preoperative optimisation of our patient's health form the time of stating the intent for surgery, and through involvement in the postoperative care, the anaesthesiologist could have an impact on a very crucial period of time in a patient's life. This would in turn require intensification of our collaboration with many other disciplines in the hospital, which in turn will be quite demanding, yet rewarding too. So, daunting as it may be, for anaesthesiologist to survive as clinical researchers, we need to find ways to overcome these obstacles. I hope to be part of a group that will.

Conclusie

Samenvatting en toekomstperspectief

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Deze thesis concentreert zich op de perioperatieve behandeling van suikerziekte. In Deel I behandelen we de huidige perioperatieve behandeling en de invloed van het type suikerziekte. We gaan ook in op het gebruik van metformine als preoperatieve behandeling voor het optimaliseren van perioperatieve suikerconcentraties. Deel II, gaat over het gebruik van "Glucagon-Like Peptide-1" voor de behandeling van stress hyperglycaemie in patiënten met en zonder suikerziekte.

Deel I

Hoofdstuk 1 geeft een samenvatting van de huidige perioperatieve behandeling van patiënten met suikerziekte in Nederlandse ziekenhuizen, zoals deze werd gerapporteerd door anesthesiologen in een enquête die we hebben uitgevoerd. Het bewijs voor de perioperatieve behandeling van suikerziekte is schaars en variabel. Onze verwachting dat de gerapporteerde praktijk dit zou reflecteren, werd dan ook bevestigd. We vonden een grote variabiliteit in de gehanteerde bloedsuiker doelen als ook in de behandeling daarvan.

Hoofdstuk 2 verkent de verschillen in glucosecontrole voor en na chirurgie tussen patiënten met suikerziekte type 1 en 2. We vonden in patiënten met type 1 een slechtere preoperatieve suikercontrole in vergelijking met de patiënten met suikerziekte type 2. In de periode tijdens en na de operatie werden alle patiënten behandeld volgens hetzelfde perioperatieve protocol. Desalniettemin vonden we ook in deze periode dat de type 1 patiënten slechter gecontroleerd waren dan de type 2 patiënten, met zowel een hogere incidentie van te lage als te hoge bloedsuikerspiegels.

Hoofdstuk 3 bestudeert het perioperatieve effect van het doorgeven van metformine voor een operatie. De meeste patiënten met suikerziekte gebruiken metformine als eerstelijnsbehandeling voor bloedsuikercontrole. Traditioneel wordt dit gestopt voor de operatie vanwege zorgen rond metformine geassocieerde melkzuur acidose. Bewijs uit klinische studies heeft laten zien dat dit risico verwaarloosbaar is. Het doorgebruiken van metformine wordt daarom nu door velen als veilig gezien. Het was onze hypothese dat het doorgebruiken van metformine voordelig zou zijn voor deze patiënten omwille van een betere glucosecontrole rond de operatie. In onze gerandomiseerde studie zagen we echter vergelijkbare bloedsuikerspiegels. Hoewel de studie te klein was om uitspraken te doen over veiligheid, waren de melkzuur waarden laag en vergelijkbaar tussen de groepen.

Deel II

Hoofdstuk 4 introduceert het hoofdonderwerp van Deel II, namelijk de behandeling met "Glucagon-Like Peptide-1" in de perioperatieve periode. In dit hoofdstuk hebben we een systematische zoektocht en samenvatting van de literatuur uitgevoerd. We vatten alle studies samen die een vorm van incretine behandeling bestudeerden in patiënten die intensieve of perioperatieve zorg nodig hadden. We vonden dat in vergelijking met placebo of standaard zorg met insuline, behandeling met incretines glucosecontrole verbeterde. Het verminderde de insulinebehoefte en verlaagde bloedsuikerspiegels zonder een verhoging in de incidentie van hypoglycaemie. Hoewel de geïncludeerde studies veelal klein waren, was het geruststellend dat er geen verschil in complicaties werd geobserveerd zoals misselijkheid, braken of zwaardere bijwerkingen.

In hoofdstuk 5 introduceren wij onze hypothese en methodologie achter de GLOBE trial, een studie die de effectiviteit in glucosecontrole vergelijkt tussen liraglutide, een GLP-1 receptor

agonist, en placebo. Het was onze primaire hypothese dat behandeling met liraglutide voor een hartoperatie de behoefte aan intra-operatieve insuline zou verlagen, wanneer deze werd gestandaardiseerd door een geprotocolleerd insuline-bolus algoritme.

De primaire resultaten van deze studie rapporteren wij in Hoofdstuk 6. Onze hypothese zoals hierboven werd bevestigd met een duidelijk verschil tussen de interventie en placebogroep voor het primaire eindpunt. Onze secundaire eindpunten gerelateerd aan perioperatieve bloedsuikerspiegels lieten ook significante verbeteringen in glucosecontrole zien voor de liraglutide groep. Dit vertaalde niet in een significant verschil in andere secundaire eindpunten gerelateerd aan postoperatieve complicaties.

Vanuit fysiologische studies en cardiovasculaire uitkomst studie in suikerziekte type 2 patiënten kwam naar voren dat GLP-1 behandeling is geassocieerd met cardio-protectieve effecten. Daarom hebben we in Hoofdstuk 7, separaat, de postoperatieve uitkomsten gerelateerd aan hartfunctie geanalyseerd. In de groep van mensen die een postoperatieve echocardiografie ondergingen, vonden we een hoger percentage patiënten met een normale linkerventrikelfunctie in de groep die liraglutide kreeg in vergelijking met hen die placebo kregen. Deze bevinding, in een substudie van ons primaire onderzoek, moet gezien worden als hypothese genererend, waarna verder onderzoek naar de cardio-protectieve effecten van behandeling met GLP-1 nodig is.

In de laatste jaren, kwamen er meer langer-werkende GLP-1 agonisten op de markt, die eens per werk gegeven worden. In hoofdstuk 8 bediscussiëren we deze nieuwe subklasse van medicatie. We beargumenteren in lijn met de rest van Deel II, dat deze medicatie effectieve alternatieven voor insuline zijn, ook in de perioperatieve periode. Verder behandelen we de verschillende veiligheidsaspecten van deze medicatie en concluderen dat het meest pragmatisch is om GLP-1 receptor agonisten door te geven in patiënten die deze reeds gebruiken.

Toekomstperspectieven

Sinds de ontwikkeling van de eerste non-insuline bloedsuikerverlagende medicatie, zijn veel verschillende medicamenten gebruikt voor de behandeling van suikerziekte type 2. Op dit moment wordt een breed repertoire van medicatie gebruikt, waarvan demeeste voorkomen in de discussie in deze thesis. Wat betreft het verlagen van de suikerziekte-gerelateerde complicaties lijken twee klassen van medicatie meest effectief: de SGLT2-inhibtoren en GLP-1 receptor agonisten. In de perioperatieve zorg lijken deze ook veelbelovend, hoewel vooralsnog het meeste onderzoek gedaan is naar GLP-1 therapieën.

De aantrekkelijkheid van het vervangen of complementeren van insuline met GLP-1 in de perioperatieve zorg is een langwerkend, stabiele glucosecontrole, zonder het verhogen van het risico op hypoglycaemie. Een idee dat in theorie aantrekkelijk is, maar nog moet worden bevestigd in de praktijk, alvorens klinische zorg kan worden aangepast. Zoals wij zagen in Hoofdstuk 4 en 5 is dit idee in ieder geval effectief in de klinische praktijk. De volgende stap zou moeten zijn, om significant grotere patiëntengroepen te onderzoeken. Gebaseerd op de correlatie tussen glucosedysregulatie en postoperatieve complicaties zoals infecties, zou mijn hypothese zijn dat een verbetering van bloedsuikercontrole met GLP-1 postoperatieve complicaties zou kunnen verminderen.

Mijn argumenten voor deze hypothese zijn verschillende. Ten eerste, terugkijkend op Deel I, observeerden we dat de klinische praktijk zeer variabel is. Alleen al binnen Nederland is er tussen verschillende ziekenhuizen grote variatie in de manier en intensiteit van glucose controle perioperatief. Het arbeidsintensieve aspect van meten, behandelen en controleren van glucose is een complicerende factor voor verschil tussen individuele artsen in het volgen van interne richtlijnen. Daarom zou de eenvoud van een eens per dag of eens per week medicatie een waardevolle bijdrage kunnen leveren aan het standaardiseren en stabiliseren van perioperatieve bloedsuikerspiegels. Ten tweede, de farmacodynamiek van GLP-1 receptor agonisten vermindert het risico op hypoglycemie, welke naast hyperglycemie tevens een onafhankelijke associatie heeft met postoperatieve complicaties. Ten slotte, bezit GLP-1 verschillende glucose-onafhankelijke orgaan-beschermende eigenschappen. De verminderede incidentie van myocardinfarcten en cardiovasculaire mortaliteit alsook de lagere progressie naar chronische nierinsufficiëntie geven een mogelijk acuut cardio-renaal protectief effect aan. Met name in een hoog-risico populatie zijn postoperatieve myocard ischemie en acuut nierfalen de meest voorkomende postoperatieve complicaties.

Dus, in opvolging van het onderzoek in deze thesis, een grotere klinische studie, gepowered op een reductie van complicaties zou nodig zijn om te bewijzen dat GLP-1 therapie de perioperatieve zorg kan verbeteren. Helaas is een dergelijke studie geen simpele opgave die een aantal significante obstakels zou moeten overkomen. Vandaag de dag is klinisch onderzoek kostbaarder dan ooit tevoren, en een voldoende grote klinische studie kost daarom meer dan wat gemiddeld wordt geworven binnen de anesthesiologie. Verder, de tijd dat een anesthesioloog betrokken is bij de zorg is gelimiteerd tot enkele uren. De korte tijd is waarschijnlijk onvoldoende om met een dergelijke interventie een belangrijk effect te bewerkstelligen. Deze uitdaging heeft twee kanten. Momenteel beperkt het anesthesiologen in hun impact op relevante uitkomsten. Anderzijds kunnen we de uitdaging aangaan door onze periode van invloed te verlengen. Door vanaf ons eerste consult, preoperatieve optimalisatie te starten en grotere betrokkenheid in de postoperatieve periode kan de anesthesiologie waarschijnlijk haar impact vergroten in deze kritische periode in het leven van haar patiënten. Hiervoor zullen we nauwer moeten samenwerken met andere disciplines. Hoewel een uitdaging, is dit mijns inziens noodzakelijk om als klinisch onderzoekers relevanter te worden. Ik hoop onderdeel te zijn van een onderzoeksgroep dit zal bewerkstelligen.

Appendices

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Biography

Abraham Hulst was born 13th March 1987 in Wageningen, the Netherlands. He attended primary school in Bennekom and Hilvarenbeek and secondary education at the St-Odulphuslyceum, Tilburg. He went on to study medicine at the KU Leuven where he graduated, magna cum laude, in 2013. He started his training in anaesthesiology in 2014 at the Academic Medical Centre, Amsterdam. He finished his training on his 33rd birthday in 2020. He combined his training with a career in clinical research leading to his PhD in 2022. At the end of his PhD, he was awarded a Rubicon grant from the Netherlands Organisation for Health Research and Development, and a Marie Skłodowska-Curie Fellowship from the European Commission. This funding enabled him to visit the Royal Melbourne Hospital and the Florey Institute of Neuroscience and Mental Health, Melbourne, for an 18-month postdoctoral research fellowship. Abraham has currently returned from Melbourne and works as an anaesthesiologist at the Amsterdam University Medical Centres, where he continues the work on his Marie Skłodowska-Curie Action as a postdoctoral researcher.

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Data curation & validation:	AHH
Formal analysis	AHH
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Writing—original draft	AHH, JH
Writing—review & editing	JH, MWH, JHDV, BP

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PhD Portfolio

BROK	1.0 ECTS
Practical Biostatistics (e-learning with exam)	1.1 ECTS
Advanced Topics in Biostatistics	2.1 ECTS
Endnote course	0.1 ECTS
Searching for a Systematic Review	0.1 ECTS
Clin Epid 1: Randomized Controlled Trials	0.6 ECTS
Clin Epid 2: Observational Epidemiology	0.6 ECTS
Clin Epid 3: Evaluation of Medical Tests	0.9 ECTS
Clin Epid 4: Systematic Reviews	0.7 ECTS
Scientific Writing in English for Publication	1.5 ECTS
Amsterdam Gastroenterology & Metabolism 2018	2.1 ECTS
Amsterdam Gastroenterology & Metabolism 2019	2.1 ECTS
Cardiovascular Disease Annual Symposium 2019	1.5 ECTS
Total	14.4 ECTS

Epilogue

Kwalitatieve retrospectieve analyse van de periode 2014 tot 2022 uit het wetenschappelijke leven van Drs. Hulst - een dankwoord.

Abraham H. Hulst

Introductie

In dit laatste hoofdstuk rapporteer ik de resultaten van een retrospectieve kwalitatieve analyse op het tijdscohort van de academische carrière van Abraham Hulst. De primaire uitkomst was wetenschappelijke productiviteit, secundaire uitkomsten waren plezier van werk en kwaliteit van leven.

Methoden

Data zijn verzameld en geanalyseerd door de eerste en enige auteur. Data punten zijn retrospectief ingevuld en missende waarden door auteur geïmputeerd. Methodes van analyse zijn nooit eerder gerapporteerd of gevalideerd. Resultaten werden door middel van notities door auteur van kleur voorzien.

Resultaten

De grootste interactie factor op de primaire uitkomst werd gevonden voor de combineerde factor van alle deelnemende patiënten in dit werk. Zonder hen was niets van dit alles tot stand gekomen. *(Als onderzoeker lijkt deelname aan jouw studie altijd een zeer redelijk voorstel, maar in een tijd van onzekerheid over gezondheid, een naderende operatie en een overvloed aan informatie van medische medewerkers is dit geen klein verzoek. Dat er zo veel bereid waren met ons mee te werken, blijft een inspiratie om onze praktijk te blijven verbeteren.)*

Een tweede positieve interactie werd gevonden voor alle clinici die meewerkten aan onderzoek in het ziekenhuis. *(Helaas ziet niet iedereen onderzoek als een kerntaak van ieder ziekenhuis en wordt de extra belasting graag tot probleem van de verantwoordelijke onderzoeker gemaakt. Ik ben daarom dankbaar voor iedere clinicus die mij en mijn collega's welkom heette in zijn werkomgeving en ons assisteerde in ons werk.)*

Secundaire analyse liet zien dat deze interactie het sterkst was voor een speciale groep collega's: het cohort van de GLOBE-study groep. *(Bas, Thierry, Mark, Bram, Arthur, Mark en al jullie collega's – geweldig bedankt voor al jullie hulp en ondersteuning. Ik hoop dat we in de toekomst nog vaker samen zullen werken en de wereld kunnen blijven tonen dat een belangrijk deel van klinisch onderzoek juist buiten de academie plaatsvindt.)*

Er werd een spurieuze correlatie gevonden voor de termen *[professor]*[Duitsland].* Drie professoren kwamen uit Duitsland speciaal om mijn carrière met hun wijsheid bij te staan – de dataset was ontoereikend om een alternatieve hypothese te testen. *(Wolfgang, Markus en Benedikt, waar de begeleiders genoemd worden in het dankwoord, is vaak de plek waar je door de regels heen leest dat de promotie niet altijd een makkelijke periode was. Ik ben blij te kunnen zeggen dat dit voor mij absoluut niet het geval was. Het blijft een plezier om met en voor jullie te werken. Bedankt voor alle ruimte, verantwoordelijkheid en vertrouwen die jullie mij gunden.)*

De vierde professor in de dataset vertrok juist naar Duitsland maar hield desalniettemin een grote invloed. (*Hans, je begeleiding en geduld voor nóg een niet-internist die zich tegen de endocrinologie aan bemoeid, is te prijzen. Je gave om een manuscript volledig rood, met inhoudelijke verbeteringen, in een paar uur terug te sturen, begeleid door een altijd positieve e-mail, is een testament van compassie. In Jeroen heb je bovendien de beste mentor opgeleid die ik me kon wensen.*)

De sterkste positieve correlatie met enig succes in mijn carrière kwam gek genoeg van een Amstelveense rockster met een Spaanse naam. (*Jeroen, bedankt dat ik aan jouw succestrein mocht aanhaken. Je enthousiasme voor onderzoek is aanstekelijk en je begeleiding frictieloos. Ik had dit onderzoek niet kunnen doen als jij de ideeën en middelen niet had gehad en ik had*

nooit mijn eigen centjes gekregen als jij me niet had laten zien hoe dat moest. Nieuwe gezamenlijke onderzoeksplannen blijven gelukkig komen, ook al doen we goed ons best niet in hetzelfde land te wonen. Ik kijk uit naar onze verdere samenwerking.)
Er was ook nog een groep factoren met vergelijkbare impact op de uitkomsten, deze waren eerder negatief op de primaire uitkomst (productiviteit), maar zeer positief op een secundaire (kwaliteit van leven). Ik aggregeerde dit cohort onder de term *[vrienden]. (Dit boekje is er eerder ondanks, dan dankzij jullie, een feit waarvoor ik iedereen zeer erkentelijk ben. Terug in Nederland hoop ik jullie allemaal weer snel en vaker te zien. Ik zie er naar uit deze mijlpaal met jullie te kunnen vieren. Beste Max en Roeland, ik ben vereerd dat jullie mij als paranimf wilden bijstaan. Het is lastig twee personen te vinden waar ik de afgelopen 17 jaar meer mee heb gedeeld. Laten we ondanks alle kinderen niet vergeten de komende jaren nog veel meer mooie avonturen op te zoeken.)*
Een cohort met grote overlap met *cohort:[vrienden]* met vooral positieve correlatie op de andere secundaire uitkomst (plezier van werk) werd gegroepeerd onder *[collega's]*. *(Zowel jullie samenwerking als afleiding werd enorm gewaardeerd. We hebben veel mooie en mindere momenten gedeeld, binnen en buiten de muren van het ziekenhuis. Je hebt een geweldige werkplek als je zoveel vrienden tussen jullie collega's treft)*

Discussie

In deze studie werden een aantal belangrijke invloeden op het werk van Abraham Hulst in de periode van 2014-2022 beschreven. Data waren subjectief en onderhevig aan ernstige achteraf-zicht bias, gezien de grote klinische relevantie werden ze echter toch het delen waard geacht.
Uiteraard kent dit werk enkele limitaties. Allereerst is dit een door tijd gelimiteerd cohort. Het is aannemelijk dat er belangrijke invloeden voorafgingen die onvoldoende in de data naar voor kwamen. De auteur wil met name twee factoren noemen: *[Chris]* en *[Coby]*. *(Lieve papa en mama, of het nu nature of nurture is, voor ieder succes ben ik jullie natuurlijk schatplichtig. In groep 4, was ik nog te afgeleid om fatsoenlijk te leren lezen en na groep 8 dacht de juf nog meer aan HAVO dan VWO. Dat ik uiteindelijk een academische carrière blijk te hebben, is niet in de laatste plaats te danken aan het feit dat jullie, op de vormende momenten, mij misschien beter kenden dan ik mijzelf.)* Een andere limitatie is de analyse van missende waarden. Hoewel voor het grootste deel van de het cohort de factor *[partner]* missende was, bleek na discussie van dit stuk dat deze toch van significante waarde was. (*Lieve Johanneke, ik ben dit boekje natuurlijk vooral dankbaar voor het verschaffen van enige balans in onze relatie. Als enige doctorandus in huis had ik natuurlijk geen enkele geloofwaardigheid in discussie met jou. Ik kijk er naar uit op gelijke voet met jou verder te kunnen en ben blij dat we een acceptabel academisch voorbeeld voor ons nageslacht hebben gezet. Op een serieuze noot ben ik je natuurlijk alle dagen dankbaar voor de duizenden manieren waarop je mijn leven verrijkt, niet in de laatste plaats door het beste cadeau dat je me hebt gegeven. Lieve Lieveke, je hebt in je korte leven al meer aandacht en verbeelding weten vast te houden dan dit hele proefschrift bij elkaar en ik kan niet wachten om te zien wat je nog allemaal gaat doen.*) In conclusie blijkt er eigenlijk sprake van zoveel correlerende factoren, dat de invloed van de veronderstelde primair drijvende factor van onbekende invloed kan worden verondersteld. Of zoals ik een bekende professor hoorde zeggen: *"The great power of science is that it allows people who are not genius level creatives to make advances in the generation of knowledge."* (Prof. J. Peterson) Dank aan eenieder die mij hierbij help. Het Nederlands tekortkomend; I will strive to pay it forward!