MANAGEMENT OF BLOOD GLUCOSE IN CRITICALLY ILL PATIENTS WITH PRE-EXISTING TYPE 2 DIABETES

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Abstract

This thesis comprises four distinct but complementary chapters on blood glucose management during critical illness, with a focus on management of patients with a pre-existing type 2 diabetes. The work submitted includes a narrative review, survey of clinical practice, study protocol and statistical analysis plan, and the conduct and report from a bi-national, multi-centre, parallel-group, randomised clinical trial.

Dysglycaemia, or disordered glucose metabolism, is almost ubiquitous with severe critical illness, with marked increases in endogenous glucose production and counter-regulatory responses. The magnitude of dysregulation is associated with severity of illness on presentation to hospital and subsequent mortality. Despite longstanding knowledge about these associations, the threshold at which hyperglycaemia causes harm remains unknown. There is a further complicating factor to understanding the relationship between hyperglycaemia and harm, is that over a quarter of patients admitted to intensive care units (ICUs) have type 2 diabetes, and a pre-existing disordered glucose metabolism. Evidence to inform the management of blood glucose in critically ill patients is predominately from studies conducted in sample populations that have only a small proportion of patients with pre-existing diabetes. This creates clinical uncertainty in discrete populations, such as those with type 2 diabetes *(Chapter 1.2)*. A survey of clinicians was performed to understand current practice and to determine whether they required further evidence to better care for patients *(Chapter 1.3)*.

Observational and exploratory studies have reported that patients with a higher HbA1c on ICU admission had a lower mortality rate if they had a modest elevation of blood glucose concentrations to >10 mmol/L during their ICU admission. Based on such data it is plausible that in patients with type 2 diabetes mild hyperglycaemia during critical illness is protective. Because hypoglycaemia has consistently been shown to be harmful to all patients, and the threshold blood glucose for harm may even be slightly greater in patients with pre-existing diabetes, 'personalising' or allowing for different blood glucose ranges based on an individual patient's pre-existing glucose metabolism has the potential to improve care. Exploratory studies indicate that such a personalised approach did not detect a signal for harm, although the studies included relatively small sample populations and study methodology risked bias, such that there was inadequate evidence to inform

practice. For these reasons, further evaluation using a rigorously designed randomised clinical trial was warranted *(Chapter 2.2)*.

Treatment of hyperglycaemia in critically ill patients typically utilises intravenous insulin, which poses a risk of causing hypoglycaemia if appropriate commencement and titration parameters are not selected. A pragmatic approach to achieving a more personalised target in patients with type 2 diabetes is to commence insulin at a greater blood glucose concentration (e.g., ≥14 mmol/L) and compare this to what occurs in usual practice (e.g., ≥10 mmol/L), which has been informed by trials conducted in populations predominately comprising patients without pre-existing diabetes. Given the strong relationships between harm and hypoglycaemia, hypoglycaemia is an appropriate outcome by which to measure the impact of an elevated commencement point for intravenous insulin administration *(Chapter 3.2)*. The multicentre, open label, randomised clinical trial was conducted in critically ill patients with pre-existing type 2 diabetes and established that day-28 incidence hypoglycemia (<4.0mmol/L) was significantly reduced by the intervention. While this study was not powered for patient-centred outcomes, there was no benefit in any of the clinical outcomes measured.

The implications for clinical practice from the trial conducted is that while optimal management of hyperglycaemia in critically ill patients with type 2 diabetes remains uncertain, current or usual practice should continue. Future trials may benefit from determination of a patients pre-existing glycaemia though HbA1c testing, as long as this can be conducted in a time efficient manner, and offers the potential to further personalise physiological targets. Technological advancements such as dynamic protocols, continuous blood glucose monitors and close-loop systems may offer the opportunity to achieve greater time within target ranges, and reduce the amount of time required to manage blood glucose. This has the potential to reduce the net cost while achieving optimal blood glucose management. Novel therapeutics, such as glucagon-like peptide-1 (GPL-1), may have innate properties that mitigate some of the limitations of intravenous insulin administration. These interventions have the possibility to improve patient outcomes and improve the care provided in intensive care units (*Chapter 4.2*).

In summary, this program of work has contributed new and important information in the fields of glycaemic management, acute glycaemic targets in critically ill patients with type 2 diabetes, and the implications of a personalised approach to blood glucose management.

List of Abbreviations

Abbreviation	Stands for
ADA	American Diabetes Association
ANZICS	Australian and New Zealand Intensive Care Society
ANZICS-CTG	Australian and New Zealand Intensive Care Society Clinical Trials Group
APACHE	Acute Physiological and Chronic Health Evaluation
BGL	Blood glucose level
CGM	Continuous blood glucose monitor
CI	Confidence interval
CoV	Coefficient of Variation
DPP-4	Dipeptidyl peptidase 4
DSMB	Data Safety Monitoring Committee
GIP	Gastric inhibitory polypeptide
GLP-1	Glucagon-like peptide 1
HbA1c	Glycated haemoglobin
HREC	Human Research Ethics Committee
ICU	Intensive care unit
IQR	Interquartile range
mmol/L	Millimole per litre
REDCap	Research Electronic Data Capture
SCCM	Society of Critical Care Medicine
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment
T2DM	Type 2 diabetes mellitus
USB	Universal serial bus

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time.

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Alexis Paul Poole

20 May 2023

Signature: _____

Date: 20-May-2023

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The project outlined in chapter 3.2 was undertaken at 16 hospitals across Australia and New Zealand. I am extremely grateful to the site investigators and research coordinators who diligently applied the study protocol and recruited participants. The altruism displayed by critically ill patients and their families who participated in this research is truly humbling. During a time of great vulnerability, they chose to contribute to research, hoping to improve the care of others. This work would not have been possible without their selflessness. My heartfelt thanks go out to them and their families.

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Format of Thesis

This thesis is by publication, supplemented by narrative, as per University of Adelaide Guidelines. The thesis comprises four distinct but complementary chapters each with a brief narrative introduction followed by the manuscripts and ending with a narrative conclusion of the major findings and future directions.

In total the thesis comprises four manuscripts; one review of the literature, one survey of current practice, one protocol and statistical analysis plan and one large randomised control trial. At the time of submission of this body of work, four of the manuscripts have been published. None of the manuscripts were solicited.

The four manuscripts are presented in the style of the publication to which they were submitted, accounting for the variance in manuscript structure, referencing style and heterogeneity in American and UK English. The references for all four publications are included in each respective manuscript and references for each chapter follow each section.

The Publications are as follows:

Alexis P Poole, M. Horowitz, and A. Deane. Optimal Glycemic Targets in Critically Ill Patients with Diabetes, Annual Update in Intensive Care and Emergency Medicine 2023
Relevant section in this thesis; Chapter 1.2

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Relevant section in this thesis; Chapter 3.2

Chapter 1:

Current approach to blood glucose management in critically ill patients with type 2 diabetes

1.1 INTRODUCTION

Hospitalised patients who are critically unwell are cared for in an intensive care unit (ICU). This is a specialised and highly-monitored area of the hospital, within which specialised care and rapid access to interventions is possible. During critical illness there are marked fluctuations in physiology. A prominent physiological derangement is disordered glucose metabolism (1).

Disordered glucose metabolism can occur in those without pre-existing metabolic abnormalities and was first recognised over a century ago (2). However, the severity of this disordered glucose metabolism is more pronounced in those with pre-existing diabetes. Despite the longstanding awareness of its existence, there remains uncertainty as to most appropriate treatment, particularly in those with pre-existing diabetes which, in the majority of ICU patients is type 2 diabetes (3).

The physiology of critical illness and the treatments administered in the ICU increase the frequency and magnitude of hyperglycaemia, hypoglycaemia and glycaemic variability in all patients (4). By convention the three domains of hyperglycaemia, hypoglycaemia and glycaemic variability are referred to as ‘dysglycaemia’. It appears that each individual domain is undesirable and this chapter will explore the current evidence underlying the management of dysglycaemia in critically ill patients with pre-existing diabetes, and outline future areas for investigation.

Hyperglycaemia (above ‘normal’ blood glucose concentrations) occurs frequently during critical illness in patients with pre-existing type 1 or type 2 diabetes. Hyperglycaemia also occurs in patients without pre-existing diabetes and in these patients is termed ‘stress hyperglycaemia’ or ‘critical illness-induced hyperglycaemia’. This taxonomy categorises patients who have normal glucose tolerance preceding and following the episode of acute

illness from those with pre-existing diabetes. The threshold blood glucose concentration that determines stress hyperglycaemia remains contentious but would logically be the minimum elevation at which harm occurs. However, conflicting data have resulted in considerable uncertainty. Despite this limitation, current guidelines consider a random plasma blood glucose threshold of 11.0 mmol/L.

The treatment of hyperglycaemia during critical illness has been evaluated in trials conducted since the 1990s. Earlier trials focused on treatment of hyperglycaemia in critically ill populations without consideration of whether it was stress hyperglycaemia or related to pre-existing diabetes. In these trials while patients with diabetes comprised between 15 and 40 percent of the study population they did not focus on this population. This has led to uncertainty as to how to treat hyperglycaemia in individuals with pre-existing diabetes.

Chapter 1 comprises two distinct sections. The first section is a manuscript is a book chapter summarising the current evidence and providing suggestions regarding clinical care. It should be appreciated that this manuscript was published after the LUCID trial was published (chapter 3) and references this trial. The second section is a manuscript details a survey that explored how clinicians currently manage disordered blood glucose levels in the context of critically ill patients with pre-existing type 2 diabetes. The context of this manuscript was vital to the design the LUCID trial.

1.1.1 **Objectives**

The objectives of the book chapter and survey were to describe treatment of dysglycaemia during critical illness.

1.2 BOOK CHAPTER

OPTIMAL GLYCAEMIC TARGETS IN CRITICALLY ILL PATIENTS WITH DIABETES

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By signing the statement of Authorship, each author certifies that:

The candidate's stated contribution to the publication is accurate (as detailed above);

Permission is granted for the candidate to include the publication in the thesis; and

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Introduction

Admission to an intensive care unit (ICU) can be precipitated by a variety of illnesses and injuries. Pre-existing diabetes markedly increases the risk of many of these illnesses [1]. Even in the absence of pre-existing diabetes, critically ill patients frequently develop hyperglycemia and insulin resistance, which has been termed 'stress hyperglycemia' [2]. Stress hyperglycemia is in part a reflection of the endogenous response to the illness or injury, including the secretion of counter-regulatory hormones, and treatments administered, including catecholamines, nutrition, and steroids, which exacerbate any disordered glucose metabolism induced by the illness or injury [3].

The rationale for treating hyperglycemia in the critically ill is underpinned by observational data consistently reporting strong associations between hyperglycemia and adverse outcomes, including increased mortality [4]. Whether such associations represent an epiphenomenon of critical illness or a causative relationship remains contentious [3].

There are observational data that glycemic variability, a metric describing the magnitude of glucose fluctuations over time, is an independent predictor of morbidity and mortality [5–7]. While a reduction in variability may be a surrogate marker for better provision of intensive care, these adverse outcomes could also reflect the harmful impact of rapidly fluctuating blood glucose concentrations, which is to induce apoptosis and increase cytokine production and oxidative stress [8, 9].

There are also well described relationships between hypoglycemia and adverse outcomes, and the impact of these physiological responses may be synergistic during episodes of critical illness. Hypoglycemia (<4.0 mmol/L) or even a single episode of severe hypoglycemia (<2.2 mmol/L) are independently associated with a greater risk of dying [10, 11].

The management of hyperglycemia in the ICU frequently involves administration of intravenous insulin [12], with the inherent risk of causing hypoglycemia as well as increased glycemic variability [13]. This is compounded by other risk factors such as, but not limited to, renal failure, sepsis, and calorie intake [14].

In this chapter, we review the management of hyperglycemia in critically ill adult patients with type 2 diabetes, which will be referred to as diabetes throughout. The following areas are the focus; early trials of glucose control during critical illness, current management guidelines, glucose metrics modified by diabetes, prevalence of diabetes in critically

patients, personalized approach to glycemic control, and recommendation for future research directions.

Early Trials of Glucose Control During Admission to the ICU

The apparent strong association between hyperglycemia and adverse outcomes in critically ill patients provided the rationale for a single center, open-label, parallel-group, randomized clinical trial of so-called 'intensive insulin therapy' in patients after major surgery admitted to an ICU [15]. Subsequently, large trials reported between 2001 and 2009 included patients irrespective of the presence of pre-existing diabetes. In the first trial [15], the intervention was 'intensive insulin therapy', which involved the strict treatment of hyperglycemia to maintain a blood glucose between 4.4 and 6.1 mmol/L with intravenous insulin. The investigators planned to include 2500 adult patients who required mechanical ventilation and primary outcome was all-cause mortality in the ICU, with secondary outcomes including in-hospital mortality and duration of ICU admission. The trial was stopped after 1548 participants due to a reduction in mortality in patients assigned intensive insulin therapy (intensive: 35 of 765 (4.6%) vs. comparator: 63 of 783 (8.0%); adjusted $p < 0.04$). Interim analyses were repeated at 3-month intervals and the trial stopped after the fourth analysis. While adjusting for repeated analysis, the p value did meet the set point for statistical significance; however, it should be appreciated that even with statistical adjustments for repeated analyses the risk of bias in an open-label trial remains [16]. The same investigators then conducted a single center, open-label, parallel-group, randomized clinical trial of 1200 patients from a medical ICU. Again, patients were eligible irrespective of previous diabetes. Between groups there was no statistically significant difference in the primary outcome of all-cause hospital mortality. A pre-planned analysis in those with greater exposure to the intervention (defined as 3 days or more) was undertaken [17]; in this subgroup a reduction in in-hospital mortality was evident in those assigned intensive insulin therapy (intensive: 121 of 386 (31.3%) vs. comparator: 145 of 38.1%); $p = 0.05$). When interpreting this observation it should be appreciated that post-randomization identification of a subgroup can be problematic, as conventional statistical methods are invalid when the post randomization factor, in this case duration of exposure, is affected by the intervention being studied [16]. The studies included 407 patients with pre-existing diabetes; there was no significant difference in

the primary outcome of hospital mortality (intensive: 48 of 207 (23.2%) vs. comparator: 44 of 200 (22.0%)) in these patients [18].

Glucontrol was a multi-center, open-label, parallel-group, randomized clinical trial comparing an intervention of intensive insulin therapy aiming for a blood glucose range of 4.4–6.1 mmol/L and a comparator group with a target blood glucose range of 7.8–10 mmol/L [19]. The trial was planned to enroll 3500 patients, but recruitment was terminated by the data safety monitoring board at the first interim analysis because of unintended protocol violations and time spent with blood glucose readings out of range. The trial was stopped after 1101 patients, with a threefold

increase in the proportion of patients having a hypoglycemia event (<2.2 mmol/L, intensive: 8.7% vs. comparator: 2.7%) and no statistical difference in 28-day mortality (intensive: 100 of 536 (18.7%) vs. comparator: 83 of 542 (15.3%); p = 0.14) [19].

The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) study was a multi-center randomized clinical trial that incorporated a two-by-two factorial design. One of the interventions tested was an intensive insulin regimen (commenced >6.1 mmol/L maintained between 4.4 and 6.1 mmol/L); in the comparator group, insulin was commenced at >11.1 mmol/L, aiming to maintain a blood glucose between 10 and 11.1 mmol/L. This branch of the study stopped following the first safety analysis at 488 participants [20]. The intensive insulin

therapy component was terminated because the data safety monitoring committee observed a substantial increase in the risk of hypoglycemia, defined as ≤2.2 mmol/L, with the intervention (intensive: 30 of 247 (12.1%) and comparator: 5 of 241 (2.1%)) [20]. All-cause day 90 mortality was not significantly different (intensive: 98 of 247 (39.7%) vs. comparator: 102 of 288 (35.4%) p = 0.31), including in the sub-group of patients with diabetes (intensive 29/72 (40.3%) vs. comparator 38/91 (41.8%) p = 0.85) [20].

While the results of subsequent trials appeared incongruent with the initial Leuven trial [15], they also demonstrated that maintaining blood glucose within strict ranges across multiple sites was particularly challenging. The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial was a multicenter, open-label, parallel-group, randomized trial evaluating intensive insulin therapy to achieve a blood glucose of (4.5–6.0 mmol/L) with a comparator group with a blood glucose <10.0 mmol/L [21]. The trial included 6100 participants and the primary outcome was all-cause mortality at day 90. In this trial, intensive insulin therapy increased 90-day mortality (intensive: 829 of 3010 (27.5%) and comparator: 751 of 3012 (24.9%);

p = 0.02) and episodes of hypoglycemia (≤2.2 mmol/L) (206 of 3016 (6.8%) and 15 of 3014 (0.5%)) [21]. Subsequent analysis of the NICESUGAR study data indicated that even with adjustment for baseline and post-randomization confounders, the association of moderate and severe hypoglycemia with mortality remained significant in the sub-group of patients with diabetes (intensive 195/615 (31.7%) vs. comparator 165/596 (27.7%); p = 0.60) [22].

Taken together, these earlier randomized clinical trials suggest that, at least outside of specialized centers, trying to achieve blood glucose concentrations consistent with the fasting state (<6 mmol/L) using intensive insulin therapy increases the risk of morbidity and mortality in critically ill patients irrespective of whether they have pre-existing diabetes [15, 21, 22].

Clinical Practice Guidelines

The 2021 American Diabetes Association (ADA) clinical practice guidelines for hospitalized patients include a recommendation that insulin is commenced when a blood glucose of 10 mmol/L or more persists, and the blood glucose range that is targeted with treatment is 7.8–10.0 mmol/L [23]. The recommendations suggest possible alternative goals for critically ill patients with diabetic ketoacidosis, other hyperosmolar states, and cardiac surgical patients—all of which should be achieved without significant hypoglycemia.

The 2012 Society of Critical Care Medicine (SCCM) guideline [24] for management of hyperglycemia in critically ill patients suggests an insulin infusion should be initiated when the blood glucose is ≥8.3 mmol/L and titrated to maintain blood glucose <10.0 mmol/L in a way that limits the risk of hypoglycemia (<4.0 mmol/L). The quality of evidence that supports these guidelines was rated as very low, due to the limitations of the included trials [24]. Collectively, the authors of the ADA and SCCM guidelines also recognize the limitations in the current literature in relation to specific populations, recommending that future research should focus on subpopulations of critically ill patients [23, 24].

Prevalence of Diabetes in Patients Admitted to the ICU

Diabetes, particularly type 2 diabetes, is a prevalent chronic health condition [25]. As a result of high prevalence and complications associated with the disease, diabetes

represents a major financial burden to the healthcare system and consumes a considerable proportion of healthcare expenditure [25]. The prevalence of patients with diabetes admitted to hospital is greater than in the general population, with estimates ranging between 11% and 35% of all patients [1]. The prevalence of critically ill patients with pre-existing diabetes is comparable to that of hospitalized patients at between 12% and 40%, and this has been established though observational and interventional studies that report diabetes as co-existing disease present on admission [26, 27]. These estimates of prevalence should be viewed circumspectly, as in the context of randomized trials, selection bias may occur to increase or decrease representation.

Diabetes that existed before ICU admission but had not been diagnosed is termed unrecognized diabetes and occurs in 6–16% of ICU admissions [27–30]. It is likely that an even greater proportion of critically patients have diabetes than are identified in studies or trials that depend on self-identification of diabetes, and more routine measurement may be warranted.

Evaluation of Previous Randomized Clinical Trials When Focusing on Patients with Pre-existing Diabetes

As described, the cohorts participating in earlier trials evaluating intensive insulin therapy included patients both with and without pre-existing diabetes. Analysis according to pre-existing diabetes has the potential to easily identify different phenotypes, with response to acute dysglycemia being dependent on pre-existing diabetes.

In a post-hoc analysis of the two Leuven studies, the signal for benefit with intensive insulin therapy was confined to those without pre-existing diabetes [18]. In patients with pre-existing diabetes, a greater reduction in blood glucose was associated with greater in-hospital mortality, albeit not reaching pre-defined statistical significance (26.2% for <6.1 mmol/L, 21.6% for 6.1–8.3 mmol/L, and 21.2% for >8.3 mmol/L) [18]. In the NICE-SUGAR study there was increased mortality with intensive insulin therapy in patients with pre-existing diabetes (intensive 31.7% vs. control 27.6%) [21]. Results from these subgroups, and more recent retrospective and prospective analyses of cohorts with pre-existing diabetes have provided insights into the impact of hypoglycemia, hyperglycemia and glycemic variability in patients without diabetes [31–33]. With the heterogeneity of treatment effect observed across critically ill patients, these results raise the possibility

that those with pre-existing diabetes should be considered a separate phenotype than patients with stress hyperglycemia.

Pre-existing Diabetes Relationship to Blood Glucose Metrics

Hyperglycemia in its most acute uncontrolled from has been clearly demonstrated to cause harm [34]. However, the threshold blood glucose concentration that is associated with harm remains to be determined. This certainly appears to be the case in patients with pre-existing chronic glycaemia (i.e., those with a HbA1c ≥7%) who appear to demonstrate a blunted or absent response to acute hyperglycemia [35, 36].

Greater glycemic variability is associated with morbidity and mortality in patients with diabetes but associations between glycemic variability and outcomes are inconsistent. In part this may reflect low patient numbers, variability or premorbid glycemic control, and/or lack of power to detect a relationship [37]. It would not be surprising that diabetic patients have adapted somewhat to glycemic variability and developed protection. To determine whether glycemic variability is indeed harmful to patients with diabetes a suitably powered and conducted study is required [38].

Hypoglycemia is strongly associated with increased morbidity and mortality in critically ill patients with or without diabetes, but the effect is more marked in those without pre-existing diabetes [4, 18, 31, 39, 40].

Rationale for a Personalized Approach to Glycemic Control

A ‘personalized’ approach to acute glycemic control, which takes into consideration an individual’s pre-existing glucose metabolism when determining an appropriate target glycemic range during a period of acute illness, has been suggested as a concept [1, 38, 41]. Results from observational and exploratory studies indicate that outcomes for patients with diabetes are different in relation to the impacts of hypoglycemia, hyperglycemia and glycemic variability (Table 1) [4, 27, 31, 42–44]. Egi and colleagues reported that patients with a higher HbA1c on ICU admission were more likely to survive if they had blood glucose concentrations >10 mmol/L during their ICU admission [31]. Subsequently, several studies have made similar observations (Table 2) [4, 27, 42–44]. Although patients with diabetes appear to have some underlying protection against acute hyperglycemia, hypoglycemia has consistently been shown to be harmful and the

threshold blood glucose for harm may even be slightly higher than for non-diabetic patients [11, 48].

Whilst these observational studies suggest that the threshold for harm is dependent on pre-morbid glycemic control, the outcomes are insufficient to affect practice. They have, however, informed further research into the use of such a 'personalized' approach to glycemic control for critically ill patient with diabetes.

Table 1. Rationale for personalized blood glucose levels

Author	Year	Study design	Number of sites	n	Diabetes n (%)	Results/main points
Egi [31]	2008	Retrospective observational	Multi-centre	4946	728 (14.7)	Diabetic patients showed no association between hyperglycaemia and ICU mortality.
Plummer [27]	2014	Prospective observational	Single centre	1000	275 (27.5)	Hyperglycaemia was not associated with mortality in patients with premorbid hyperglycaemia.
Egi [42]	2016	Retrospective observational	multi-centre	3084	1057 (34.3)	Increased pre-morbid hyperglycaemia the greater the risk of death in patients experiencing any hypoglycaemic episode.
Krinsley [43]	2017	Retrospective observational	two centres	6387	1872 (29.3)	No relationship between mean BG level and mortality for patients with DM. hypoglycaemia <4.0mmol/L was associated with mortality in all patients.
Lin [44]	2020	Retrospective observational	multi-centre	33680	8701 (25.8)	Patients with diabetes, an elevated admission glucose does not appear to be associated with 28 day mortality.
Krinsley [4]	2020	Retrospective observational	Single centre	5567	1161 (20.1)	Increased BG increased mortality for patients with HgbA1c <6.5%, but decreased mortality for patients with HgbA1c ≥ 8.0%
Ma [37]	2022	Retrospective observational	Single centre	958	238 (24.8)	Greater GV and a higher rate of hypoglycaemia was associated with mortality in patients with diabetes. Hyperglycaemia impact on mortality were nonsignificant in diabetics.

BG: blood glucose; HbA1c: glycated hemoglobin

Table 2. Studies of personalised blood glucose control

Author	Year	Method	Sites	n	Diabetes n (%)	Intervention target range (mmol/L)	control target range (mmol/L)
Di Muzio [45]	2016	Sequential period	Single centre	80	80 (100)	10.0 to 14.0	6.0 to 10.0
Kar [32]	2016	Sequential period	Single centre	83	83 (100)	10.0 to 14.0	6.0 to 10.0
Krinsley [46]	2017	Retrospective observational	Single centre	1979	406 (20.5)	6.1 to 8.9	5.0 to 6.7
Luethi [33]	2018	Sequential period	Single centre	700	700 (100)	10.0 to 14.0	6.0 to 10.0
Bohé [30]	2021	RCT	Multi centre	1917	468 (24.4)	Figure 1.	
Poole [47]	2022	RCT	Multi centre	434	434 (100)	10.0 to 14.0	6.0 to 10.0

*RCT randomized controlled trial

Studies of More Personalized Approach to Glucose Control

There are only a few studies of a 'personalized' approach to blood glucose based on the presence of diabetes and allowing mild to moderate hyperglycemia (≥10 mmol/L). Kar and colleagues [32] conducted a prospective, single center, sequential period study in adult patients with diabetes and chronic hyperglycemia (HbA1c ≥7%). During the initial 'standard care' period, insulin was commenced when blood glucose concentrations reached >10 mmol/L and titrated to maintain them between 6 and 10 mmol/L. During the liberal period, insulin administration was started once blood glucose was >14 mmol/L, which was then titrated to target blood glucose concentrations between 10 and 14 mmol/L. The 'standard care' period included 52 participants, the liberal period included 31 participants: peak blood glucose concentrations where comparable between the groups (standard group 15.8 (3.5) vs. 16.2 (3.9)). During the liberal phase, the time-weighted blood glucose concentrations were predictably higher. During the standard care period, 18 patients (35%) had an episode of moderate-severe hypoglycemia (13 patients had moderate hypoglycemia and five had severe hypoglycemia) and during the liberal period five patients (16%) had an episode of hypoglycemia (four moderate and one patient severe). After adjustment for varying periods of observation, there was a tendency for fewer episodes of moderate-severe hypoglycemia during the liberal period [Relative risk: 0.47 (95% CI 0.19–1.13): p = 0.09]. Recurrent hypoglycemia was more common in the standard care phase, with ten patients having recurrent moderate-severe hypoglycemia

compared to only one patient in the liberal phase. No signal for harm was observed and patient centered outcomes were similar in the two groups.

Luethi and colleagues [33] conducted a larger single center, sequential period study. They included 350 consecutively admitted patients with diabetes in whom the blood glucose target as 6–10 mmol/L during the standard care period. During the liberal period, a further 350 patients with diabetes received insulin once blood glucose levels were >14 mmol/L, with the insulin titrated to maintain a blood glucose between 10 and 14 mmol/L. The diagnosis of diabetes was determined pragmatically from medical records, or patient or relative report. In the liberal phase, median time-weighted average blood glucose concentrations were again greater than during the control period (11.0 [IQR 8.7–12.0] vs. 9.6 [IQR 8.5–11.0] p = <0.001). Fewer patients received insulin in the liberal compared with the control period (132 (37.7%) vs. 188 (53.7%) p = <0.001). In the sub-group of patients with chronic hyperglycemia (HbA1c >7%), the liberal approach was associated with a reduction in the number of episodes of hypoglycemia (≤3.9 mmol/L) (liberal: 9 (3%) vs. control: 22 (7%) p = 0.03).

Recently, Bohé and colleagues reported results from the CONTROLING trial; which was a blinded randomized clinical trial of a 'personalized approach' to blood glucose management based on the admission HbA1c [30]. The trial included 1917 patients and made use of a blinded, computer-generated algorithm to guide nursing staff on management of glycemia. In the comparator group, blood glucose concentrations were managed once they exceeded 10 mmol/L. The intervention group, who received the 'personalized approach', included patients with HbA1c ≤4.96% where the blood glucose target range was more stringent, i.e., 6.2 mmol/L compared to 12.1 mmol/L for those with HbA1c of ≥8.67% (Fig. 1). Implementation of such a complex intervention across multiple sites to patients with dynamic disease processes and interventions is challenging, and, not surprisingly, the target range was only achieved half of the time. However, the treatment separation was modest with only a small difference in time-weighted mean blood glucose levels in the reported cohort of 1828 (it was just 0.7 mmol/L). As could be expected, insulin administration was greater in the personalized group, with 25% more patients receiving insulin. Episodes of severe hypoglycemia, defined as <2.2 mmol/L, were not statistically different between groups (personalized: 37 of 942 (3.9%) vs. comparator: 24 of 975 (2.5%); p = 0.09). However, hypoglycemia, defined as <4 mmol/L, was more frequent with the intervention (personalized: 294 of 942 (31.2%) vs. comparator: 154 of 975 (15.8%) p = <0.0001). As with previous studies, moderate and

severe hypoglycemia were associated with increased mortality; with the low likelihood of benefit from the intervention in terms of 90-day mortality, the data safety monitoring committee recommended early trial cessation. The study predominately included participants that did not have diabetes, and, of those with diabetes, only 14% had an HbA1c >7%. Accordingly, while this study reaffirms that hypoglycaemia is harmful, patients with pre-existing diabetes only represented a small proportion of the participants.

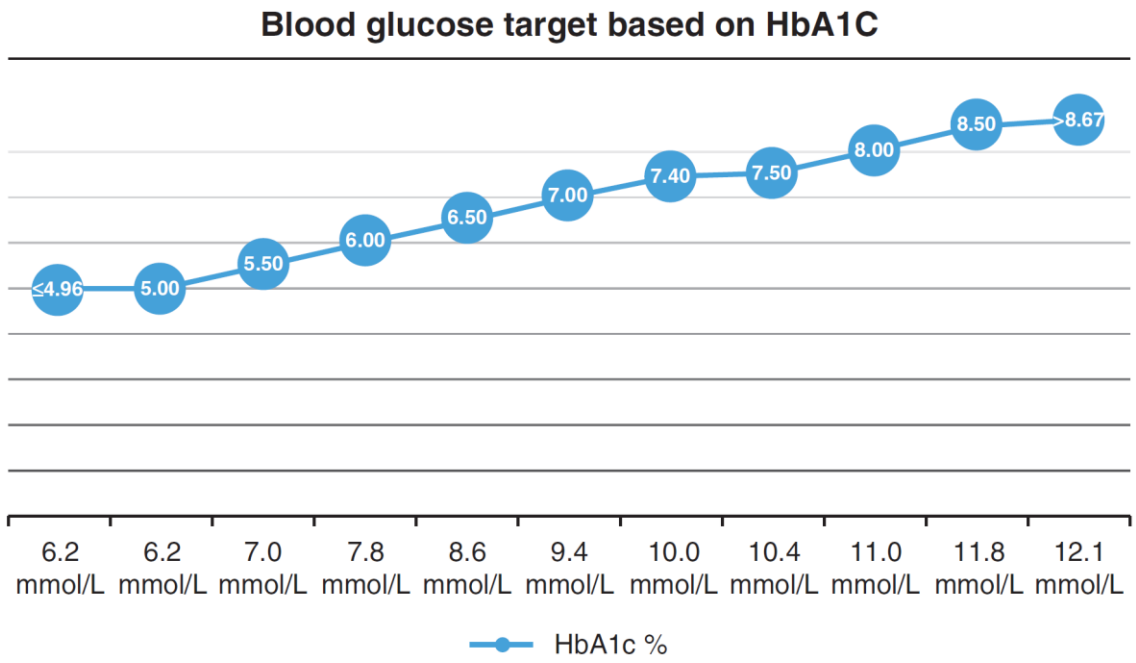

Figure 1 Personalized blood glucose targets used for intervention group in the CONTROLING study [30]. HbA1c*: glycated hemoglobin*

More recently, we published the LUCID trial, a multicenter, open label, randomized clinical trial conducted in critically ill patients with pre-existing diabetes. With the liberal approach, insulin was commenced at >14.0 mmol/L and in the comparator group insulin was commenced at >10.0 mmol/L (Fig. 2) [47]. This is the first randomized trial to explore a liberal approach in critically ill patients with pre-existing diabetes. The study randomized 434 patients with diabetes, irrespective of their HbA1c (at randomization the median HbA1c was 7.3% in both groups). The median blood glucose was 11.8 mmol/L in the intervention group compared to 9.3 mmol/L in the comparator group. As with several other pragmatic trials, blood glucose concentrations were outside the target range about 50% of the time. The primary endpoint of the study was 28-day incidence of hypoglycemia, defined as <4.0 mmol/L, which was significantly lower in the intervention group (10 (5%) versus 38 (18%), IRR 0.36, 95% CI 0.11–1.14). Although the trial was

not powered for patient-centered outcomes, 90-day mortality was numerically greater in the intervention arm. Accordingly, these findings suggest that a liberal approach should not be implemented outside of a well-designed clinical trial, and further consideration of admission HbA1c and use of technology to improve time-in-range may also be beneficial.

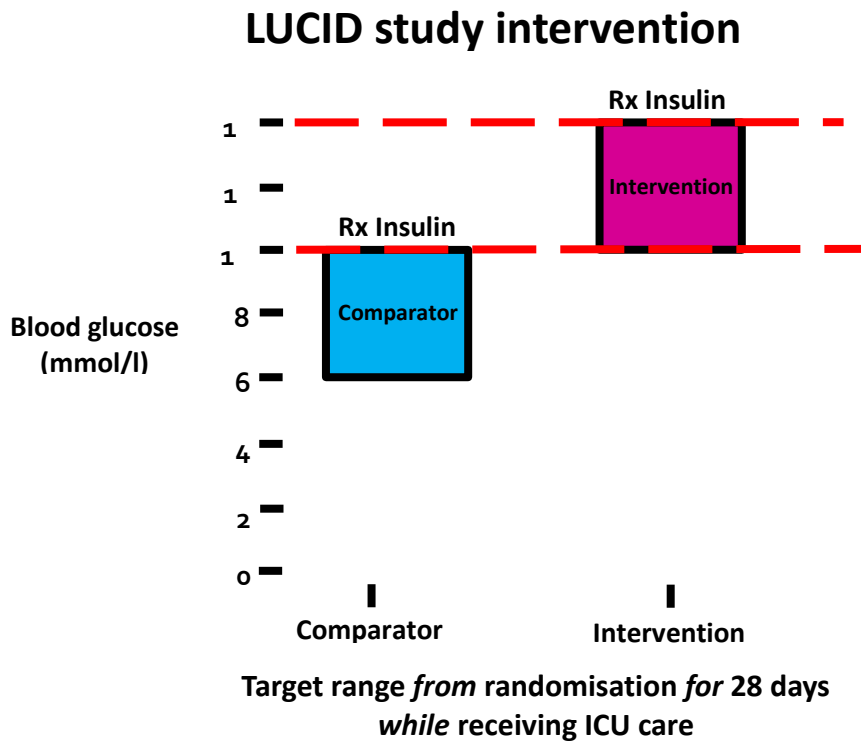

Figure 2 Blood glucose target ranges used in the LUCID study [47].

Future Research

Information from retrospective and prospective observational studies and from interventional studies, has provided considerable insight into critically ill patients with pre-existing diabetes and supports future exploration of a more personalized approach to glycemic control. The most recent studies—CONTROLING and LUCID—have provided insight into optimal study designs for future investigation of blood glucose management in critically ill patients with diabetes. With the recent advent of various technologies, such as continuous glucose monitoring, point-of-care HbA1c machines, and close-loop continuous glucose monitoring, we suggest further adequately powered trials in patients with the phenotype of diabetes are warranted. Outside of specific target ranges and methods for achieving these, investigations into alternate nutrition formulas have commenced, and may represent a method to reduce the amount of insulin required [49].

Given the consistent evidence that hypoglycemia and mortality are related in this population, glucose lowering therapies that are less likely to induce hypoglycemia would appear to be worthy of further investigation. A number of small studies have explored the use of these incretin-based therapies to reduce blood glucose with a lower risk of hypoglycaemia [50]. They could potentially be used alone or in combination with insulin, as is the case in ambulatory type 2 diabetes.

Conclusion

The optimal blood glucose target for critically ill patients with pre-existing diabetes remains uncertain, as outcomes of recent trials are neither definitive nor practice changing. Future studies are required to provide clinical insight, as a more personalized approached is intuitively likely to be more effective. Future approaches to management of hyperglycemia should minimize the potential for hypoglycemia.

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1.3 MANUSCRIPT

OPINIONS AND PRACTICES OF BLOOD GLUCOSE CONTROL IN CRITICALLY ILL PATIENTS WITH PRE-EXISTING TYPE 2 DIABETES IN AUSTRALIAN AND NEW ZEALAND INTENSIVE CARE UNITS

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Overall percentage (%)	80
Certifcation	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would

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Opinions and practices of blood glucose control in critically ill patients with pre-existing type 2 diabetes in Australian and New Zealand intensive care units

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Keywords

Attitude, Blood glucose, Critical care, Critical illness, Diabetes mellitus, Type 2, Surveys and questionnaires, Intensive care units

Abstract

Background: Approximately 9000 patients with type-2 diabetes mellitus (T2DM) are admitted to an intensive care unit (ICU) in Australia and New Zealand annually. For these patients, recent exploratory data suggest that targeting a more liberal blood glucose range during ICU admission may be safe and potentially beneficial. However, the current approach to blood glucose management of patients with T2DM in Australia and New Zealand ICUs is not well described, and there is uncertainty about clinician equipoise for trials of liberal glycaemic control in these patients. Aim: The aim is to describe self-reported blood glucose management in patients with T2DM by intensivists working in

Australian and New Zealand ICUs and to establish whether equipoise exists for a trial of liberal versus standard glycaemic control in such patients.

Method: An online questionnaire of Australia and New Zealand intensivists conducted in Julye September 2016.

Results: Seventy-one intensivists responded. Forty-five (63%) used a basic nomogram to titrate insulin. Sixty-six (93%) reported that insulin was commenced at blood glucose concentrations >10 mmol/L and titrated to achieve a blood glucose concentration between 6.0 and 10.0 mmol/L. A majority of respondents (75%) indicated that there was insufficient evidence to define optimal blood glucose targets in patients with T2DM, and 59 (83%) were prepared to enrol such patients in a clinical trial to evaluate a more liberal approach.

Conclusion: A majority of respondents were uncertain about the optimal blood glucose target range for patients with T2DM and would enrol such patients in a comparative trial of conventional versus liberal blood glucose control.

Introduction

Patients with type-2 diabetes mellitus (T2DM) are frequently admitted to an intensive care unit (ICU).[1,2] Hyperglycaemia, defined as >10 mmol/L, occurs frequently in this group, and management of hyperglycaemia in ICU is nearly always proto-colised.[3-5] Such protocols promote uniformity of practice and improve the overall quality of care; however, if applied uniformly across all patient subgroups, as a consequence of inadequate data, may lead to harm.[6]

The current approach to blood glucose management is to implement the same protocol for those with and without diabetes, typically to target a range of 6-10 mmol/l. Such practice has largely been informed by the findings of the Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial.[7] More recent observational and exploratory data suggest that, for patients with diabetes, titrating intravenous insulin to target blood glucose concentrations between 10 and 14 mmol/l during ICU admission may be safe and potentially beneficial.[1,8-13] Moreover, the excessive administration of insulin may itself lead to a disturbance in the ability of the body to regulate glucose concentration effectively and may be associated with increased mortality.[7] Because of these effects, and the potential impact on survival, allowing a

'liberal' approach to glucose control (a tolerance of higher blood glucose concentrations than are targeted in patients with previously normal glucose tolerance) may be beneficial for patients with T2DM.[1,8-15] Before any large randomised controlled trial to evaluate a more liberal approach in this cohort, it is important to have an understanding of Australian and New Zealand practice and clinician concerns and preferences toward such a liberal approach.

In response, we surveyed intensivists in Australian and New Zealand to study their attitudes, preferences, and self-reported practice of glucose management for patients with T2DM admitted to ICU. In particular, we wanted to identify how intensivists monitor and respond to blood glucose concentrations and their level of concern about a liberal glucose management approach. Finally, we enquired whether intensivists would be willing to enrol patients with T2DM in a randomised trial comparing the safety and efficacy of liberal versus conventional glycaemic management in the ICU.

Methods

Survey

We used an anonymous, structured, multichoice online questionnaire to survey intensivists (https://www.surveymonkey.com/r/55G785D). The questionnaire consisted of twenty-two questions divided into four parts: (1) the basic demographic details of respondents, (2) current approach to blood glucose monitoring, (3) current management of glycaemia, and (4) opinions on the current evidence for management of glycaemia in critically ill patients with T2DM. This survey was approved by the Royal Adelaide Hospital Human Research Ethics Committee.

Target population and questionnaire administration

Australian and New Zealand intensivists were identified using the Australian and New Zealand Intensive Care Society (ANZICS) and the ANZICS Clinical Trails Group (ANZICS-CTG) databases. This target population included paediatric and adult intensivists. Each intensivist was invited by email to respond to the online questionnaire. Eight weeks after the initial email invitation, a single reminder email was sent. All responses were recorded during an 11-week period, from 12/07/2016 to 29/09/2016.

Data management and analysis

Response data were downloaded from SurveyMonkey™ directly into an Excel spreadsheet (XLS, Microsoft Excel®). Responses are shown as number (%) for each given question, with 95% exact binomial confidence intervals (CIs). Data were analysed using descriptive statistical procedures to calculate means and percentages. No imputation was undertaken for missing data. All quantitative analyses were performed using Excel 2010 (Microsoft®).

Results

Cohort characteristics and glucose monitoring

The survey invitation email was sent to 1605 ANZICS and ANZICS-CTG subscribers, with 71 (4%) responding to the survey with their cumulative responses recorded in Table 1. The majority 49/70 (70%, CI: 57.9-80.4) were primarily employed in public metropolitan hospitals, 14/70 (20%, CI: 11.4-31.3) practices in New Zealand ICUs, 56/70 (80%, CI: 68.7-88.6) from Australian ICUs with Victoria, New South Wales, and the North Island of New Zealand representing 44/70 (63%) of respondents, and 37/70 (53%) of respondents had more the 10 years of ICU specialist experience (Supplemental Table 1). Excluding protocols for patients with diabetic ketoacidosis,[16] 38/70 (54%, CI: 41.3-65.5) reported that their ICU had no specific protocol for patients with T2DM. Glucometers 36/71 (51%, CI: 38.6-62.8) and arterial blood gas analysers 35/71 (49%, CI: 37.2-61.4) were equally reported as the predominant method used to monitor blood glucose concentrations.

Management of blood glucose concentrations

Forty-five of 71 (63%, CI: 51.1-74.5) respondents reported using a basic nomogram to titrate therapy with intravenous insulin (Table 2). Sixty-six of 71 (93%, CI: 84.3-97.7) respondents replied that insulin is commenced with a blood glucose concentration above 10 mmol/L and titrated to achieve blood glucose concentrations between 6 and 10 mmol/L (Table 2).

Type 2 diabetes

With regard to patients with pre-existing diabetes, 4/70 (6%, CI: 1.6-14.0) respondents had major concerns, and 48/70 (68%, CI: 56.4-79.1) did not have major concern with causing harm by not treating blood glucose concentrations at a threshold of 10 mmol/L;

27/71 (38%, CI: 26.8-50.3) strongly agreed, and 28/71 (39%, CI: 28.0-51.7) agreed that the results of NICE-SUGAR have influenced the approach to glycaemia in ICU (Table 2). There is currently sufficient evidence to determine the optimal blood glucose range for patients with T2DM admitted to the ICU; 15/70 (21%, CI: 12.5-32.9) agreed, 16/70 (23%, CI: 13.7-34.4) neutral, 26/70 (37%, CI: 25.9-49.5) disagreed, and 11/70 (16%, CI: 8.1-26.4) strongly dis-agreed (Table 2). Four of 71 (6%, CI: 1.6-13.8) strongly agreed, and 20/71 (41%, CI: 29.3-53.2) agreed that they were concerned about an increased risk of infection with liberal glycaemic control (Table 2). Thirty-three of 71 (46%, CI: 34.5-58.7) were concerned about the potential risk of hypoglycaemia (<4.0 mmol/L) when aiming for blood glucose concentrations between 6 and 10 mmol/L in patients with T2DM, with 35% of respondents were not concerned (Table 2). Forty-one of 71 (58%, CI: 45.4-69.4) respondents considered that blood glucose concentration range between 6 and 10 mmol/L was safe for T2DM (Table 2). Seventeen of 71 (24%, CI: 14.6-35.5) strongly agreed, and 28/71 (39%, CI: 28.0-51.7) agreed that they were willing to enrol T2DM patients in a trial of liberal glycaemic control, regardless of the admission diagnostic category, but fewer physicians were willing to enrol postoperative than medical patients with T2DM (Table 2). Forty-four of 71 (63%, CI: 49.7-73.2) participants think that it is feasible to have two glucose protocols done for patients with diabetes and one for patients without diabetes.

Discussion

The intensive care specialists who responded from Australia and New Zealand suggest that the most frequently targeted blood glucose range for patients with T2DM is 6-10 mmol/L, with less than half of intensivists responding and reporting a specific protocol for patients with T2DM. There was no consensus as to whether there was sufficient evidence to guide management in critically ill patients with T2DM, and only a minority would be unwilling to evaluate a more liberal strategy in this group of patients.

Our study provides some insights into the management and concerns with glucose control in T2DM patients as reported by surveyed ANZ intensivists. The respondents came from a mixture of adult ICUs and spread across most states, territories, and New Zealand. There are, however, significant limitations. Invitations were sent using the ANZICS and ANZICS-CTG databases and may not be fully representative of the broader community of ICU specialists. Responses were self-reported and so may not reflect actual practice.

Electronic surveys conducted via email invitations traditionally have low response rates,[17] as was the case with this survey, and such responses may not reflect wider population opinions.[17,18] However, the response rate for our survey was consistent with others using this method[18] and reflect the uncertainty within the literature.[9,19]

Implications

Recent literature reviews have focused on glycaemic control in critically ill patients with T2DM, particularly regarding the potential for harm from hypoglycaemia and the rationale for a different approach than that used for critically ill patients without diabetes.[20] Such observations are supported by recent exploratory studies.[8,9,12,14] The recent observational data have suggested that blood glucose concentrations that are frequently associated with harm in patients with 'normal' glucose tolerance may be less desirable in patients with T2DM.[1,4,6,8,14] The majority of responses provided replies that were consistent with the uncertainty. No studies have specifically explored the current practice of blood glucose management of critically ill patients with T2DM in Australian and New Zealand ICUs, and while limited in scope, this study provides some insights into the current practice of the respondents. Based on this uncertainty, a phase II trial has been planned to further evaluate this issue (ACTRN number 12616001135404).

Future research

Additional studies are required to establish the current practices for managing critically ill patients with T2DM; different study methodologies may provide a more robust refection of practice. The exploration of global blood glucose management practice of critically ill T2DM patients is the area that could be explored to understand how ANZ compares different regions.

Conclusion

Australian and New Zealand intensivists remain uncertain about optimal blood glucose targets in patients with T2DM, with half of the respondents feeling that there is insufficient evidence for blood glucose management in patients with T2DM. Presently, the majority (93%) would aim for the NICE-SUGAR targets of between 6.0 and 10.0 mmol/L with 87% commencing intravenous insulin to achieve these targets. Within our sample, there was sufficient equipoise to support conducting a trial evaluating a more liberal approach to blood glucose control in ICU patients with T2DM.

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Tables

Table 1. Monitoring and management of blood glucose concentrations for patients with type 2 diabetes admitted to ICU.

Clinical scenarios and response options	Responses n (%[a])	CI
Predominant method to measure blood glucose (71[b])		
Point of care glucometer	36 (51%)	38.6, 62.8
Arterial blood gas machine	35 (49%)	37.2, 61.4
Central laboratory	0 (0%)	0.0, 5.1
Excluding protocols for patients admitting for diabetic ketoacidosis, does your ICU have a blood glucose management protocol that is specific to patients with diabetes? (70[b])		
No	38 (54%)	41.3, 65.5
Yes	28 (40%)	28.0, 51.7
Unsure	4 (6%)	1.6, 13.8
How frequently (on average) do you think that blood glucose concentrations are measured in your ICU from patients with diabetes with an arterial line in situ? (71[b])		
At least 4 hourly	36 (51%)	38.6, 62.8
At least 6 hourly	26 (37%)	25.5, 48.9
At least 2 hourly	7 (10%)	4.1, 19.3
Hourly	1 (1%)	0.0, 7.6
Daily	1 (1%)	0.0, 7.6
Continuously	0 (0%)	0.0, 5.1
Never	0 (0%)	0.0, 5.1

ICU, intensive care unit; CI, confidence interval.
a) Percentage of the total number of responses for that question.
b) Number of responses.

Table 2. Current practice and current evidence for glucose control in patients with type 2 diabetes admitted to ICU.

Clinical scenarios and response options	Responses n (%[a])	CI
Of the following options, please indicate what algorithm you predominantly use when treating hyperglycaemia in patients within your ICU. (71[b,c])		
Basic nomogram	45 (63%)	51.1, 74.5
Dynamic protocol	13 (18%)	10.1, 29.3
Dynamic protocol that incorporates nutritional intake as well	2 (3%)	0.3, 9.8
Computerised protocols	3 (4%)	0.9,11.9
No protocol used	8 (11%)	5.0, 21.0
Which of the following methods would you initially use when treating hyperglycaemia in T2DM patients expected to stay longer than 24 h in ICU: (71[b,c])		
Subcutaneous insulin administration only	3 (4%)	0.9, 11.9
Subcutaneous insulin followed by intravenous insulin administration	3 (4%)	0.9, 11.9
Intravenous insulin therapy only	39 (55%)	42.7, 66.8
Intravenous insulin therapy followed by subcutaneous insulin	23 (32%)	21.8, 44.5
I do not mind which mode of therapy is initially used, so I let the junior medical staff decide	3 (4%)	0.9, 11.9
In the unit that you predominantly work and according to that protocol when is insulin commenced in ICU patients. (71[b])		
Insulin is started for blood glucose ≥ 6.1 mmol/L and titrated to achieve blood glucose concentrations 4.5 - 6.0 mmol/L as per Leuven studies	0 (0%)	0.0, 5.1
Insulin is started for blood glucose ≥ 10.1 mmol/L and titrated to achieve blood glucose concentrations between 6.0 and10.0 mmol/L as per the NICE- SUGAR	66 (93%)	84.3, 97.7
Neither, as insulin is started at a threshold blood glucose concentration greater than Leuven but less than the NICE-SUGAR (i.e. but less than the NICE-SUGAR (i.e. between 6.1 and 10.0 mmol/L)	2 (3%)	0.3, 9.8
Neither, as insulin is started at a threshold greater than the NICE- SUGAR.	3 (4%)	0.9, 11.9
In patients with diabetes, when would you commence treatment for a blood glucose level of >14 mmol/L? (71[b])		
<1 Hour	42 (59%)	46.8, 70.7

1-2 Hours	23 (32%)	21.8, 44.5
2-4 Hours	4 (6%)	1.6, 13.8
4-6 Hours	2 (3%)	0.3, 9.8
>6 Hours	0 (0%)	0.0, 5.1
Never	0 (0%)	0.0, 5.1
Please indicate how concerned you are about inducing further harm associated with not treating blood glucose concentrations >10 mmol/L in patients without pre-existing diabetes? (70[b,c])		
Yes, this is a major concern	11 (15%)	8.0, 26.0
Yes, but not a major concern	49 (69%)	56.9, 79.5
No, it is not a concern	11 (15%)	8.0, 26.0
Please indicate how much you are concerned about inducing further harm associated with NOT treating blood glucose concentrations > 10 mmol/L in patients with diabetes? (70[b])		
Yes, this is a major concern	4 (6%)	1.6, 14.0
Yes, but not a major concern	48 (68%)	56.4, 79.1
No, it is not a concern	18 (26%)	16.0, 37.6
The results of NICE-SUGAR have impacted blood glucose concentrations I target in the ICU. (71[b])		
Strongly agree	27 (38%)	26.8, 50.3
Agree	28 (39%)	28.0, 51.7
Neutral	12 (17%)	9.0, 27.7
Disagree	2 (3%)	0.3, 9.8
Strongly disagree	2 (3%)	0.3, 9.8
There is currently sufficient evidence to determine the optimal blood glucose range for patients with T2DM admitted to the ICU. (70[b])		
Strongly agree	2 (3%)	0.3, 9.9
Agree	15 (21%)	12.5, 32.9
Neutral	16 (23%)	13.7, 34.4
Disagree	26 (37%)	25.9, 49.5
Strongly disagree	11 (16%)	8.1, 26.4
I would be prepared to enrol ICU patients with T2DM into a randomised trial of liberal blood glucose control (10-14 mmol/L). (71[b,c])		
Strongly agree	17 (23%)	14.6, 35.5
Agree	28 (39%)	28.0, 51.7
Neutral	14 (20%)	11.2, 30.9
Disagree	9 (13%)	6.0, 22.7
Strongly disagree	3 (4%)	0.9, 11.9

I am concerned about the potential for increased risk of infection if T2DM patients only had insulin commenced for blood glucose concentrations ≥14 mmol/L (71)		
Strongly agree	4 (6%)	1.6, 13.8
Agree	29 (41%)	29.3, 53.2
Neutral	24 (34%)	23.0, 46.0
Disagree	11 (15%)	8.0, 26.0
Strongly disagree	3 (4%)	0.9, 11.9
I am concerned about the potential for hypoglycaemia (<4.0 mmol/L) when aiming for blood glucose concentrations between 6-10 mmol/L in patients with T2DM (71[b,c])		
Strongly agree	8 (11%)	5.0, 21.0
Agree	25 (35%)	24.2, 47.5
Neutral	13 (18%)	10.1, 29.3
Disagree	23 (32%)	21.8, 44.5
Strongly disagree	2 (3%)	0.3, 9.8
The lowest blood glucose concentration that I think is safe for patients with T2DM to tolerate during ICU admission is (71[b])		
Between 6.0 and 10.0 mmol/L	41 (58%)	45.4, 69.4
Between 4.0 and 5.9 mmol/L	27 (38%)	26.8, 50.3
Between 3.0 and 3.9 mmol/L	3 (4%)	0.9, 11.9
Between 2.3 and 2.9 mmol/L	0 (0%)	0.0, 5.1
Please select the specific patient groups you would be willing to enrol into a liberal blood glucose concentrations study for T2DM patients (tick all that apply). (54[b,d])		
Cardiothoracic	32 (59%)	45.0, 72.4
Neurosurgical	32 (59%)	45.0, 72.4
Elective surgery	43 (80%)	66.5, 89.4
Trauma	40 (74%)	60.3, 85.0
Medical	53 (98%)	90.1, 100
Do you think it would be feasible to have two glucose protocols one for patients with and one for without diabetes? (71b)		
Strongly agree	7 (10%)	4.1, 19.3
Agree	38 (53%)	41.3, 65.5
Neutral	11 (15%)	8.0, 26.0
Disagree	11 (15%)	8.0, 26.0
Strongly disagree	4 (6%)	1.6, 13.8

NICE-SUGAR, Normoglycaemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation; ICU, intensive care unit.
a) Percentage of the total number of responses for that question.

b) Number of responses.
c) Percentage may not total 100 because of rounding.
d) Respondents could pick multiple each could total 100.

1.4 CONCLUSIONS

1.4.1 Introduction

This chapter summarises the evidence for the management of dysglycaemia in critically ill patients with diabetes, and the outcomes of a survey of ICU clinicians to understand their approach to management of dysglycaemia and evaluate their willingness to a randomised clinical trial in this cohort. As stated previously, the book chapter titled 'Optimal Glycemic Targets in Critically Ill Patients with Diabetes' was written after the LUCID trial was completed. Within the book chapter the student summarised recent evidence, including the LUCID trial and its context with earlier studies, as well as a discussion of priorities for future research in this area. Within the second manuscript, the student evaluated current variability of clinical practice and determined willingness to participate in a randomised clinical trial.

1.4.2 Contribution of work described in this thesis to the understanding of current clinical evidence of blood glucose control in critically ill type 2 diabetes.

Blood glucose management is part of routine care of critically ill patients with type 2 diabetes but there is limited high-quality evidence to inform clinical practice (5). The latter is largely informed by trials of study populations that predominately comprised those with stress hyperglycaemia, with limited evidence from trials of critically ill patients with pre-existing (usually type 2) diabetes (6, 7). The book chapter reported in chapter 1.2 provides an overview of current understanding (8). It also describes exploratory studies which underlie the rationale that an elevated blood glucose target range may be beneficial in patients with pre-existing diabetes. These data are derived from observatory or exploratory studies with major methodological weakness and were, therefore, insufficient to inform practice. The high prevalence of disordered glucose metabolism in critically ill patients with pre-existing diabetes means that treatment decisions regarding the optimal blood glucose range to target is one that clinicians face frequently. This book chapter provides a contemporaneous summary of what is currently known as well as future priorities for investigation.

1.4.3 Contribution of work described in this thesis to the understanding of current clinical practice in the management of blood glucose levels in critically ill type 2 diabetes.

Intravenous insulin is administered routinely to critically ill patients with type 2 diabetes to treat hyperglycaemia. However, there is a lack of evidence from high quality trials to inform what range of blood glucose should be targeted. Understanding current clinical practice as described by those prescribing the treatment is important when considering how to design an appropriate clinical effectiveness study. The study described in chapter 1.3 is the first to explore current management of blood glucose levels in critically ill patients with type 2 diabetes in Australian and New Zealand. It also appears that prior to LUCID clinical practice was largely be informed by the NICE SUGAR study. However, the NICE-SUGAR study included patients with stress hyperglycaemia and pre-existing diabetes, with only 19% having diagnosed pre-existing type 2 diabetes (9). The healthcare workers who responded to the survey were also of the opinion that existing evidence did not reliably inform practice, and future research to determine the optimal blood glucose target range for critically ill patients with type 2 diabetes was needed. The survey provided insights into which blood glucose target ranges would be acceptable to treating clinicians, and the blood glucose concentration they consider to be safe for critically ill patients with type 2 diabetes.

1.5 FUTURE DIRECTIONS

The explorations made in chapter 1.2 establish that critically ill patients frequently have pre-existing type 2 diabetes, leading to clinicians needing to make decision on how best to manage disordered blood glucose in these patients. Retrospective studies have explored outcomes from this patient population and that their relationship (including threshold) at which harm from blood glucose levels occurs is substantially greater than in critically ill patients without diabetes. Such associations have been repeated in various datasets and informed the development of exploratory studies evaluating the safety of alternate blood glucose target ranges in patients with pre-existing diabetes. Taking into consideration an individual patient's underlying metabolic state may be important when targeting a blood glucose range. A so-called more 'personalised approach'. While an intuitively appealing construct, the optimal treatment range for the latter has not been established. Prior to the

work described in chapter 2, a novel intervention studied was the use of a threshold for the commencement of insulin of ≥14 mmol/L with a target range 10-14 mmol/L. Importantly, the majority of respondents to the study presented in chapter 1.3 were comfortable with enrolling patients into a trial with this as a target range. Based on these investigations and the outcomes of previous research a randomised control trial of personalised blood glucose control in critically ill patients with type 2 diabetes (the LUCID trial) was warranted.

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Chapter 2:

Rationale for ‘liberal’ blood glucose management in approach to glycaemia in critically ill patients with type 2 diabetes

2.1 INTRODUCTION

The management of hyperglycaemia in the critical care setting predominately utilises intermittent measurement of blood glucose levels with either arterial blood gas machine or point of care glucometers. The frequency of these measurements and the devices utilised to measure blood glucose varies depending on local practice and resources (1). While target blood glucose ranges varies, within Australia and New Zealand, clinical practice is largely informed by the NICE-SUGAR trial (2). While a number of therapies could achieve target blood glucose ranges, the most frequently used and cost-effective intervention is an intravenous insulin infusion. However, this approach can be time consuming for staff to deliver and monitor regular blood results to prevent hypoglycaemia and the associated harm.

The pragmatic approach to explore an alternative target range is to adjust the commencement threshold for intravenous insulin. This approach is also based on information provided by a survey of clinicians (chapter 2). The proposed benefit of this approach being a reduction in hypoglycaemic episodes and associated harms. The protocol and statistical analysis plan contained in this chapter provides a detailed explanation of the population, intervention and analysis that will be utilised in the study present in chapter 3.

Publication of a clinical trial protocol and statistical analysis plan prior to study completion and data analysis ensures transparent presentation of the eventual results (3). This approach is recommended by Enhancing the QUAlity and Transparency Of health Research network (EQUATOR Network) (4). The risk of bias is mitigated by clear statement of intentions for analysis of the primary and secondary outcomes (5). It also provides the opportunity to detail the sample population and the power calculation utilised

to determine the sample size required to adequately assess the primary outcome (6). These are objectives of the EQUATOR networks Standard Protocol Items: Recommendations for Interventional Trials (SPRINT) (3). The SPRINT statement was utilised to ensure all important information was provided in the protocol and statistical analysis plan (3).

The objective of chapter 2 was to clearly and transparently articulate the intention and method of the LUCID trial. The LUCID trial is presented in chapter 3.

2.1.1 **Objectives**

The objectives of the protocol and statistical analysis plan were to pre-publish the study methodology and data process plan prior to study completion. This process is considered the gold standard when conducting a randomised control trial. It also providing greater explanation of the study methodology that may be beyond the final study manuscript.

2.2 MANUSCRIPT

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN FOR LIBERAL GLUCOSE CONTROL IN CRITICALLY ILL PATIENTS WITH PRE-EXISTING TYPE 2 DIABETES (LUICD) TRIAL.

Statement of authorship

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Contribution to paper	Conceptualisation of work, its realisation wrote manuscript and acted as corresponding author.		
Overall percentage (%)	80		
Certifcation	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	21-May-2023

Co-Author Contributions

By signing the statement of Authorship, each author certifies that:

The candidate's stated contribution to the publication is accurate (as detailed above);

Permission is granted for the candidate to include the publication in the thesis; and

The sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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Full title

Study protocol and statistical analysis plan for the Liberal Glucose Control in Critically Ill Patients with Pre-existing Type 2 Diabetes (LUCID) trial

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Abstract

Background: Contemporary glucose management of intensive care unit (ICU) patients with type 2 diabetes is based on trial data derived predominantly from patients without type 2 diabetes. This is despite the recognition that patients with type 2 diabetes may be relatively more tolerant of hyperglycaemia and more susceptible to hypoglycaemia. It is uncertain whether glucose targets should be more liberal in patients with type 2 diabetes.

Objective: To detail the protocol, analysis and reporting plans for a randomised clinical trial — the Liberal Glucose Control in Critically Ill Patients with Pre-existing Type 2 Diabetes (LUCID) trial — which will evaluate the risks and benefits of targeting a higher blood glucose range in patients with type 2 diabetes.

Design, setting, participants and intervention: A multicentre, parallel group, open label phase 2B randomised controlled clinical trial of 450 critically ill patients with type 2 diabetes. Patients will be randomised 1:1 to liberal blood glucose (target 10.0–14.0 mmol/L) or usual care (target 6.0–10.0 mmol/L).

Main outcome measures: The primary endpoint is incident hypoglycaemia (< 4.0 mmol/L) during the study intervention. Secondary endpoints include biochemical and feasibility outcomes.

Results and conclusion: The study protocol and statistical analysis plan described will delineate conduct and analysis of the trial, such that analytical and reporting bias are minimised.

Trial registration: This trial has been registered on the Australian New Zealand Clinical Trials Registry (ACTRN No. 12616001135404) and has been endorsed by the Australian and New Zealand Intensive Care Society Clinical Trials Group.

Introduction

It is advocated that blood glucose concentrations are closely monitored and maintained within a range considered safe during critical illness. Following the publication of a single centre, open-label randomised clinical trial of surgical intensive care unit (ICU) patients that reported a reduction in mortality with an intensive insulin treatment regimen,[1] many guidelines recommended targeting blood glucose concentrations below 6.1 mmol/L.[2,3]

However, this beneficial effect on mortality was not reproduced in a general ICU population by the same research group[4] nor by other researchers.[5-7]

The Normoglycemia in Intensive Care Evaluation — Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial[8] was a multinational randomised clinical trial comparing intensive insulin therapy (4.5–6.0 mmol/L) with conventional glucose control (6.0–10.0 mmol/L) in a heterogeneous cohort of critically ill patients.[8] The study indicated that targeting a blood glucose below 6.1 mmol/L increased 90-day all-cause mortality when compared with targeting 6.0–10.0 mmol/L.[8] The results from NICE-SUGAR have been incorporated into all major critical care and diabetes guidelines, with recommendations for insulin to be administered at blood glucose of 10.0 mmol/L or greater and titrated to a target below 10.0 mmol/L, regardless of pre-existing glycaemic status.[9,10]

Type 2 diabetes is a common comorbidity in critically ill patients,[11-15] and the observational data strongly support the concept that there is a signal of benefit from higher blood glucose in patients with type 2 diabetes.[16-19] Conversely, hypoglycaemia (absolute and relative) and increased fluctuations in blood glucose concentrations known as glycaemic variability, which are more likely to occur with administration of insulin, are strongly associated with increased mortality in patients with type 2 diabetes.[20,21]

The outcomes of single centre sequential period studies, which have compared a so-called liberal approach to glycaemic control (insulin initiated when blood glucose > 14.0 mmol/L; target 10.0–14.0 mmol/L) with usual care (insulin initiated when blood glucose > 10.0 mmol/L; target 6.0–10.0 mmol/L), suggest that a more liberal strategy is beneficial.[22-24] Kar and colleagues[23] studied 52 patients with pre-existing type 2 diabetes (4047 hours) receiving usual care and 31 patients (3244 hours) receiving liberal target care. Time-weighted blood glucose concentrations were predictably greater during the liberal period. The primary outcome of moderate to severe hypoglycaemia (< 4.0 mmol/L) occurred for 61 hours during the usual care period and for 12 hours during the liberal period. Participants allocated to the liberal approach were less likely to experience episodes of moderate to severe hypoglycaemia, with five compared with 18 participants during the usual care period (relative risk [RR], 0.47; 95% CI, 0.19–1.13).[23] Luethi and colleagues[24] studied 700 patients with type 2 diabetes who received either a liberal or usual approach to glycaemic management. In patients with poor pre-morbid blood glucose control (glycated haemoglobin [HbA1c] > 53 mmol/mol), hypoglycaemia

occurred in 9.6% of patients receiving standard care and in 4.1% of patients with liberal glucose targets ($P = 0.053$).[24] A liberal approach to glycaemia was not associated with an increased risk of hospital-acquired infectious, cardiovascular, renal or neurological complications.[25]

Despite the recognition that critically ill patients with type 2 diabetes may benefit from a more liberal approach to management of hyperglycaemia with insulin compared with current recommended glycaemic control,[26,27] this hypothesis has not been tested within a randomised controlled clinical trial. The objectives of the Liberal Glucose Control in Critically Ill Patients with Pre-existing Type 2 Diabetes (LUCID) trial are to evaluate the acute physiological effects of a liberal approach to glucose lowering with insulin and to determine whether a phase 3 randomised controlled trial of a liberal approach compared with usual care in critically ill patients with type 2 diabetes is appropriate and feasible.

Methods

Design

Multicentre, parallel group, open-label phase 2B randomised controlled clinical trial.

Setting

LUCID will be conducted in 23 ICUs in Australia and New Zealand.

Intervention

The trial will compare two blood glucose thresholds with complementary target ranges for the initiation and management of insulin therapy in critically ill patients with type 2 diabetes.

Participants assigned to the intervention of a liberal approach will have insulin commenced at a blood glucose level greater than 14.0 mmol/L and titrated to a target blood glucose in the range 10.0–14.0 mmol/L. If the blood glucose is below 10.0 mmol/L, no attempt to lower or increase blood glucose will be made, with the exception of local protocols for management of hypoglycaemia.

Participants assigned to the usual care group will have the usual care for the institution, which will be aligned to the NICE-SUGAR results, with insulin initiated at a blood

glucose level greater than 10.0 mmol/L and titrated to a target blood glucose level in the range of 6.0–10.0 mmol/L.

At each site, the approach to maintaining blood glucose within the relevant ranges will be informed by local practice and will employ local institutional blood glucose and insulin algorithms rather than a standardised protocol across all sites. This pragmatic approach will facilitate external validity and enable real-world comparisons.

Screening

All patients admitted to a participating ICU will be considered for enrolment. Patients will be eligible if they fulfil all the inclusion criteria and none of the exclusion criteria (Table 1). Inclusion and exclusion of patients (including reasons for exclusion) will be reported according to the Consolidated Standards for Reporting of Trials (CONSORT) guidelines (Figure 1).[28]

Assignment of intervention

Randomisation will be performed using a secure, web-based interface, with allocation concealment maintained using a permuted, variable size block randomisation stratified by site. Randomisation will not be performed until a participant fulfils all eligibility criteria and can be assigned to study treatment. Group assignment will be unblinded for all involved in the trial.

Baseline data

Baseline data will be recorded and presented (Online Appendix).

Outcome data

The primary outcome is incident hypoglycaemia defined as blood glucose below 4.0 mmol/L. Other outcomes, broadly categorised as feasibility, physiological and clinical outcomes, and processes of care will be reported (Table 2). When using the term “blood glucose”, we are referring to “point of care blood glucose” or “laboratory plasma

glucose", given that the test used for each glucose concentration may vary, the measurement technique of each sample is being collected. On Days 1–7, blood glucose will be recorded as the nearest sample to four time points (00:00 h, 06:00 h, 12:00 h and 18:00 h). If no sample is taken within 3 hours of the designated interval, data will be recorded as missing. If the daily minimum or maximum blood glucose concentration occurred outside of these periods, these will be recorded separately. On study days 8–14, the blood glucose closest to 08:00 hours will be recorded. Blood glucose will not be recorded after Day 14.

Hypoglycaemia will be defined as a blood glucose level below 4.0 mmol/L, obtained from arterial, capillary or venous blood and measured using point of-care glucometer, arterial blood gas analyser or hospital laboratory testing. An incident event will be defined as hypoglycaemia in the absence of recorded hypoglycaemia in the preceding 4 hours. Because recurrent hypoglycaemia may cause greater harm than a single episode,[20,29] the number of episodes of hypoglycaemia per patient and the proportion of patients experiencing episodes will be reported. Relative hypoglycaemia will also be recorded and defined as a more than a 30% reduction from pre-morbid estimated average glucose, which will be calculated by the formula: (mmol/L) = 1.59 × HbA_{1c} (%) − 2.59.[20,21] Glycaemic variability will be reported using both the coefficient of variation (CoV) and standard deviation (SD) over the first 7 study days.[30] Maximum, minimum and group mean glucose will also be reported.

Feasibility outcomes include recruitment and consent rates. The number of study participants assigned to usual care who subsequently receive insulin and the number of overall participants in whom blood glucose is 10.0 mmol/L or greater will be reported, given that insulin-induced hypoglycaemia and glycaemic variability are proposed as key mechanisms underlying harm of usual care.[29] Time within blood glucose range and protocol adherence will also be reported. The time outside of blood glucose range does not equate to non-adherence to the protocol. Rather, protocol non-adherence will be restricted to episodes when the assigned blood glucose is no longer being targeted. Non-adherence will be recorded using a categorisation process to discriminate between clinical (eg, the clinician determines that the assigned blood glucose target is no longer in the patient's best interest) and research-related (eg, consent withdrawal) reasons.

Criteria for discontinuing or modifying allocated intervention

Study participants will continue to receive the intervention while in the ICU or censored at 28 days from randomisation. Glucose management outside the ICU will be at the discretion of the treating physician. The intervention will cease if consent is withdrawn before Day 28, the treating clinician determines that it is in the patient's best interest to cease the trial intervention, or the treating clinician wishes to transition the participant to an alternative regimen, such as long-acting insulin or oral agents, before discharge from ICU.

Clinical outcomes

Clinical outcomes include 90-day all-cause mortality; length of ICU and hospital stay, with death as a competing risk; hospital discharge destination; and location at Day 90. Infectious complications will be recorded as the number of patients with established blood stream infections and sternal wound infections in cardio-thoracic surgical patients up to Day 28 (Online Appendix).[31] To evaluate for a potential difference in infectious complications that may not be apparent as blood stream infections, the highest daily white blood cell count and C-reactive protein concentration will be reported if collected as part of routine care.

Protocol registration and endorsement

The concept for the trial was presented at the Australian and New Zealand Intensive Care Society Clinical Trials Group (ANZICS-CTG) 2016 Annual Meeting on Clinical Trials in Intensive Care. The protocol was subsequently drafted, registered with the Australian New Zealand Clinical Trials Registry (2 August 2016, Trial ID: ACTRN12616001135404), and endorsed as an ANZICS-CTG trial (10 November 2016).

Funding and support

The trial has received funding from four separate project grants:

- the Royal Adelaide Hospital Research Committee Project Grant (2017);

- the Intensive Care Foundation Fisher and Paykel Research Project Grant (2017);
- the Diabetes Australia Research Trust Project Grant (2018); and
- the Melbourne Academic Centre for Health Rapid Applied Research Translation Grant (2019).

Alexis Poole enrolled in a PhD program and will include these data. He receives a University Postgraduate Scholarship (Faculty of Health Sciences Divisional Scholarship and Royal Adelaide Hospital Research Committee Dawes Top-up Scholarship) to support his involvement. The trial is managed within the Centre of Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide. The members of the Management Committee and participating sites are listed in the Online Appendix.

Participant safety

Patients will be withdrawn from the trial if the treating clinician determines that it is in the patient's best interest to cease the trial intervention. Adverse and serious adverse events will be recorded along with relationship to therapy and action taken (Online Appendix).

Analysis and reporting of results

Data management

Study data will recorded on paper case report forms and then entered into REDCap — a secure web-based data capture tool.[32] On-site source monitoring will be conducted by the coordinating centre and will include 25% source data verification for the primary endpoint. Source data verification will be completed for all data points for the first two patients at each centre and partial source data verification will be completed randomly thereafter (20% of total recruitment).

Presentation of outcome data

The proposed table and figures are shown in Table 3. A complete set of mock tables and figures is provided in the Online Appendix.

Sample size

The sample size was based on pilot data from a single-centre exploratory study of liberal glucose control against usual care, with the relative risk of hypoglycaemia being 0.47,[23] and assumed a baseline rate for incident hypoglycaemia of 17.5% from NICE-SUGAR.[8] A sample size of 408 participants would provide 80% power (α 0.05; Δ 9.3%) to determine a reduction in hypoglycaemic episodes. An additional 10% was added to account for refused consent, loss to follow-up and an unexpected short period of observation. Accordingly, 450 participants will be included in the trial.

Analysis of primary and secondary outcomes

Data will be presented as *n*/*N* (%), mean (SD) or median (interquartile range [IQR]), with between-group comparisons using χ^2, *t* test or rank-sum test as indicated. Because of the consent model, the main analyses will be conducted on a modified intention to treat basis (Figure 1).[33]

The primary outcome will be reported as the incident rate with corresponding 95% confidence interval (CI) and as the raw number of events per group and the proportion of individuals experiencing one or more events. Secondary outcomes will be presented as point estimates with 95% CI. Group point estimates and confidence intervals will be adjusted for within-subject correlation using generalised estimating equations regression with robust standard errors. The incident rate will be standardised to a defined ICU exposure interval; for example, incident rate = X (95% CI) events per *N* ICU days.

Mortality at Day 90 will be analysed by χ^2 test and adjusted for pre-set covariates (age, sex, Acute Physiology and Chronic Health Evaluation [APACHE] II, invasive mechanical ventilation and post-operative admission) by logistic regression, with standard errors adjusted for ICU site.

Pre-defined subgroup analyses

An exploratory subgroup analysis will be conducted based on HbA_{1c} 53 mmol/mol or greater, taken to reflect chronic hyperglycaemia or suboptimal glycaemic control.

Stratified randomisation based on this subgroup will not be employed, as this information will frequently be unavailable at randomisation.[34]

Interim analysis

An interim safety analysis will be conducted after 200 patients are enrolled. An independent Data Safety Monitoring Board (DSMB), composed of an experienced clinical researcher and biostatistician without other connection to the LUCID trial, will operate under a charter based on the recommendations of the DAMOCLES Study Group[35] (Online Appendix). Analysis will include primary, secondary, feasibility, clinical and safety outcomes, although not outcomes of interest for the final dataset, ICU and hospital mortality will be included, in addition to 90-day mortality, to facilitate the interim analysis time frame.

Missing data

No imputation will be undertaken for missing data. Rates for missing data will be reported in the supplement when more than 10% values are missing.

Ethical considerations

Ethics approval

The Royal Adelaide Hospital/Central Adelaide Local Heath Network Human Research Ethics Committee has approved the current protocol version 3 dated 26 May 2017 (HREC/16/ RAH/220 and Online Appendix). Under the National Mutual Acceptance (NMA) Scheme, this covers all sites in South Australia, Victoria, New South Wales and Queensland, except for the Alfred Hospital in Victoria. The Alfred Hospital Human Research Ethics Committee has approved a modified protocol allowing only prior written informed consent (Project No. 411/17). The protocol has been approved by the Central Australian Human Research Ethics Committee (Alice Springs Hospital, HREC-16-446) and by the Northern A Health and Disability Ethics Committee in Auckland for sites in New Zealand (ethics reference No. 18/ NTA/144).

Consent process

As many patients eligible for this trial will be too unwell to provide informed consent, the approach to obtaining consent in Australia will be based on that developed from the guidelines in Chapter 4.4 of the National Health and Medical Research Council National Statement[36] and is consistent with local laws. The approach is a hierarchical consent model. For competent patients, informed consent will be obtained before enrolment. For patients who do not have capacity to consent, the approach to consent will be via the medical treatment decision maker. For patients who do not have capacity and for whom there is no immediately available medical treatment decision maker, patients can be enrolled and consent to continue participation obtained. Consent to continue participation will be obtained at the earliest opportunity and the time will be recorded. The approach to inform the substitute decision maker of study participation if the patient dies before this process is completed is provided in the Online Appendix.

In New Zealand, we will use an approach consistent with section 7.4 of the Health and Disability Code,[37] which outlines the appropriate approach to providing treatment to patients who are unable to consent for themselves. The specific approach will be:

- to consider whether participation is in the best interest of each individual patient; and
- as soon as it is practical and reasonable to do so, to seek the advice of persons interested in the patient's welfare to establish that study participation is consistent with the patient's wishes.

All participants who recover sufficiently will be given the opportunity to provide informed consent for ongoing study participation and for the use of data collected for the study.

Approach to co-enrolment

The ANZICS-CTG policy on co-enrolment will be followed.[38] Site investigators may co-enrol participants in LUCID and other trials, as long as the intervention in other trials is unrelated to glycaemic control and does not require a specific blood glucose target. Trials with co-enrolment approval are listed in the Online Appendix.

Knowledge translation

Data sharing statement

De-identified individual participant data reported in this trial will be made available to researchers who provide a written, methodologically sound proposal between 3 and 7 years after publication. Proposals should be directed to the Principal Investigator. If approved, requestors will be required to enter into a data access and confidentiality agreement.

Information distribution

After completion of the trial, results will be presented at relevant national and international meetings and published in a peer-reviewed journal.

Summary

This study will provide important information to inform future research on the management of patients with type 2 diabetes admitted to an ICU. Our pre-specified statistical analysis plan was prepared before the completion of recruitment and data collection. This published plan provides a detailed description of the principles and methods for analysis and reporting of the study results.

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Tables

Table 1. Study inclusion and exclusion criteria

	Description
Inclusion criteria	• Adult patients (aged ≥ 18 years) • Patients expected to remain in the ICU until the day after tomorrow • The patient has either an arterial or central line in situ, or the placement of an arterial or central line is imminent (within the next hour) as part of routine management • The patient has type 2 diabetes • The treating clinician believes that that there is a reasonable likelihood that a blood glucose concentration ≥ 10.0 mmol/L will be recorded at some stage during the ICU admission
Exclusion criteria	• Death during ICU admission is deemed to be inevitable • Admitted to the ICU for treatment of diabetic ketoacidosis or hyperosmolar state • Patients who have “juvenile” type 1 diabetes • Requirement for specific blood glucose target as determined by the treating doctor; that is, the treating clinician believes either intervention or standard care arms of LUCID would not be in the best interests of the patient • The patient is expected to be eating before the end of the next calendar day • Patients who have previously had hypoglycaemia without documented full neurological recovery • The patient cannot provide prior informed consent and there is documented evidence that the patient has no legal surrogate

	decision maker, and it appears unlikely that the patient will regain consciousness or sufficient ability to provide delayed informed consent
	• The patient has been in the study ICU or another ICU for ≥ 24 h during the index admission
	• The patient has previously been enrolled in LUCID
	• Women who are pregnant or suspected to be pregnant determined by a positive serum or urine hCG test

hCG = human chorionic gonadotropin; ICU = intensive care unit; LUCID = Liberal Glucose Control in Critically Ill Patients with Pre-existing Type 2 Diabetes trial.

Table 2. Study outcomes

	Description
Primary outcome	• Incident hypoglycaemia (blood glucose < 4.0 mmol/L) ➢ Reported as event rate per unit time adjusted for within-patient correlation ➢ Also reported as the raw number of events and proportion of patients experiencing one or more events
Secondary outcomes	
Feasibility outcomes	• Consent rate: feasibility rate ≥ 75% • Recruitment rate: feasibility rate ≥ 1.8 patients per site per month • Insulin administration: ≥ 70% usual care receiving insulin • Protocol adherence: ≥ 80% of time enrolled being allocated to the assigned protocol
Physiological outcomes	• Minimum blood glucose ➢ Relative hypoglycaemia defined as a > 30% reduction from pre-morbid estimated average glucose ➢ Glycaemic variability indicated by CoV and SD over the first 7 study days • Group mean estimate of blood glucose • Maximum blood glucose
Clinical outcomes	• 90-day all-cause mortality • ICU and hospital length of stay • Percentage of patients with proven blood stream infection • Hospital discharge destination • Location at Day 90
Processes of care	• Blood glucose measurement technique

- Days of administration of nutrition, corticosteroids and/or catecholamines

CoV = coefficient of variation; ICU = intensive care unit; SD = standard deviation.

Table 3. Planned tables and figures

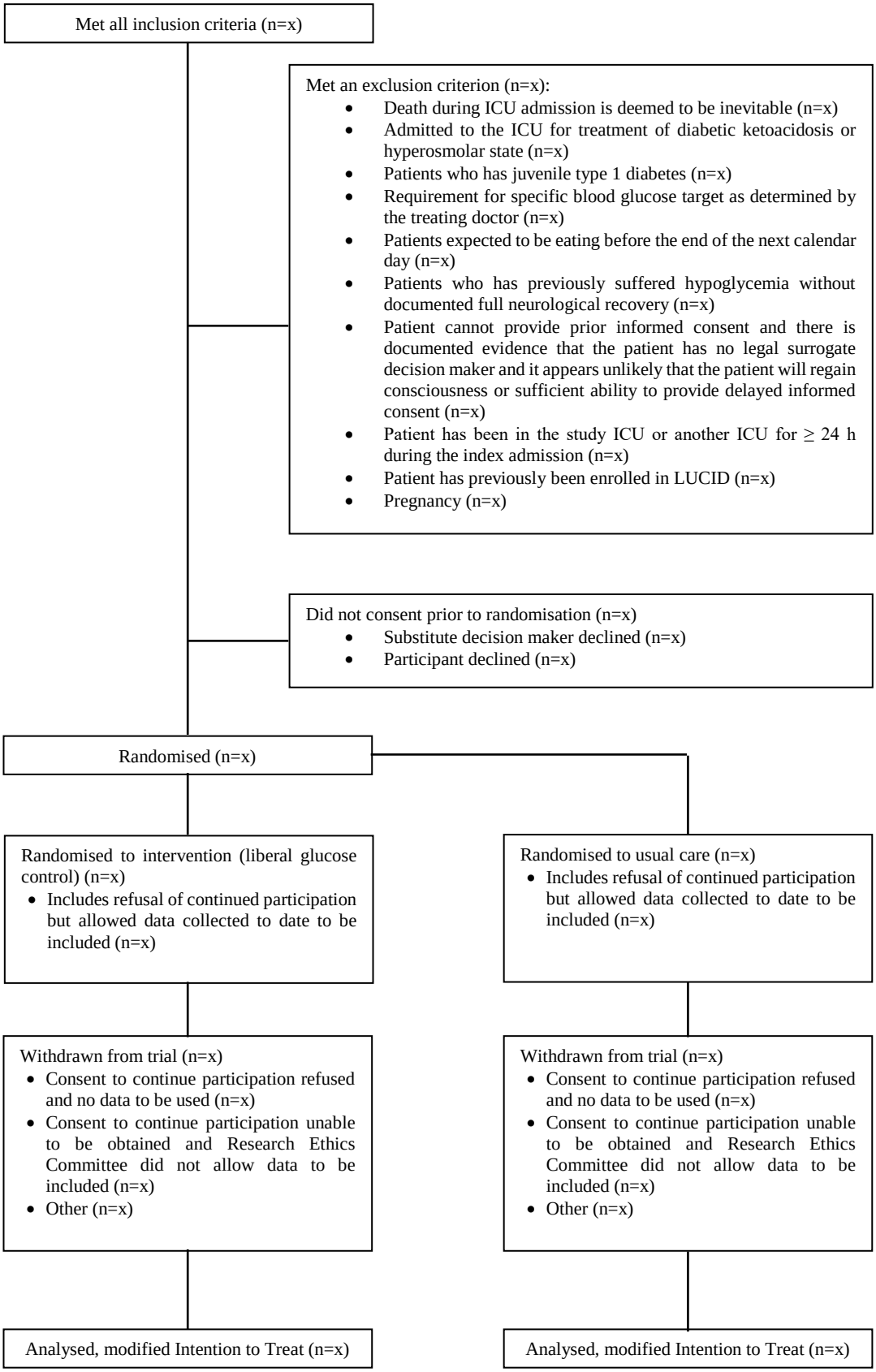
Proposed tables and figures	Table/ figure	Description
For the manuscript	Table 1	Baseline patient characteristics (by treatment group)
	Table 2	Primary and secondary outcomes (by treatment group)
	Figure 1	Flow of participants through the trial (see Figure 1)
	Figure 2	Population-averaged mean blood glucose (by treatment)
For the online Appendix	Table S1	Description of consent process
	Table S2	Process of care measured in ICU (blood glucose measurement technique, insulin nutrition, corticosteroids and catecholamines administered)
	Table S3	Subgroup analysis (primary and secondary outcomes for $HbA_{1c} \geq 53$ mmol/mol
	Table S4	Summary of protocol deviations/adverse events
	Figure S1	Insulin administration v time (units per day)
	Figure S2	Population-averaged mean blood glucose (by treatment) for subgroup $HbA_{1c} \geq 53$ mmol/mol
	Figure S3	Cumulative incident plots for the subhazards (ICU or hospital discharge), with death as a competing risk

HbA1c = glycated haemoglobin; ICU = intensive care unit.

Figures

Figure 1. Consolidated Standards for Reporting of Trials (CONSORT): study flow

Diagram



Supplemental material

Table of Contents

Baseline data

Infective complications reported

Management Committee

Proposed tables and Figures for Manuscript

Table 1: Baseline patient characteristics by treatment group

Table 2: Primary and secondary outcomes by treatment group

Figure 1: Flow of participants through the trial (see Figure 1)

Figure 2: Population-averaged mean blood glucose (by treatment)

Proposed tables and figures for the supplementary appendix

Table S1: Description of consent process

Table S2: Process of care measured in ICU

Table S3: Subgroup analysis (primary and secondary outcomes for HbA1c ≥ 7.0%)

Table S4: Summary of protocol deviations/adverse events

Figure S1: Insulin administration vs. time (Units per day)

Figure S2: Population-averaged mean blood glucose (by treatment) for subgroup HbA1c ≥ 7.0%

Data Safety Monitoring Committee (DSMB) Charter

Consent process

List of mutually agreed co-enrolment studies

Baseline data

- Patient demographics
- ICU admission diagnosis (as collected for ANZICS APD)
- Admission category (elective/emergency | surgical/medical)
- APACHE II/III score (as collected for ANZICS APD)
- SOFA score (closest prior to randomisation)
- Mechanical ventilation (within 1 hour prior to randomisation)
- Renal replacement (within 1 hour prior to randomisation)
- HbA1c (at admission or on recruitment)
- Blood lactate (Level closest but prior to randomisation)
- Serum creatinine (Level closest but prior to randomisation)
- Corticosteroids (Y/N and equivalent dose of hydrocortisone)
- Catecholamines (Y/N and equivalent μg/min of noradrenaline) *only if the participant is receiving noradrenaline, adrenaline, vasopressin or terlipressin.
- Duration of diabetes
- Treatment of diabetes (oral metformin, oral other, s/c insulin once or twice a day and units/24 h, s/c insulin > 2 times a day and units/24 h, and s/c other) *if receiving multiple treatments, hierarchy will be S/C over oral).
- How was the diagnosis of T2DM determined? (patient notes, direct questioning of patient, direct questioning of substitute decision maker or other)
- Presence or absence of known cardiovascular disease (Y/N/Unknown)
- Presence or absence of known retinopathy (Y/N/Unknown)
- Presence or absence of known nephropathy (Y/N/Unknown)

Infective complications reported

All positive blood cultures after randomisation with an organism not recorded prior to randomisation, except for 'frequent contaminant' organisms.

- Designated 'frequent contaminant' organisms:
- Coagulase-negative staphylococci
- Corynebacterium
- Bacillus
- Propionibacterium

However, if the latter organisms (of the same sub-type or with an identical anti-biogram) are reported in more than one bottle in a 24 hour period it will be recorded as a blood stream infection.

Management Committee

Authors

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Supplemental material 4

Proposed tables and Figures

Proposed tables and figures for the manuscript	
Table 1:	Baseline patient characteristics by treatment group
Table 2:	Primary and secondary outcomes by treatment group
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Figure S2:	Population-averaged mean blood glucose (by treatment) for subgroup HbA1c ≥ 7.0%

Table 1. Baseline patient characteristics.

Characteristic	Liberal	Standard
Number (%)		
Age (years), median [IQR]		
Sex (male), no. (%)		
Weight (kg), median [IQR]		
Body-mass index (kg/m2), median [IQR]		
Admission category, no. (%) Medical / Surgical Elective / Emergency		
ICU admission source, no. (%) Emergency department Ward Other hospital Other ICU Operating or recovery room		
APACHE II Score, median [IQR]		
APACHE III Score, median [IQR]		
Organ failure or dysfunction, No. (%)		
Respiratory Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Coagulation Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Liver Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Cardiovascular Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Central Nervous System Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Renal Dysfunction (SOFA score 1,2) Failure (SOFA score 3,4)		
Estimated duration of type II diabetes, no. (%) <1 year 1-5 years 6-19 years		

≥20 years Unknown		
Treatment of diabetes, no. (%) Diet Oral metformin Oral other S/C Insulin		
Relevant past medical history, no. (%) Chronic cardiovascular Retinopathy Nephropathy		
Glycated haemoglobin (%), median [IQR]		
Glucose (mmol/L), median [IQR]		
Creatinine (μmol/L), median [IQR]		
Lactate (mmol/L), median [IQR]		
Invasive Ventilation, no. (%)		
Renal replacement therapy, no. (%)		
Systemic Corticosteroids Number (%) Equivalent hydrocortisone dose (mg/day)		
Catecholamines, no. (%) None Low ≤ 5 mcg/min Medium 6-30 mcg/min High > 30 mcg/min		
Nil		
Nutrition – no. /total no. (%) Fasted Oral diet Enteral nutrition Parental nutrition Combination		

Table 2. Outcomes (modified intention to treat).

Outcome	Liberal	Standard
Primary		
Incident hypoglycaemia (BGL < 4.0mmol/L) Total events, no. (%) Proportion of patients (≥1 event), n (%) Incident rate per study period exposure		
Secondary		
Blood glucose (mmol/L) Patient minimum, median [IQR] Patient maximum, median [IQR] Population averaged mean (sd)		
Glycaemic control episodes, n. (%) Relative hypoglycaemia (1 or more episodes) Glucose > goal limit (14 or 10 mmol/L)		
Clinical outcomes		
Mortality (90-days), no. (%)		
Length of Stay (days), med [IQR] Intensive care unit Hospital		
Patients with blood stream infection no. (%)		
Cardio-thoracic surgical patients with sternal wound infection no. (%)		
White blood cell count (x109/L), median [IQR])		
C-Reactive protein (mg/L), median [IQR])		
Hospital discharge destination, no. (%) Home Rehabilitation Other acute ICU Other acute hospital Long term care Other		

Table S1. Description of consent process

Initial Consent Type	
Prior participant consent - n. (%)	
Prior medical treatment decision maker - n. (%)	
Delayed participant consent - n. (%)	
Delayed medical treatment decision maker - n. (%)	
Initial Consent Type	
Prior participant consent - n. (%)	

Table S2. Process of care measured in ICU

End Point	**Liberal**	**Standard**
Blood glucose measurement technique, no. (%) Local laboratory Blood gas analyser Point of care glucometer Unknown		
Nutrition, days of, no. (%) Enteral Nutrition Parenteral nutrition Fasted Oral nutrition Combination of nutrition		

Table S3. Primary and secondary outcomes for subgroup analysis (HbA1c > 7.0%)

Outcome	**Liberal**	**Standard**
Primary		
Incident hypoglycaemia (BGL < 4.0mmol/L) Total events, no. (%) Proportion of patients (≥1 event), n (%) Incident rate per study period exposure		
Secondary		
Blood glucose (mmol/L) Patient minimum, median [IQR] Patient maximum, median [IQR] Population averaged mean (sd)		
Glycaemic control episodes, n. (%) Relative hypoglycaemia (1 or more episodes) blood glucose ≥ goal limit (14 or 10 mmol/L)		
Clinical outcomes		
Mortality (90-days), no. (%)		

Length of Stay (days), med [IQR] Intensive care unit Hospital		
Patients with blood stream infection no. (%)		
Cardio-thoracic surgical patients with sternal wound infection no. (%)		
White blood cell count (x109/L), median [IQR])		
C-Reactive protein (mg/L), median [IQR])		
Hospital discharge destination, no. (%) Home Rehabilitation Other acute ICU Other acute hospital Long term care Other		

Table S4. Summary of protocol deviations/adverse events

Protocol Deviations	**Liberal** (N=x)	**Standard** (N=y)
Patient randomised and not eligible, no. (%)		
Adult patient aged < 18 years		
Patient did not have either an arterial or central line in situ		
Patient does not have type 2 diabetes		
At time of enrolment death during ICU admission is deemed to be inevitable, not committed to full active treatment		
Admitted to the ICU for treatment of diabetic ketoacidosis or hyperosmolar state		
Patient has juvenile type 1 diabetes		
Requirement for specific blood glucose target as determined by the treating doctor		
Patient has previously suffered hypoglycemia without documented full neurological recovery		
At time of enrolment patient had been in the study ICU or another ICU for ≥ 24 h during the index admission		
Patient has previously been enrolled in LUCID		
Females who are pregnant or suspected to be pregnant determined by a positive serum or urine human chorionic gonadotropin (hCG) test		
Insulin administered outside of protocol parameters		
Insulin administration outside of protocol parameters, no. (%) Administration error Patient safety Wrong insulin protocol used Other		

Adverse event / Serious adverse event, no. (%) Adverse event Serious adverse event		
Suspected relationship of AE to therapy, no. (%) Not related Unlikely Possibly Probably Definitely		
Action taken on insulin protocol, no. (%) None Temporarily held Permanently discontinued		
Outcome of Event, no. (%) Resolved Resolved with sequelae		
Serious Adverse Event (SAE) type, no. (%) Death Prolonged hospitalisation/readmission Life threatening Permanent disability Congenital anomaly Medically important		

Data Safety Monitoring Committee (DSMB) Charter

This Charter is based on the recommendations of the DAMOCLES Study Group[1].

Members

Prof Bala Venkatesh (Chair) Senior Clinician University of Queensland

Prof Michael Bailey Senior Statistician Monash University

Introduction

The DSMB will meet via telephone once after 200 patients have been enrolled. The LUCID Project Manager (Mr Alex Poole) will provide support in setting up this teleconference but will not attend the teleconference. All DSMB members must be on the teleconference for a decision to be made. The LUCID biostatistician (Dr Mark Finnis) will provide access to trial data to the DSMB biostatistician (Prof Michael Bailey) so that the interim analysis can be completed. Access to these data will be provided two weeks prior to the DSMB meeting. Prior to, or following their meeting, the DSMB may request any additional trial data from the LUCID Management Committee.

DSMB Objectives

To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.

DSMB Terms of Reference

The DSMB should receive and review the progress and conduct an interim analysis based on data as specified in the statistical analysis plan (below), and then provide advice on the conduct of the trial to the LUCID Management Committee.

1. The DSMB should not advise the LUCID Management Committee to cease the trial based on either futility or that the intervention appears superior to standard care.

2. The DSMB should advise the LUCID Management Committee to cease the trial if the intervention appears to be causing harm. Determination of trial stopping rules remains the prerogative of the DSMB.

3. The DSMB should assess mean (SD) glucose in the standard group and report to the LUCID Management Committee whether patients in this group are achieving mean blood glucose concentrations within the standard range.

4. The DSMB should report the number of patients in the standard group who have received insulin in the first 48 hours and report to the LUCID Management Committee whether the eligibility criteria are satisfactory to identify a group that will receive insulin during the study period.

5. The DSMB should assess mean (SD) and daily peak glucose in the intervention group and report to the LUCID Management Committee whether patients in this group are at risk from blood glucose concentrations in excess of the range targeted.

6. The DSMB should comment to LUCID Management Committee the feasibility of the trial based on current recruitment per site per month

7. The DSMB should report on the safety of the trial based on the number of protocol deviations and serious adverse events.

Trial synopsis

LUCID is a 450 patient, multicentre, parallel group, single blinded, RCT to compare the outcomes of targeting 'liberal' blood glucose concentrations (10-14 mmol/L) to 'standard care' glucose control (6-10 mmol/L) in critically ill patients with T2DM.

450 critically ill adults (≥18 years of age) with known T2DM and arterial or central venous access who are expected to remain in the ICU for >48 hours will be eligible to be enrolled. Study participants will receive the intervention whilst in ICU or until 28 days

from randomisation. Blood glucose will be measured every 1-4 hours according to each local ICU existing protocol.

The trial will compare two thresholds to start insulin and target blood glucose concentrations:

1. In the 'liberal' group, insulin (actapid) will be commenced when blood glucose >14.0 mmol/L and blood glucose targeted to 10-14 mmo/l.

2. 'Standard' care will be commencement of insulin (actapid) when blood glucose is > 10.0 mmo/l to target blood concentrations at 6-10 mmol/L.

The primary outcome is incident hypoglycaemia, defined as blood glucose < 4.0 mmol/L.

Secondary physiological outcomes include: the severity of hypoglycaemia (nadir), frequency of hypoglycaemia, relative hypoglycaemia, glycaemic variability, population-averaged mean glucose and peak blood glucose.

Secondary feasibility outcomes include: the consent rate is ≥75% of substitute decision makers approached to consent, chose to participate in the study, in the standard care group insulin administration is required in ≥ 70% of study participants, recruitment rate ≥ 1.8 patients per site per month, protocol adherence ≥ 80% of time spent enrolled and in ICU.

Tertiary outcomes include all-cause mortality and infections.

The trial is registered (ANZCTR number 12616001135404).

Statistical analysis plan for an interim analysis

Patient population eligible to the interim analysis

Inclusion criteria: The first 200 patients enrolled in the study censored 7 days after the 200th patient is enrolled.

Exclusion criteria: Patients who withdrew the consent of participation to the study.

Data used in the interim analysis

Baseline data: (age, gender and HbA1c).

Primary outcome data: Number of hypoglycaemic events.

Secondary outcome data: Nadir of hypoglycaemic events.

Secondary outcome data: ICU daily data on blood glucose concentrations (mean ±SD) for all time-points censored at day 7.

Secondary outcome data: ICU daily data on blood glucose concentrations maximum and minimum censored at day 7.

Feasibility data: Number of patients in standard care arm who have received any insulin during this first 48 hours.

Feasibility data: Recruitment per site per month.

Feasibility data: Consent data (number prior consent, consent to continue, consent not obtained).

Tertiary outcome data: ICU daily data on number of blood cultures positive censored at day 14.

Tertiary outcome data: Day 28 assessment (alive, dead or lost to follow up).

Safety data: All protocol deviations including number of patients randomised and not eligible and number of patients consent to continue was withdrawn.

Safety data: All reported serious adverse event.

Timing

The interim analysis will be conducted when all the data for the analysis of the first 200 patients are entered for the 28 day outcome assessment.

DSMB report

If the DSMB is concerned that study participants are being harmed by the intervention or the conduct of the trial, the DSMB Chair will contact the LUCID Management Committee

Chair as soon as possible (within 72 hours) to recommend cessation of recruitment. This advice will be followed-up with a written report and recommendations that will be emailed to the LUCID Management Committee Chair (carbon copy to the project manager and biostatistician) within 28 days of this advice.

If the DSMB recommends continuation of the trial with modifications to the protocol these should be compiled into a written report and emailed to the LUCID Management Committee Chair (carbon copy to the project manager and biostatistician) within 28 days of the meeting.

If the DSMB recommends continuation of the trial without modification to the protocol, this advice should be emailed to the LUCID Management Committee Chair (carbon copy to the project manager and biostatistician) within 28 days of the meeting.

References

1. Damocles Study Group NHSHTAP. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet 2005;365(9460):711-722.

Human Research Ethics Committee Approvals

Central Adelaide Local Health Network – Human Research Ethics Committee

HREC Reference: HREC/16/RAH/316

Initial approval: 23rd September 2016

Central Australian Human Research Ethics Committee

HREC Reference: HREC-16-446

Initial approval: 7th March 2017

Northern A Health and Disability Ethics Committee

Consent process

If the substitute decision maker remains in the hospital and the investigator at that site considers it appropriate, the substitute decision maker will be approached prior to leaving the hospital. It is anticipated that this would happen infrequently.

- If the substitute decision maker has left hospital or the investigator at that site considers it inappropriate to immediately approach them, between 7 and 14 days after death the research coordinator from each site will call the listed substitute decision maker to arrange a meeting with the investigator from that site.

- If the substitute decision maker declines to attend the research coordinator will provide information via phone and if the substitute decision maker agrees a follow up information sheet will be sent.

- If the research coordinator is unable to speak with the substitute decision maker after making three attempts, they will send an information sheet to the substitute decision maker.

At some institutions delayed consent is not permitted due to legal and local governance requirements, in these locations prior next of kin consent or prior participant consent will only be used.

List of mutually agreed co-enrolment studies

PLUS	A multi-centre, blinded, randomised, controlled trial to determine whether fluid resuscitation and therapy with a "balanced" crystalloid

	solution (Plasma-Lyte 148®) decreases 90-day mortality in critically ill patients requiring fluid resuscitation when compared with the same treatment using 0.9% sodium chloride (saline).
SPICE III	A prospective multicentre randomised controlled trial of early goal directed sedation compared with standard care in mechanically ventilated patients in intensive care
ICU-ROX	A phase 2b, multicentre, randomised, single blinded clinical trial parallel groups comparing liberal versus conservative oxygen therapy in mechanically ventilated adults in the ICU
VITAMINS	A pilot, multi-centre, randomised, open-label controlled, feasibility study to compare the administration of vitamin C, thiamine and hydrocortisone vs hydrocortisone alone in critically ill patients with septic shock
STARRT-AKI	Standard versus accelerated initiation of renal replacement therapy in acute kidney injury
SOFter	Skeletal Outcomes Following Intensive Care: Effect of denosumab on bone turnover markers in critically ill women - A safety and feasibility, randomised, placebo controlled trial
INTENT	Intensive nutrition therapy compared to usual care in critically ill adults randomised controlled trial
TAME	Targeted therapeutic mild hypercapnia after resuscitated cardiac arrest: A phase III multi-centre randomised controlled trial
TTM2	Targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest 2, a randomised clinical trial
Neb-Hep	A multi-centre, randomised, double blind, placebo controlled trial of nebulised heparin for lung injury
SuDDICU	A cluster RCT of the clinical effectiveness and cost-effectiveness with a contemporaneous study of the ecological impact of selective decontamination of the digestive tract in critically ill patients treated in ICUs

2.3 CONCLUSIONS

2.3.1 Introduction

The objective of the manuscript presented in this chapter were to provide a detailed description of the LUCID trial, which is presented in chapter 3. The pre-publication of trial methodology and analysis allows accurate interpretation of results. These details are also critical should trial replication be warranted. For critical appraisal of study methodology and trial results to occur, a detailed explanation of trial methodology is important and should occur prior to trial completion. The details provided in this chapter allow this to occur.

2.3.2 Contribution of the work described in this thesis to the understanding liberal glucose targets in critically ill patients with pre-existing type 2 diabetes.

The manuscript presented in chapter 2.1 is a thorough and detailed explanation of the population of interest who were considered likely to benefit from the intervention studied in the LUCID trial (chapter 3). While existing exploratory data suggests benefit in this population, this is the first detailed explanation of a randomised control trial in the critically ill with pre-existing type 2 diabetes. The aim of this randomised clinical trial was to include those likely to remain in the ICU for a reasonable duration, which would ensure reasonable exposure to treatment and allow sufficient time for the primary outcome (hypoglycaemia) to occur. Exclusion criteria included those presenting with diabetic ketoacidosis and hyperosmolar states. These criteria were chosen as specific approaches are used in these conditions.

The greater duration of ICU admission will increase the primary outcome (hypoglycaemia) and the greater the baseline event rate will reduce required sample size (7). However, the eventual duration of ICU admission is a post-randomisation event and may be impacted by the intervention (8). Given these considerations it was important to utilise incident rate ratio to determine the primary outcome. The reporting method for the primary outcome allowed interpretation of whether a greater threshold for the commencement of insulin decreases the incidence of hypoglycaemic events (<4.0 mmol/L). The primary outcome (hypoglycaemia) has been associated with mortality in the critically ill population, making it an appropriate biomarker for a large phase 2 randomised clinical trial.

The secondary outcomes of LUCID included feasibility outcomes, as these would provide information on any subsequent phase 3 trial. Mortality outcome was exploratory in the

LUCID trial, as the sample size was insufficient to detect a difference in mortality that was plausible. By collecting data on mortality, the LUCID trial informed whether conducting a further phase 3 trial was warranted. A predefined subgroup analysis was planned for those which would regularly be classed a poorly controlled diabetics determined by a HbA_{1c} > 7% (53mmol/mol).

2.4 FUTURE DIRECTIONS

The descriptions and explanations made in chapter 2.1 provide the method and analysis approach that was utilised in the LUCID trial. These pre-stated approaches ensure subsequent results can be trusted and inform practice and or future research into this population or treatment approach.

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Chapter 3:

Multicentre randomised clinical trial of liberal blood glucose management in critically ill patients with type 2 diabetes

3.1 INTRODUCTION

Existing evidence indicates that for patients with pre-existing type 2 diabetes blood glucose targets other than those used for stress hyperglycaemia may be beneficial and reduce harm associated with hypoglycaemia (1, 2). This concept has been hypothesised based on the outcomes of observational studies that in critically ill patients with pre-existing type 2 diabetes chronic hyperglycaemia attenuates the relationships between acute hyperglycaemia, hypoglycaemia, as well as glycaemic variability and outcomes (3). In addition, exploratory studies utilising sequential period study design indicate that an increased threshold before commencing insulin infusions and titrating to higher blood glucose ranges is feasible (1, 2, 4). However, due to small sample sizes and the risk of bias with the exploratory study design, such findings are insufficient to inform practice.

As current practice and guidelines are informed by studies that have studied heterogenous patient populations, it is important to establish whether the current targets are deleterious to individuals with pre-existing type 2 diabetes. This is particularly important given that the percentage of patients with pre-existing type 2 diabetes who are admitted to the intensive care unit (ICU) is substantially greater than that of the general population (5).

Chapter 3 describes the conduct and results of the largest multicentre randomised controlled trial to compare a liberal approach to usual care in the blood glucose management of critically ill patients with pre-existing type 2 diabetes. The primary objective of this study was to determine if an elevation in blood glucose threshold from 10 mmol/l to 14 mmol/l for the commencement of insulin would have an impact on the incidence of hypoglycaemia. Hypoglycaemia was chosen as a biomarker because it has the potential to be impacted by the intervention (intravenous insulin) and there are strong

relationships between the incidence of mortality and insulin-induced hypoglycaemia in critically ill patients.

3.1.1 **Objectives**

The objectives of this multicentre randomised controlled trial of liberal blood glucose control were to determine the impact of a higher blood glucose concentration are commencement point for insulin would have on hypoglycaemic episodes and other glucose metrics, and provide an estimate as to the impacts on patient-centred outcomes. This is the first randomised control trial to explore this approach and is likely to inform clinical care in critically ill patients with type 2 diabetes.

3.2 MANUSCRIPT

THE EFFECT OF A LIBERAL APPROACH TO GLUCOSE CONTROL IN CRITICALLY ILL PATIENTS WITH TYPE 2 DIABETES A MULTICENTER, PARALLEL-GROUP, OPEN-LABEL RANDOMIZED CLINICAL TRIAL

Statement of authorship

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Overall percentage (%)	70		
Certification	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
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Permission is granted for the candidate to include the publication in the thesis; and

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The Effect of a Liberal Approach to Glucose Control in Critically Ill Patients with Type 2 Diabetes

A Multicenter, Parallel-Group, Open-Label Randomized Clinical Trial

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Abstract

Rationale: Blood glucose concentrations affect outcomes in critically ill patients, but the optimal target blood glucose range in those with type 2 diabetes is unknown.

Objectives: To evaluate the effects of a "liberal" approach to targeted blood glucose range during ICU admission.

Methods: This mutlicenter, parallel-group, open-label randomized clinical trial included 419 adult patients with type 2 diabetes expected to be in the ICU on at least three consecutive days. In the intervention group intravenous insulin was commenced at a blood glucose >252 mg/dl and titrated to a target range of 180 to 252 mg/dl. In the comparator group insulin was commenced at a blood glucose >180 mg/dl and titrated to a target range of 108 to 180 mg/dl. The primary outcome was incident hypoglycemia (<72 mg/dl). Secondary outcomes included glucose metrics and clinical outcomes.

Measurements and Main Results: By Day 28, at least one episode of hypoglycemia occurred in 10 of 210 (5%) patients assigned the intervention and 38 of 209 (18%) patients assigned the comparator (incident rate ratio: 0.21 [95% confidence interval (CI), 0.09 to 0.49]; P<0.001). Those assigned the intervention had greater blood glucose concentrations (daily mean, minimum, maximum), less glucose variability, and less relative hypoglycaemia (P<0.001 for all comparisons). By Day 90, 62 of 210 (29.5%) in the intervention and 52 of 209 (24.9%) in the comparator group had died (absolute difference, 4.6 percentage points [95% CI, -3.9% to 13.2%]; P = 0.29).

Conclusions: A liberal approach to blood glucose targets reduced incident hypoglycemia but did not improve patient centered outcomes.

Clinical trial registered with Australian New Zealand Clinical Trials Registry (ACTRN 12616001135404).

Keywords: blood glucose; critical illness; diabetes; hypoglycemia; intensive care

Introduction

Patients with type 2 diabetes are frequently admitted to the ICU (1, 2). During critical illness, glucose metabolism is markedly affected (3). In the ICU, blood glucose concentrations are monitored and maintained within a specified range using intravenous

insulin (4). Data from multicenter trials of critically ill patients indicate that targeting a blood glucose concentration in the range of 108 to 180 mg/dl (6.0–10 mmol/L) with intravenous insulin leads to better outcomes than targeting 81 to 108 mg/dl (4.5–6.0 mmol/L) (5, 6). However, previous trials included only a small proportion of patients with type 2 diabetes.

Observational studies in critically ill patients without preexisting diabetes consistently identify associations between hyperglycemia and harm; however, data from patients with type 2 diabetes suggest that blood glucose up to 252 mg/dl (14 mmol/L) may not be harmful and may even be beneficial in such patients (1, 7–9).

Hypoglycemia provides a plausible mechanistic link between insulin therapy and adverse patient outcomes (2, 10–12). Treatment with insulin increases the risk of hypoglycemia, and this risk is exacerbated in critically ill patients with diabetes (2, 13–16). Moreover, in critically ill patients with diabetes, blood glucose concentrations substantially less than the prehospital admission average, termed "relative hypoglycemia," are associated with harm even in the absence of absolute hypoglycaemia (17, 18). Finally, marked changes in blood glucose, so-called "glycemic variability," are exacerbated in this group and may also be harmful (19).

Given that the physiological response to acute hyper- and hypoglycemia appears to differ based on pre-existing diabetes (20–22), and the evidence supporting a target range of 108 to 180 mg/dl comes predominantly from trials that included few patients with diabetes (23), a randomized clinical trial was conducted to evaluate the effects of a liberal approach to blood glucose control in critically ill patients with pre-existing type 2 diabetes. The primary hypothesis was that in patients with pre-existing type 2 diabetes, targeting a more liberal blood glucose range when compared with usual care would reduce incident hypoglycemia.

Methods

Trial Design

This was an investigator-initiated, parallel group, open-label randomized clinical trial. The trial was registered at the Australian New Zealand Clinical Trials Registry (August

2, 2016; ACTRN Trial ID: 12616001135404). The trial protocol and statistical analysis plan have been published (24).

Ethics approval was provided by all relevant local institutional review boards. An independent data and safety monitoring board provided trial oversight. Written informed consent for enrolment or consent to continue participation was obtained from each patient or their legal surrogate. LUCID was conducted in 23 ICUs in Australia and New Zealand.

Study Participants

Eligible patients were 18 years of age or older with type 2 diabetes who were expected to remain in the ICU beyond the calendar day after randomization (i.e., for at least three consecutive days), had either an arterial or central venous catheter in situ, and for whom the treating intensivist believed there was a reasonable likelihood that a blood glucose ≥180mg/dl would be recorded at some stage during the ICU admission.

Patients were excluded because of type 1 diabetes, previous hypoglycemia without neurological recovery, admission to the ICU for ≥24 hours before randomization, death in the ICU was considered inevitable, pregnancy, an expectation they would be eating before the end of the next calendar day, previous participation in the LUCID (Liberal Glucose Control in Critically Ill Patients with Pre-Existing Type 2 Diabetes) trial, admission for treatment of diabetic ketoacidosis or hyperosmolar state, or the treating doctor determined that a specific blood glucose target was required (5, 25). Before randomization, patients had insulin commenced and titrated as per the preexisting protocol for that institution.

Study Randomization

The concealed 1:1 ratio random allocation sequence was generated by the statistical coordination center (University of Adelaide) using computer-generated random numbers with variable permuted block sizes stratified by site. The sequence was then embedded into the Research Electronic Data Capture (REDCap) system (26). Randomization was performed using REDCap at each study site, with the allocation sequence concealed from all investigators, site personnel, and participants.

Data Verification

On-site source data monitoring was conducted by the primary author, including >20% source data verification for the primary endpoint and partial source data verification of other variables for >20% of patients.

Intervention and Comparator

Two blood glucose thresholds, with nonoverlapping target ranges, for the initiation and management of insulin therapy in critically ill patients with type 2 diabetes were compared.

Participants assigned to liberal glucose control (the intervention group) had intravenous insulin commenced at a blood glucose >252 mg/dl and titrated to a target range of 180 to 252 mg/dl. If the blood glucose was <180 mg/dl, no attempt to increase blood glucose was made, with the exception of local protocols for management of hypoglycemia.

Participants assigned to usual care (comparator group) had intravenous insulin commenced and titrated as per preexisting protocols for the institution. These protocols were aligned with the NICE-SUGAR (Normoglycemia in Intensive Care Evaluation—Survival Using Glucose Algorithm Regulation) results, with insulin commenced at blood glucose >180 mg/dl and titrated to a target range of 108 to 180 mg/dl (5).

Study Protocol

Frequency of blood glucose measurement and the changes to insulin administration were achieved at each site according to local hospital protocols.

Once enrolled, study participants were managed as intervention or comparator while in the ICU for a maximum of 28 days from randomization. The intervention or comparator was ceased if consent was withdrawn, the treating clinician determined that it was in the patient's best interest, or the treating clinician wished to transition the participant to an alternative regimen (e.g., long-acting insulin or oral agents) in preparation for discharge from the ICU.

Blood glucose concentrations on Days 1 to 7 that were recorded as part of routine clinical care nearest to the trial time points of 06:00, 12:00, 18:00, and 24:00 were recorded as trial blood glucose values. If no sample was taken as part of routine clinical care within 3 hours of the designated interval, this time point was recorded as missing. If the daily minimum or maximum blood glucose concentrations obtained as part of routine clinical care occurred outside of the set trial time points (06:00, 12:00, 18:00, and 24:00), these values were recorded separately. On study Days 8 to 14, the blood glucose closest to 08:00 was recorded. The choice of arterial, venous, or capillary blood and testing technique was at the discretion of the treating clinician.

All processes of care, including nutrition, steroid, and catecholamine administration occurred as per local policy and as directed by the treating clinician. The mode of nutrition and use of exogenous steroid was recorded daily for the first 14 days and catecholamine infusion for 7 days. When glycated hemoglobin (HbA1c) was measured before randomization, this was recorded (27).

Outcomes

The primary outcome was incident hypoglycemia within 28 days of randomization. This threshold was <72 mg/dl (<4.0 mmol/L) (13, 28) and reported as the event rate adjusted for within-patient correlation. An incident event was defined as hypoglycemia without recorded hypoglycemia within the preceding 4 hours. The raw number of hypoglycemic events and proportion of patients experiencing one or more events were also assessed.

Secondary glycemic outcomes

Relative hypoglycemia was defined as >30% drop from premorbid estimated average glucose, calculated using the formula: mg/dl = 18 × (mmol/L = 1.59 × HbA1c (%) − 2.59) (17), and severe hypoglycemia <39.6 mg/dl. Glycemic variability was recorded using both the coefficient of variation (CoV) and standard deviation (SD) over the first 7 study days (17, 18). Maximum, minimum, and group mean glucose concentrations were also reported.

Clinical outcomes

Clinical outcomes, including Day 90 all-cause mortality, length of ICU and hospital stay, hospital discharge destination, location at Day 90, and infectious complications were planned outcomes of interest. Participants who survived to hospital discharge were contacted at Day 90 to determine if they remained alive. To assess for a potential difference in infectious complications, positive blood cultures were recorded as those likely to be pathogenic (online supplement), as well as highest daily white blood cell count and C-reactive protein concentrations. ICU-free survival days was a post hoc analysis.

Statistical Analyses

Results are presented as proportions (n/N, %) for categorical data, mean and standard deviation (SD), or median and interquartile range (IQR) for continuous data, with between-group comparisons by difference in proportions, t test, or generalized Hodges-Lehmann median difference with 95% confidence interval (CI). The incident rate of hypoglycemia was estimated using Poisson regression referenced to the hours of study exposure, with the corresponding 95% CI based on robust standard errors to allow for overdispersion. This outcome is also presented as the raw number of events per group and the proportion of individuals experiencing one or more events. P values were only calculated for the primary outcome, and no adjustment was made for repeated interim analysis. Secondary outcomes are presented as point estimates with 95% CIs adjusted for within-subject correlation using generalized estimating equations regression with robust standard errors.

Mortality at Day 90 was analyzed as the difference in proportions, with 95% CI, and by logistic regression adjusted for predefined covariates (age, sex, Acute Physiology and Chronic Health Evaluation II score, invasive mechanical ventilation, and postoperative admission), with standard errors adjusted for ICU site. Missing data were not imputed. Based on an observational study reporting reduced mortality in patients with HbA1c $\geq$7% (53 mmol/mol) and mean blood glucose >180 mg/dl during ICU admission (7), a planned exploratory subgroup analysis was conducted for this group. A post hoc analysis was conducted using the American Diabetes Association and the European Association for the Study of Diabetes position statement hypoglycemic threshold of <54 mg/dl (29).

Sample size was based on a relative risk of hypoglycemia of 0.47 (30) and assumed baseline incident hypoglycemia of 17.5% (5) (online supplement). A sample size of 408 participants provided 80% power to detect a reduction of 9.3% in incident hypoglycemia with an α error of 0.05. This sample size was inflated by 10% to 450 to allow for consent refusal, loss to follow-up, and unexpectedly short periods of observation. All analyses were performed using Stata MP/16.1 (StataCorp LLC).

Data Safety Monitoring Committee

An interim safety analysis was planned after 200 patients. The independent Data Safety Monitoring Committee identified that a substantial proportion of patients in both arms had not been maintained within the intended glycemic range, and the number of deaths in the intervention arm was numerically greater. Given these findings, the trial was paused for several months while the management committee sought to improve the time in range through additional training, and an additional interim analysis was recommended after the 350th patient had complete 90-day data. Given the primary study aims had been effectively addressed, the lower-than-anticipated loss to follow-up (recruited n = 419), and the nonsignificant point estimate of increased mortality in the intervention group, the management committee was advised to cease ongoing recruitment. The Data Safety Monitoring Committee was working within a prewritten Charter that stipulated advice to stop was the prerogative of the Data Safety Monitoring Committee, with no predetermined stopping rules.

Results

Study Participants

From May 2017 to November 2020 we identified 2,525 patients in 16 ICUs in Australia and New Zealand who met inclusion criteria, with 2,056 meeting at least one exclusion criterion and 434 being randomized (Figure 1). Fifteen patients (8 [3.7%] in the intervention and 7 [3.2%] in the comparator groups) either withdrew, refused consent to continue participation, or were randomized in error, leaving 419 participants. Primary outcome analysis included 210 participants in the intervention and 209 participants in the

comparator group (Figure 1). There were no marked between-group differences at baseline (Table 1).

Blood Glucose Measurements and Insulin Administration

There were 9,067 blood glucose measurements recorded (intervention = 4,425 and comparator = 4,642), most being from a blood gas analyzer (blood gas analyzer 62%, glucose meter 37%, local laboratory <1%). The method used to measure blood glucose was similar between groups (see Figure E1 in the online supplement).

Insulin was administered on any study day in 188 (90%) patients in the intervention group and 198 (95%) patients in the comparator. The intervention group received less insulin per patient per day (median [IQR], 34 [10 to 72] vs. 52 [22 to 91] units; group difference −13.3 [95% CI, −21.4 to −5.3] units; Figure E2). The proportion of blood glucose concentrations within target range was approximately 50% in both groups (Figure 2).

Primary Outcome

At least one episode of hypoglycemia occurred in 10 of 210 (5%) patients assigned the intervention and 38 of 209 (18%) the comparator. When adjusting for duration of observation, the intervention reduced incident hypoglycemia (incident rate ratio, 0.21 [95% CI, 0.09–0.49]; $P < 0.001$). When analyzed as the number of events per patient (Table 2) or using a different threshold to define hypoglycemia (Table E1), results were consistent.

Secondary Outcomes

Blood glucose

The mean blood glucose per patient per day, (median [IQR], 212 [191–227] vs. 167 [152–190] mg/dl; group difference, 36 [95% CI, 31–42] mg/dl) and mean blood glucose over time (Figure 3) were greater with the intervention. Both the minimum (median [IQR], 122 [99–142] vs. 92 [77–108] mg/dl; difference, 28.8 [95% CI, 23.4–34.2] mg/dl) and maximum (median [IQR], 304 [270–337] vs. 265 [225–312] mg/dl; difference, 37.8 [95%

CI, 25.2–50.4] mg/dl) blood glucose measurements per patient were greater in the intervention group.

Glucose variability, as the percent coefficient of variation (median [IQR], 23% [19% to 30%] vs. 29% [23% to 34%]; median difference, −4.8 [95% CI, −6.4 to −3.1]), and relative hypoglycemia (median [IQR], 18% [5.9% to 43%] vs. 50% [29% to 78%]; median difference −25 [95% CI, −31 to −19]) were reduced in the intervention group; however, there was no difference in glucose variability when measured as SD (median [IQR], 48 [38 to 64] vs. 47 [38 to 61] mg/dl; difference, 0.59 [95% CI, −2.95 to 4.17]). Mean (95% CI) blood glucose concentrations by site and study group (Figure E3) support no meaningful heterogeneity between sites ($I^2 < 1\%$ and $P > 0.99$).

There were three patients with severe hypoglycemia (<39.6 mg/dl, one intervention and two comparator).

Clinical outcomes

A total of 62 of 210 (29.5%) patients in the intervention group and 52 of 209 (24.9%) in the comparator group had died by Day 90 (absolute difference, 4.6 percentage points [95% CI, −3.9% to 13.2%]). Findings were not materially affected when mortality was adjusted for predefined covariates (Table E2). Given the observed mortality, a post hoc decision was made to plot time to death as Kaplan-Meier curves (Figure E4), with no significant difference between curves observed ($P = 0.20$).

There was no significant difference for the duration of ICU admission (median [IQR], 127 [83 to 206] vs. 154 [77 to 252] h; median difference, −12.3 [95% CI, −32.4 to 5.8] h) and hospital admission (median [IQR], 14 [8 to 24] vs. 16 [9 to 27] d; difference, −1.4 [95% CI, −3.6 to 0.7] d) and ICU-free survival days (median [IQR], 83 [0 to 87] vs. 82 [16 to 87] ICU-free days; median difference, 0 [−1.0 to 0] ICU-free days). These durations remained nonsignificant when analyzed by competing risks regression (Tables E3 and E4). At Day 90, there were no marked differences in the proportions of survivors remaining in the hospital or discharged to rehabilitation or a long-term care facility (Table E5).

Ten (5%) participants in the intervention group and 12 (6%) in the comparator group recorded a new positive blood culture. When analyzed as pathogenic, the result was

similar (6 [3%] vs. 9 [4%]). Biomarkers of infection were not different between groups (Figures E5 and E6).

Processes of care

The nutrition mode was liquid enteral 1,205 (57.1%), fasted 499 (23.7%), oral diet 306 (14.5%), parenteral 58 (2.8%), and combined (enteral and oral and/or parenteral) 42 (2.0%) of study days. There was no difference between groups in the route of nutrition or administration of vasopressors or steroids (Figures E7 and E8).

Protocol deviations and adverse and serious adverse events

Randomization occurred in nine participants who were ineligible (Table E6). Protocol deviations related to insulin administration were documented on 30 occasions and referred to concerns for patient safety on four occasions (Table E6). Adverse events were reported on eight occasions, with no serious adverse events (Table E6).

Subgroup analyses

HbA1c was available in 316 (75%) participants, with 98 in each group recording a value ≥7%. Mean daily blood glucose profiles (Figure E9) and point estimates for outcomes in this preplanned subgroup are reported in Tables E7–E9.

Discussion

This randomized clinical trial was conducted in critically ill patients with type 2 diabetes to evaluate the effect of a liberal approach to blood glucose control. The rate of incident hypoglycemia was reduced with the liberal approach. When compared with titrating insulin to target blood glucose <180 mg/dl, the liberal approach also reduced glycemic variability and relative hypoglycemia, with increased minimum, mean, and maximum blood glucose concentrations. Based on the observed 95% CIs in this sample, the true effect of a liberal approach on glucose control could have been to increase Day 90 mortality by up to 13.2% or reduce it by 3.9%.

This trial evaluated glucose control exclusively in critically ill patients with preexisting type 2 diabetes. Similar to the majority of glucose management trials conducted in the ICU, it was open label, with the associated risk of bias. The incidence of hypoglycemia in studies that have included a high proportion of patients with diabetes is reported between 9% and 35% (5, 6, 18, 30, 31). Accordingly, the observed reduction in hypoglycemia is not due to an inflated event rate in the comparator group.

This trial has additional limitations. Only target ranges were compared, and, due to the pragmatic nature of this trial, sites were allowed to pursue these blood glucose targets using local practices, rather than implementing strict protocols or using sophisticated technology. This approach has been used by other multicenter trials (5) and has the advantage that the comparator group better represents usual care at trial sites. However, before participating, no site had a specific protocol for blood glucose control in patients with diabetes (32). This, combined with insulin resistance in patients with diabetes (33), may explain why the mean blood glucose concentration in the comparator group (167 mg/dl) was greater, and time in range was less than expected. In this trial, 46% and 51% of blood glucose measurements were in range for the intervention and comparator, respectively. Although previous multicenter trials reporting time in range found similar periods out of range (6), the results of this trial may have been different had protocols or technology that are more effective at maintaining blood glucose concentrations within a target range been used (34–36). To prevent contamination bias, a target population was identified as soon as possible after ICU admission, which was dependent on a diagnosis of preexisting diabetes. Although pragmatic, this is somewhat simplistic, in that "personalization" of glucose control during critical illness may be more nuanced than dichotomizing patients based on an existing diagnosis (21, 37). The trial was designed with a single interim analysis planned, but after this the Data Safety Monitoring Committee recommended one more interim analysis and subsequently advised early termination. Early termination does increase the risk of an α error occurring (38).

This trial was designed with statistical power to detect a difference in an important biomarker of harm, hypoglycemia, rather than a patient-centered outcome. The biomarker of hypoglycemia was chosen because it is strongly associated with harm; there are plausible mechanistic pathways linking frequency, depth, duration, and recurrent hypoglycemia with adverse clinical outcomes, and it had the capacity to be affected by the intervention (39). Despite observing a significant decrease in incident hypoglycemia

with the intervention, a corresponding improvement in patient-centered outcomes was not observed. Indeed, the point estimate of Day 90 mortality treatment effect suggested a higher possibility of harm than benefit. Although this trial was not adequately powered to determine the effect on mortality, the results suggest that the use of a liberal or personalized approach to blood glucose in critically ill patients should not be implemented outside carefully designed clinical trials. As quantification of HbA1c becomes quicker, trialists can more robustly test whether targeting blood glucose during critical illness based on preexisting glucose metabolism improves outcomes.

Conclusions

When compared with commencing insulin at 180 mg/dl and targeting a range of 108–180 mg/dl, a liberal approach to blood glucose reduced incident hypoglycemia but was not associated with improvement in patient-centered outcomes.

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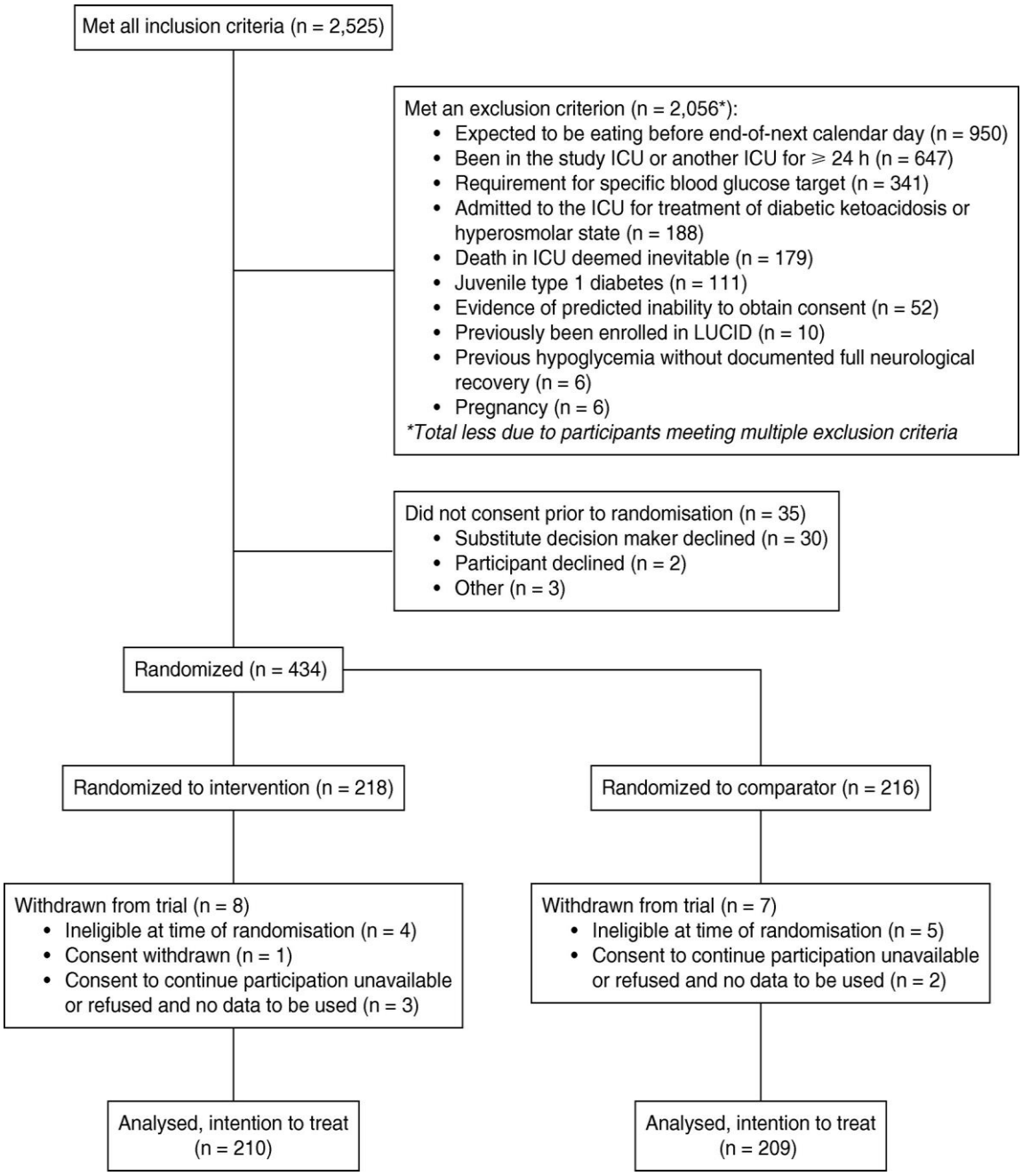

Figure 1. Screening and randomization in the LUCID (Liberal Glucose Control in Critically Ill Patients with Pre-Existing Type 2 Diabetes) trial of a liberal approach to glucose control in critically ill patients with type 2 diabetes.

Table 1. Baseline Characteristics

	Intervention	Comparator
Study subjects, *n*	210	209
Age, yr	67 (58–75)	66 (58–73)
Male	138 (66)	136 (65)
APACHE II score	20 (16–26)	20 (16–26)
APACHE III score	74 (55–95)	71 (58–93)
SOFA score	8 (6–10)	7 (6–10)
HbA1c measured	159 (76)	157 (75)
N ≥ 7% (53 mmol/mol)	94/159 (59)	91/157 (58)
Premorbid estimated average glucose, mg/dl*	162 (137–200)	162 (139–205)
Diabetes management		
Diet only†	32/181 (18)	29/190 (15)
Oral metformin‡	130/196 (66)	129/195 (66)
Other oral agent(s)§	79/189 (42)	69/184 (38)
Insulin (subcutaneous)	76/210 (36)	80/209 (38)
Insulin regimen	76	80
≤2 doses per day‖	51 (67)	53 (66)
>2 doses per day¶	11 (15)	17 (21)
Other**	14 (18)	10 (13)
APACHE III admission diagnosis		
Postoperative	82/209 (39)	74/206 (36)
Trauma	26/209 (12)	23/206 (11)
Sepsis/septic shock	25/209 (12)	34/206 (17)
Cardiothoracic surgery	22/209 (11)	19/206 (9)
ICU source of admission	210	209
Emergency department	77 (37)	61 (29)
Ward	33 (16)	46 (22)
Other hospital	20 (9.5)	16 (7.7)
Other ICU	6 (2.9)	11 (5.3)
OT/recovery (elective)	28 (13)	23 (11)
OT/recovery (emergency)	46 (22)	52 (25)
Mechanical ventilation	187 (89)	191 (91)
Chronic cardiovascular disease††		
No	96 (46)	93 (45)
Yes	111 (53)	113 (54)
Unknown	3 (1)	3 (1)
Retinopathy‡‡		
No	162 (77)	157 (75)
Yes	23 (11)	31 (15)
Unknown	25 (12)	21 (10)
Nephropathy§§		
No	154 (74)	149 (71)
Yes	41 (20)	41 (20)
Unknown	15 (7)	19 (9.1)

Definition of abbreviations: APACHE = Acute Physiology and Chronic Health Evaluation; HbA1c = glycated hemoglobin; OT = operating theatre; SOFA = sequential organ failure assessment.
Data are presented as median (interquartile range), *n* (%), or *n/N* (%), unless otherwise noted.
*Premorbid estimated average glucose calculated as (mg/dl) = 18 × (1.59 × HbA1c (%) − 2.59).
†Diet only recorded if the participant used diet and no medication to control blood glucose before hospitalization.
‡Oral metformin recorded if the participant was taking metformin before hospitalization.
§Oral other recoded if the participant was taking other oral therapies including but not limited to sulfonylureas before hospitalization.
‖Insulin subcutaneous ⩽2 recorded if the participant administered any type of subcutaneous insulin less than or equal to two times per day before hospitalization.
¶Insulin subcutaneous >2 if the participant administered any type of subcutaneous insulin more than twice per day before hospitalization.
**Insulin via infusion or other means, or used another subcutaneous drug (e.g., Exenatide) before hospitalization.
††Chronic cardiovascular disease recorded any documented chronic cardiovascular disease including, but not limited to, hypertension or ischemic heart disease.
‡‡Retinopathy recorded any documented preexisting diabetes-related disease of the retina.
§§Nephropathy recorded documented preexisting diabetes-related nephropathy.

Blood glucose ranges:

- Below the comparator target range < 108 mg/dL (< 6 mmol/L)
- Within the comparator target range 108 – <180 mg/dL (6 – <10 mmol/L)
- Within the intervention target range 180 – <252 mg/dL (10 – <14 mmol/L)
- Above the intervention target range ⩾ 252 mg/dL (⩾ 14 mmol/L)

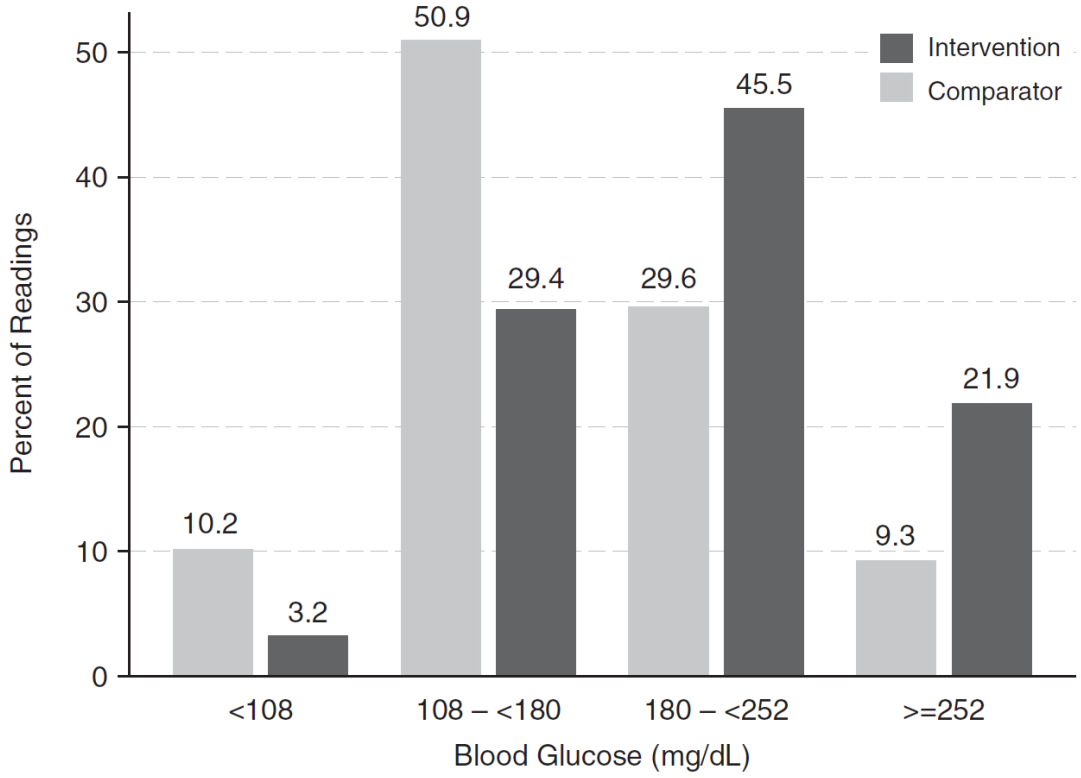

Figure 2. Proportion of blood glucose measurements within defined ranges by study group, Days 1–7.

Table 2. Hypoglycemic Episodes

Hypoglycemic Episodes	Intervention (*n* = 210)	Comparator (*n* = 209)	*P* Value
1	9 (4)	28 (13)	<0.001
2	0 (0)	6 (2.9)	
3	1 (1)	3 (1.4)	
4 or more	0 (0)	1 (0.5)	

Data presented as *n* (%). Raw number of events without adjusting for hours of exposure using chi-square analysis. Hypoglycemic episode defined as blood glucose < 72 mg/dl (< 4.0 mmol/L).

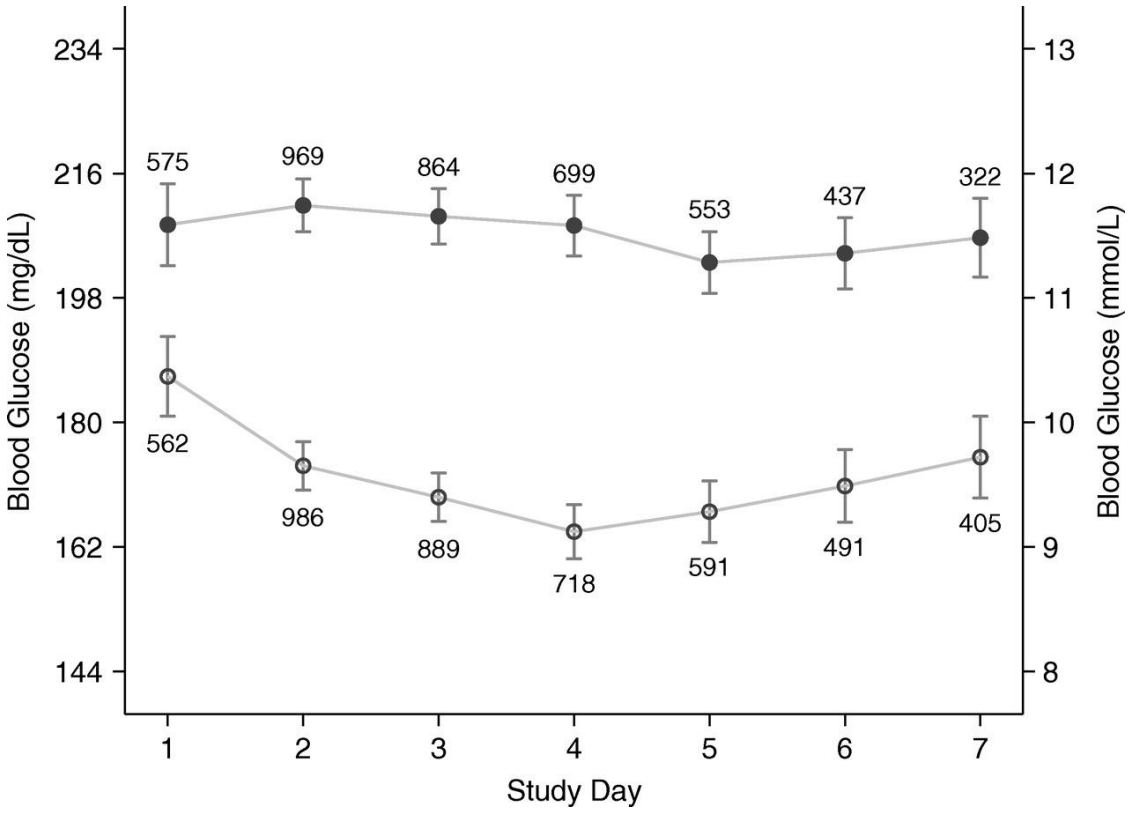

Figure 3. Mean blood glucose concentrations by study group for Days 1–7. Solid circles = intervention; open circles = comparator group; error bars = 95% confidence interval for the mean, with the number of observations shown adjacent.

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List of participating sites

Alice Springs Hospital, Auckland District Health Board – Cardiothoracic and Vascular Intensive Care Unit, Auckland District Health Board – Department of Critical Care Medicine, Austin Hospital, Flinders Medical Centre, Footscray Hospital (Western Health), Logan Hospital, Lyell McEwin Hospital, Princess Alexandra Hospital, Royal Adelaide Hospital, Royal Melbourne Hospital, St Vincent's Hospital Melbourne, Sunshine Hospital (Western Health), The Alfred Hospital, University Hospital Geelong (Barwon Health) and Wellington Hospital

The LUCID Investigators

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Hospital Geelong); Charlie Latimer-Bell, Kirsha Delaney, Deborah Hendry, Cassie Lawrence, Eden Lesona, Alexandra Milington, Leanlove Navarra, Shaanti Olatunji, Raulle Sol Cruz, Rose Sol Cruz, Chelsea Young and Paul Young (Wellington Hospital)

Data safety monitoring committee

Bala Venkatesh and Michael Bailey

Study protocol and statistical analysis plan

The protocol was registered with the Australian New Zealand Clinical Trials Registry on 2 August 2016 (ACTRN: 12616001135404).

The date of submission of the study protocol and statistical analysis plan was 24 October 2019. The reference for this manuscript is: Critical Care and Resuscitation 2020 Jun;22(2):133-141.

Pathogenic blood culture

To determine that a blood culture was acquired in hospital (i.e., not the precipitating cause of ICU admission) and was pathogenic, the following criteria were used

Organism cultured from blood obtained from **day 3** onward

AND

Organism was a **recognized pathogen**

A 'recognized pathogen' was defined as a microorganism not usually regarded as a common skin contaminant, i.e., organism other than diphtheroids, Bacillus spp., Propionibacterium spp., coagulase-negative staphylococci, or micrococci

OR

A common skin contaminant (e.g., diphtheroids, Bacillus spp., Propionibacterium spp., coagulase-negative staphylococci, or micrococci) that was cultured from two or more blood cultures drawn on separate occasions (including one drawn by venipuncture)

Sample size calculation

Sample size was based on a test of two independent proportions, control proportion 17.5% (0.175) and RR = 0.47, in Stata/MP v16.0:

.power twoproportions 0.175, test(chi2) rrisk(0.47)

Estimated sample sizes for a two-sample proportions test

Pearson's chi-squared test

H0: p2 = p1 versus Ha: p2 != p1

Study parameters:

alpha = 0.0500

power = 0.8000

delta = 0.4700 (relative risk)

p1 = 0.1750

p2 = 0.0822

rrisk = 0.4700

Estimated sample sizes:

N = 408. N per group = 204

Table E1. Post-hoc analysis of hypoglycaemic episodes <54 mg/dL (3.0 mmol/L).

This unplanned post-hoc analysis was performed based on the position statement from the American Diabetes Association and European Association for the Study of Diabetes. This statement was published after the study protocol had been approved by the lead hospital research ethics committee and registered with ANZCTR. In addition, the threshold at which harm occurs in critically ill patients is unknown and previous trials had used < 72 mg/dL (4.0 mmol/L).

	Intervention, n=210	**Comparator, n=209**	**p-Value[1]**
Hypoglycaemic Episodes (BGL<54 mg/dL), n (%)			
1	2 (1.00)	8 (3.80)	0.093
2	0 (0.00)	1 (0.50)	

1. Fisher's exact test

Table E2. Logistic regression for Death at Day 90

Adjusted odds ratio for the Intervention vs. Comparator group. Including only significant covariates ($p<0.1$) as per the statistical analysis plan, employing robust standard (SE) errors to adjust for within site correlation.

	Odds ratio	Robust SE	95% CI
Intervention	1.29	0.24	0.89 – 1.87
APACHE II Score	1.10	0.03	1.05 – 1.15

Of the pre-set covariates (age, sex, APACHE II score, invasive mechanical ventilation and post-operative admission): there were insufficient numbers to analyze admission diagnosis and only the APACHE II score was independently associated with day 90 mortality.

Table E3. Competing risks regression for 'Live ICU Discharge' (c.f. length of stay).

Sub-hazard ratio (SHR) for the Intervention vs. Comparator group, with death treated as a competing event, employing robust standard errors to adjust for within site correlation.

	Subhazard ratio	Robust SE	95% CI
Intervention	0.88	0.11	0.68 – 1.13

Note – a SHR < 1.0 implies a lower rate of 'live discharge', which is consistent with a longer length of stay, once death is accounted for.

Table E4. Competing risks regression for 'Live Hospital Discharge' (c.f. length of stay).

Sub-hazard ratio (SHR) for the Intervention vs. Comparator group, with death treated as a competing event, employing robust standard errors to adjust for within site correlation.

	Subhazard ratio	Robust SE	95% CI
Intervention	0.93	0.10	0.75 – 1.15

Note – a SHR < 1.0 implies a lower rate of 'live discharge', which is consistent with a longer length of stay, once death is accounted for.

Table E5. Proportions of survivors remaining in hospital, rehabilitation or a long-term care facility.

	Intervention n=210	**Comparator n=209**	**Difference (95%CI)**
Length of Stay, median [IQR]			
Intensive care unit (hours)	127 [83, 206]	154 [77, 252]	-12.3 (-32.4, 5.8)
Hospital (days)	14.0 [8.2, 24.3]	15.9 [9.1, 27.4]	-1.4 (-3.6, 0.7)
Patient Death, n (%)			
In hospital	57 (27.1)	42 (20.1)	7.0 (-1.1, 15.2)

At Day 90	62 (29.5)	52 (24.9)	4.6 (-3.9, 13.2)
Survivor Location at Day 90, n (%)	146/148	157/157	
Home	111 (76)	127 (81)	P = 0.31 (Fisher's exact)
Rehabilitation	17 (12)	10 (6.4)	
Other acute ICU	0 (0)	1 (0.6)	
Other acute hospital	2 (1.4)	5 (3.2)	
Long term care	5 (3.4)	8 (5.1)	
Still in hospital	8 (5.5)	5 (3.2)	
Other	3 (2.1)	1 (0.6)	

Table E6. Summary of protocol deviations/adverse events.

Protocol Deviations	**Intervention** (N=218)	**Comparator** (N=216)
Patient randomized who were ineligible, n (%)	4 (1.8)	5 (2.3)
Patient does not have type 2 diabetes	0	1
Patient has juvenile type 1 diabetes	0	1
Requirement for specific blood glucose target as determined by the treating doctor	0	1
At time of enrolment patient had been in the study ICU or another ICU for ≥ 24 h during the index admission	3	1
Patient has previously been enrolled in LUCID	0	1
At time of enrolment death during ICU admission is deemed to be inevitable	1	0
Insulin administered outside of protocol parameters, n (%)	21 (9.6)	9 (4.2)
Administration error	8	0
Patient safety	2	2
Wrong insulin protocol used	5	6
Other	6	1
Adverse event / Serious adverse event, n (%)		

Adverse event	1 (0.46)	7 (3.2)
Serious adverse event	0	0
Suspected relationship of AE to therapy, n.		
Not related	1	1
Unlikely	0	6
Possibly	0	0
Probably	0	0
Definitely	0	0
Outcome of Event, n.		
Resolved	1	6
Resolved with sequelae	0	1

Table E7. Hypoglycemic episodes by study group, for the pre-defined sub-group (HbA1c ≥ 7%).

	Intervention	**Comparator**	**p-Value**
Hypoglycemic Episodes (BGL < 72 mg/dL), n (%)	94	91	0.04
0	86 (92)	70 (77)	
1	7 (7.4)	18 (20)	
2	0	2 (2.2)	
3 or more	1 (1.1)	1 (1.1)	

Table E8. Poisson Regression for hypoglycemic events by study group, for the pre-defined subgroup (HbA1c ≥ 7%).

Poisson regression estimating the incidence rate ratio (IRR) per 100 study hours for hypoglycemic events (blood glucose < 72 mg/dL = 4.0 mmol/L), with robust standard errors (SE) to adjust for within patient correlation and over-dispersion. N=316. Interaction effect for (treatment)*(HbA1c ≥7 subgroup), P=0.43

	Incident-rate ratio	Robust SE	95% CI

Intervention	0.36	0.21	0.11 – 1.14

Table E9. Logistic regression for Death at Day 90 for the pre-defined subgroup (HbA1c ≥7%).

Odds ratio for the intervention vs. comparator group, adjusted for APACHE II score, employing robust standard errors to adjust for within site correlation. N=316. Interaction effect for (treatment)*(HbA1c ≥7 subgroup), P=0.68

	Odds ratio	Robust SE	95% CI
Intervention	1.25	0.36	0.71 – 2.21

Figure E1. Number of tests by test-type per study group per day.

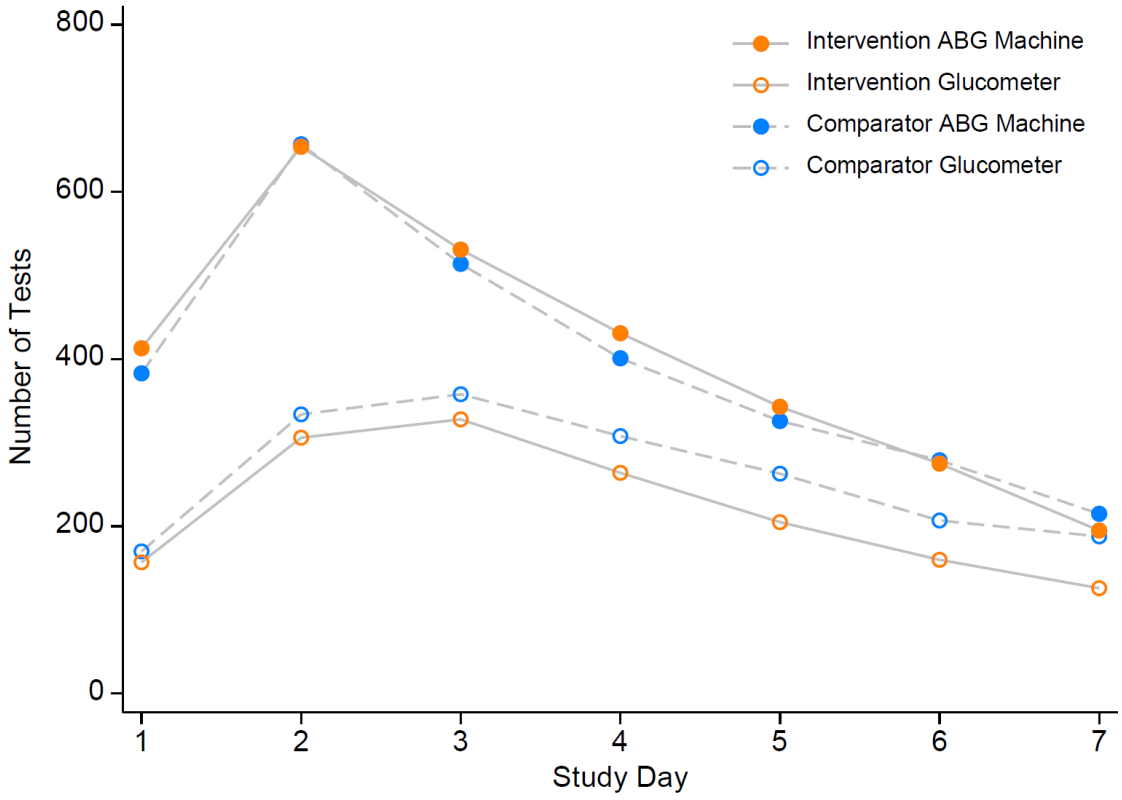


Figure E2. Mean total insulin units per day by study group for study days 1 to 7.

Solid orange circles = intervention, open blue circles = comparator group, error bars = 95% confidence interval for mean adjusted for within patient correlation using generalized estimating equations regression; with the number of patients/observations shown adjacent. Patients receiving no insulin are included in the mean estimates as zero units.

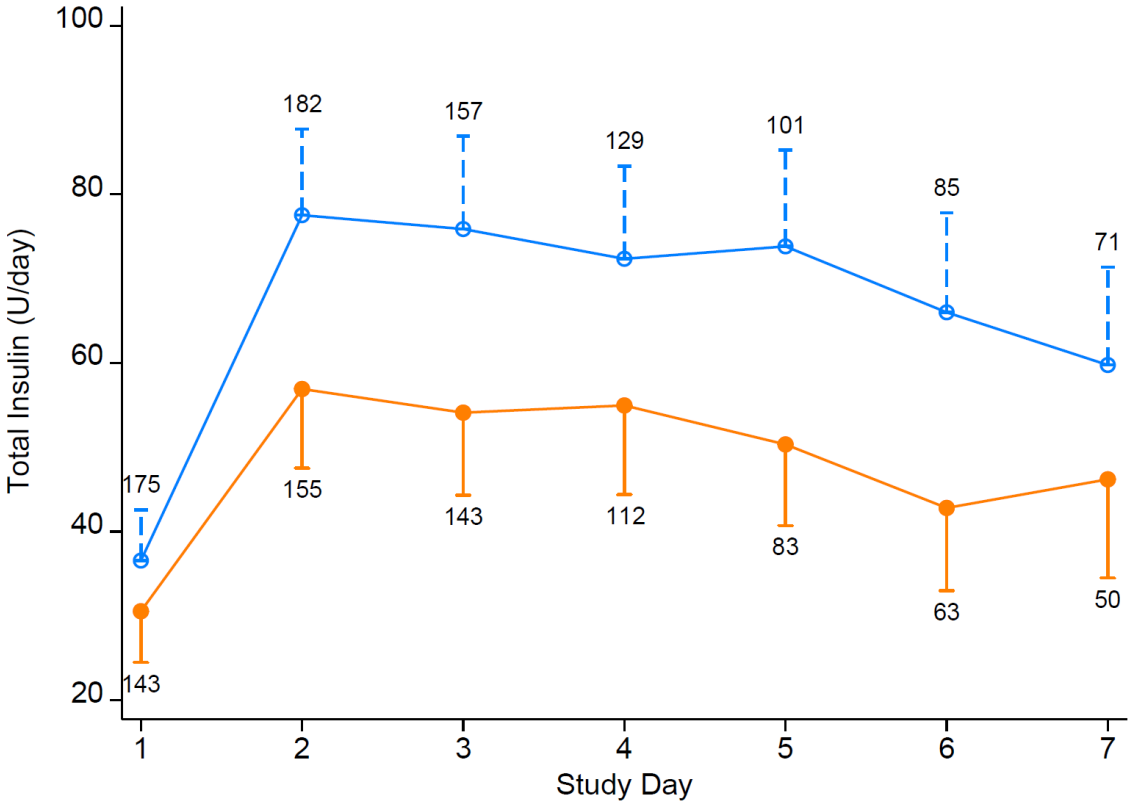


Figure E3. Distribution of blood glucose measurements (mg/dL) by site and treatment group allocation.

Mean with 95%CI, weights by inverse variance. Tests for heterogeneity between sites, within comparator and interventions groups, I^2<1% and P >0.99 respectively; and between subgroups I^2<1% and P = 0.07.

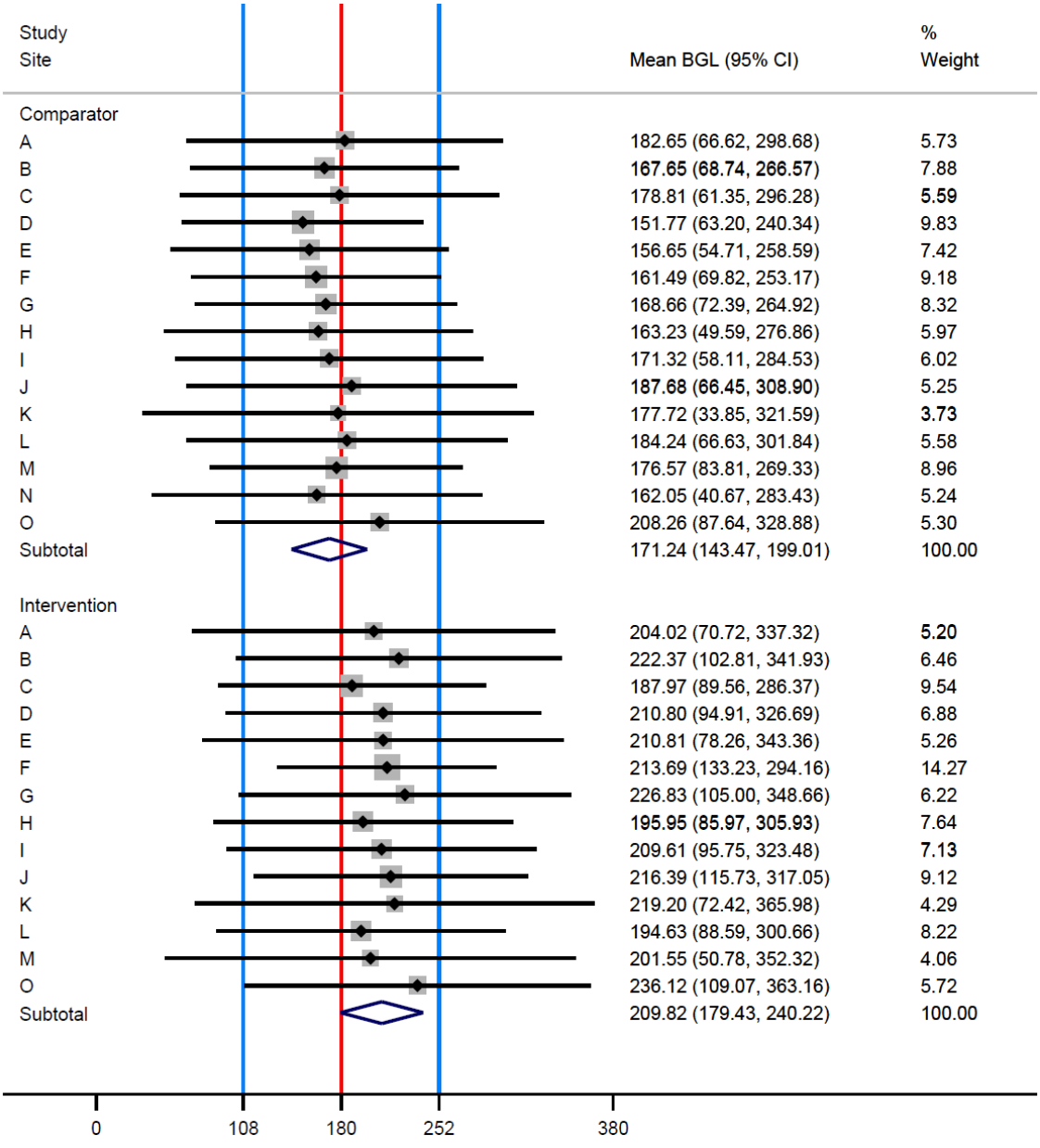
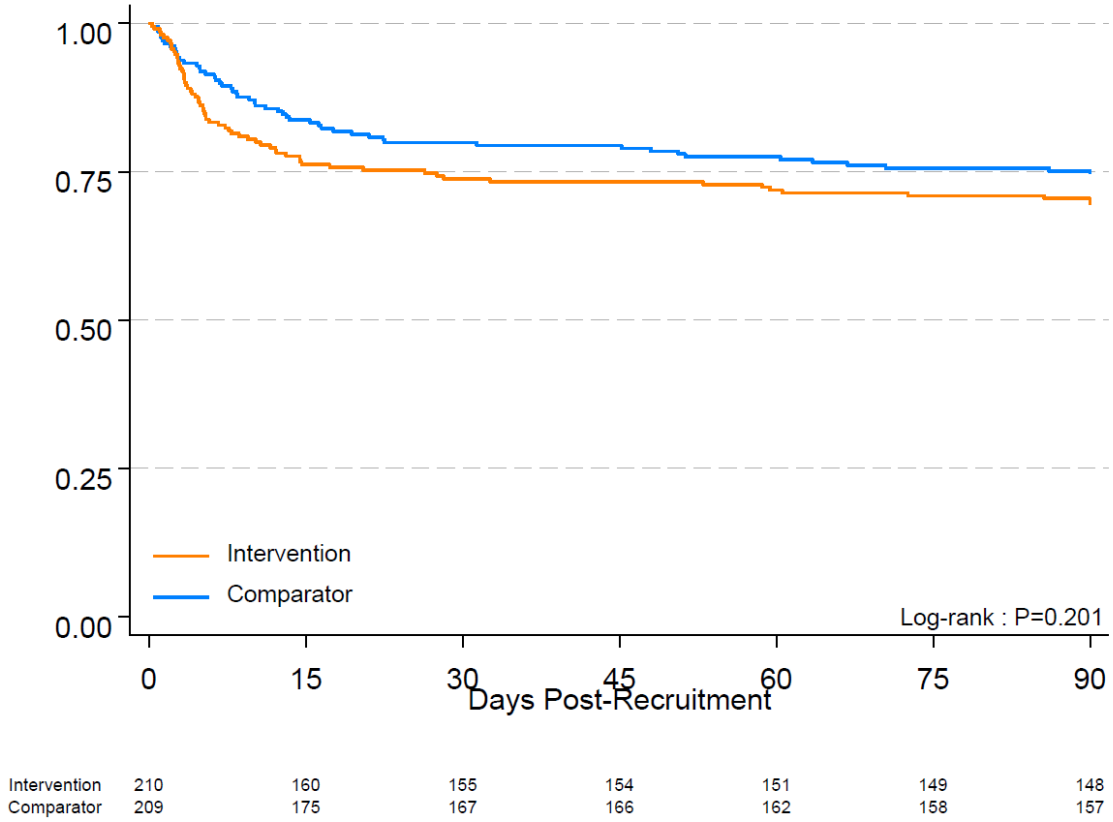


Figure E4. Kaplan-Meier survival curve for death up to 90 days post-recruitment by Study group.

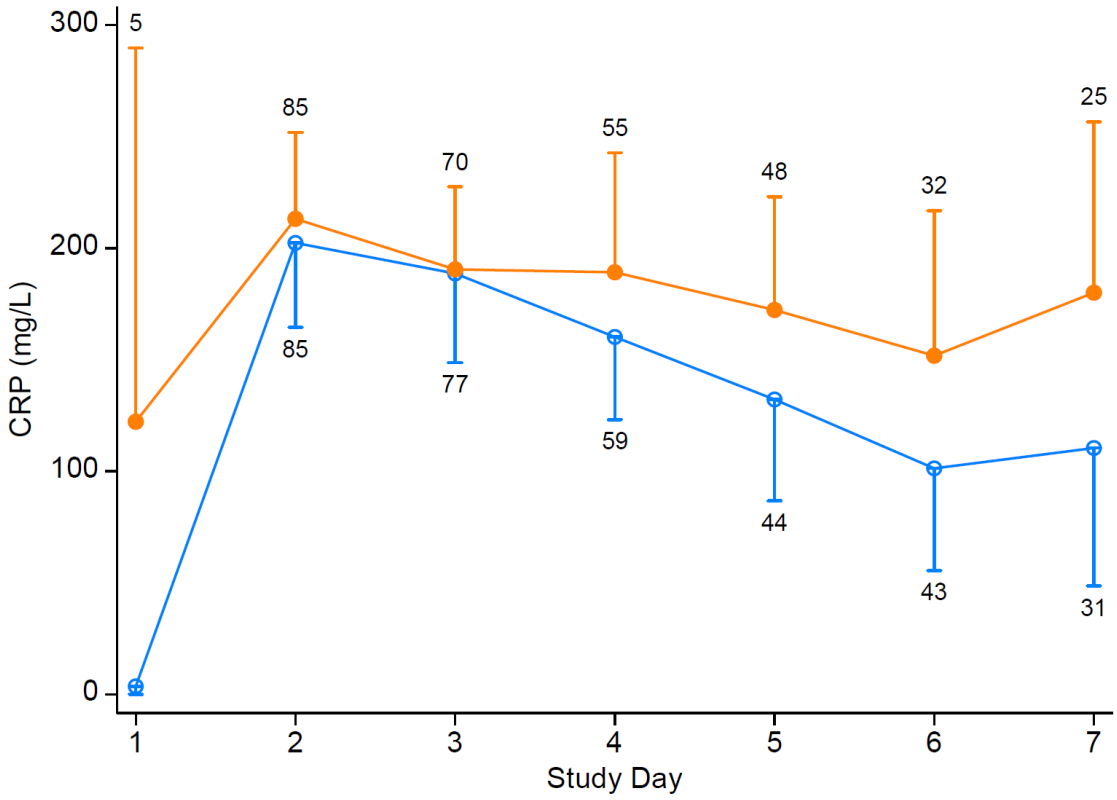
Post-hoc analysis with day 90 outcome independently verified. Log-rank test for equality of survivor functions, P=0.20.



Intervention	210	160	155	154	151	149	148
Comparator	209	175	167	166	162	158	157

Figure E5. Mean plasma C-reactive protein (CRP) by study group and day.

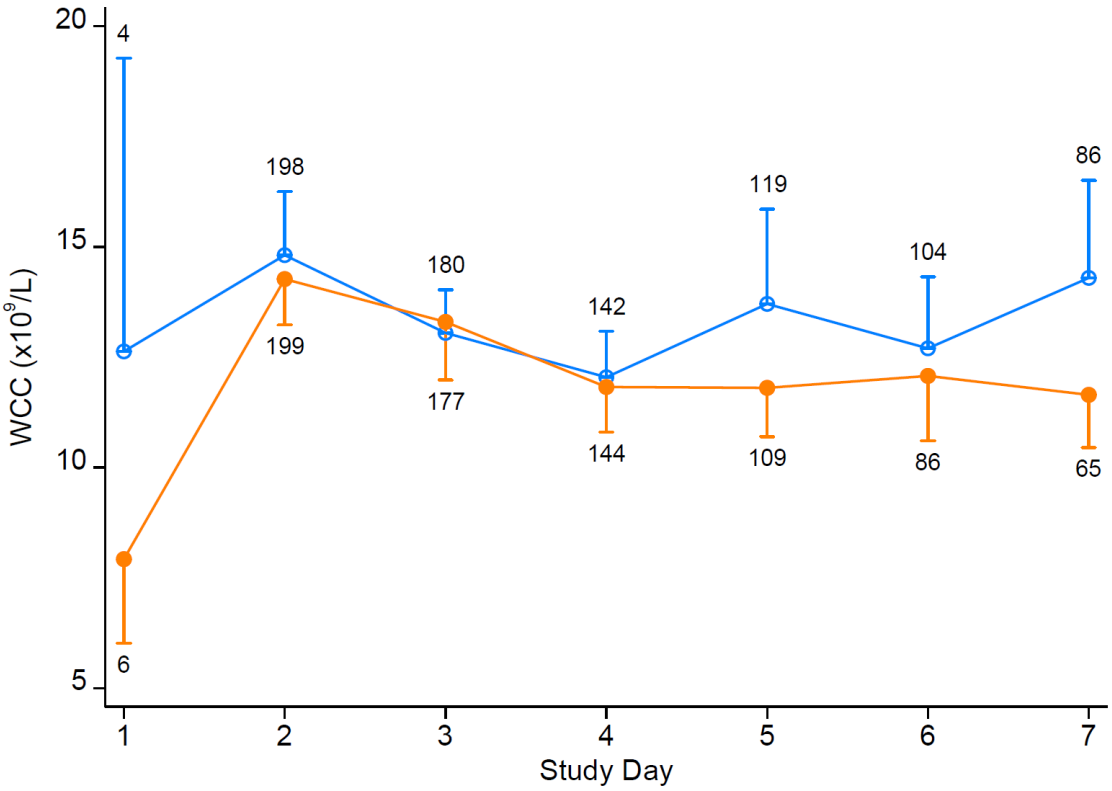
Solid orange circles = intervention, open blue circles = comparator group. Error bars represent 95% confidence intervals, with the number of observations adjacent.



Day 1 was a 'partial day' and only results obtained after randomization were included. Given the majority of patients in trial ICUs have routine blood tests done in the early morning, the small number of test results available for day 1 are expected.

Figure E6. Mean blood white cell counts (WCC) by study group and day.

Solid orange circles = intervention, open blue circles = comparator group. Error bars represent 95% confidence intervals, with the number of observations adjacent.



Day 1 was a 'partial day' and only results obtained after randomization were included. Given the majority of patients in trial ICUs have routine blood tests done in the early morning, the small numbers for day 1 are expected.

Figure E7. Predominant feeding modality per group per study day 1-7.

Closed circles = intervention, open circles = comparator.

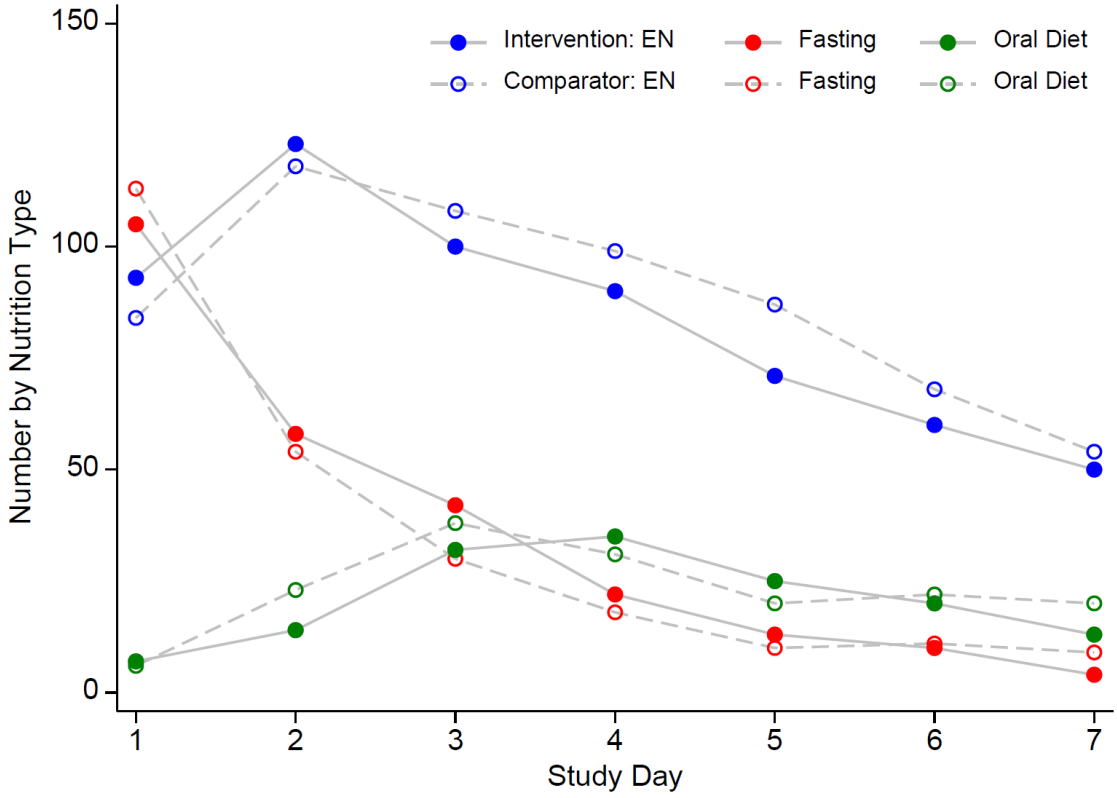


Figure E8. Vasopressor (any) and steroid administration per group per day.

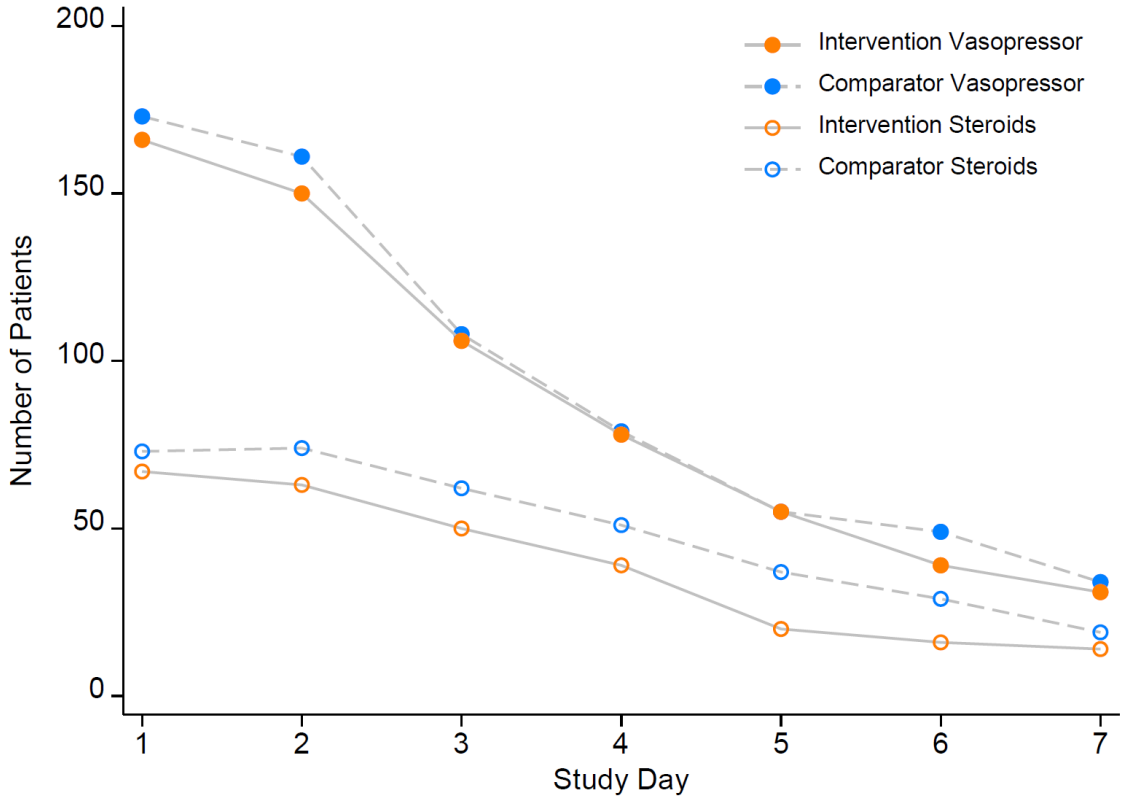
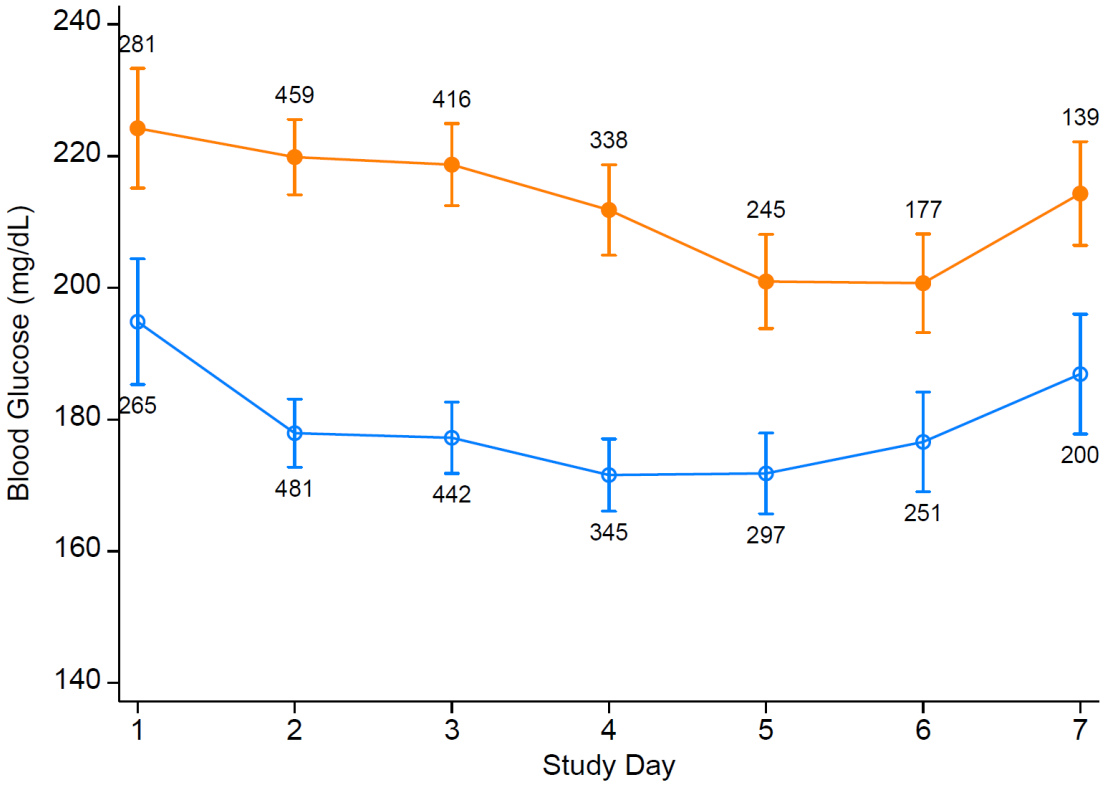


Figure E9. Mean blood glucose levels by study group, study days 1 to 7, for the sub-group HbA1c ≥ 7%.

Solid orange circles = intervention, open blue circles = comparator group, error bars = 95% confidence interval, with the number of observations shown adjacent.



3.3 CONCLUSIONS

3.3.1 Introduction

The high prevalence of type 2 diabetes in patients admitted to the ICU, and the effect of critical illness to exacerbate pre-existing glycaemic control, dictate that clinicians are frequently required to decide how to manage hyperglycaemia in this patient population. However, prior to the trial reported in this thesis, there was no high-quality, randomised control trial evidence which related specifically to patients with pre-existing type 2 diabetes. The existing evidence did, however, provide a persuasive rationale to evaluate the effect of a more liberal approach to the management of hyperglycaemia.

3.3.2 Contribution of the work described in this thesis to the understanding liberal or more personalised glucose targets in critically ill patients with pre-existing type 2 diabetes.

While a number of large and well-conducted studies have explored specific blood glucose thresholds to commence insulin and target blood glucose ranges during treatment, these were conducted in heterogenous critically ill patient populations that included a minority of patients with pre-existing type 2 diabetes the majority of patients had stress-induced hyperglycaemia (6-10). Accordingly, benefit of the currently established thresholds and target ranges for glycaemic control during critical illness for those with pre-existing diabetes remains uncertain. This is highlighted by the outcome of the survey of clinicians presented in Chapter 1 of this thesis and comments in clinical care guidelines (11). The trial presented in Chapter 3 is the largest and first multicentre randomised control trial of elevated and more personalised commencement points for the use of insulin in critically ill patients with pre-existing type 2 diabetes. This work outlines the potential benefits and risks associated with this approach. It also established the feasibility of this approach and provided information about the challenges associated with conducting a study with this approach. Finally, it provides important evidence to inform current practice and future research associated with blood glucose management in critically ill patients with type 2 diabetes.

3.4 FUTURE DIRECTIONS

The outcomes reported in Chapter 3.1 establish that a liberal, or ‘personalised’, commencement point of a blood glucose of 14 mmol/L for an insulin infusion markedly

reduces incident hypoglycaemic events. This randomised controlled trial was underpowered for clinical outcomes such as day 90 mortality and is a phase IIb trial it was anticipated that an increase in hypoglycaemia would be a biomarker predictive of greater mortality to be evaluated in any subsequent, adequately powered, phase III trial. However, the point estimate for this trial demonstrated increased mortality in patients allocated to the liberal group. This observation suggests that current practice should continue unchanged until additional well-conducted multicentre randomised controlled trials have been undertaken. Data from ongoing trials such as the TGC-fast, will be reported soon and will inform clinical practice and avenues for further research (12). Future trials in critically ill patients with pre-existing type 2 diabetes may benefit from using alternative approaches to control blood glucose rather than static protocols informed by intermitted blood glucose measurement and the use of glucose lowering therapies that are not associated with a risk of hypoglycaemia, such as glucagon-like-peptide 1 and its agonists. Nonetheless, underlying glycaemic control may be an important factor to consider when targeting acute blood glucose ranges, and utilisation of HbA1c on admission to the ICU, may present the opportunity to provide a more personalised approach in such trials.

3.5 REFERENCES

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Chapter 4:

Future of blood glucose management in critically ill patients with type 2 diabetes

4.1 INTRODUCTION

While the results reported in chapter 3.1 provide insights as to the impact of a liberal or more personalised approach to blood glucose control in critically ill patients with type 2 diabetes; these results are insufficient to change clinical practice or be considered definitive. Further evaluation of interventions that reduce incident hypoglycaemia and to establish the ideal blood glucose range to target in this patient population is warranted.

The results presented in chapter 3 pose some important challenges for future research. A major challenge is the mortality estimate while the 95% confidence interval does include the potential for both a reduction and increase in mortality the point estimate favoured the comparator (i.e. commencing insulin at 10 mmol/L). Although there was considerable imprecision and uncertainty around the estimate of effect on mortality, the point estimate does impact the design of future research relating to the optimal management of blood glucose levels in critically ill patients with type 2 diabetes.

4.1.1 **Objectives**

The objectives of this chapter are to outline future directions and areas of inquiry for blood glucose management in critically patients with pre-existing type 2 diabetes. The main objective is to describe interventions and approaches that may improve the implementation of a more personalised approach or a complement future trial(s) to determine the optimal approach to glucose management in this group.

4.2 FUTURE DIRECTIONS

Participants most likely to benefit from personalised blood glucose control

Future studies investigating personalised blood glucose control should consider participant selection criteria carefully to maximise the potential benefits. While using a pre-existing diagnosis of type 2 diabetes is a pragmatic and cost-effective approach, it would inevitably lead to the inclusion of individuals with well-controlled diabetes, who are intuitively less likely to benefit from an alternative approach. Measurement of HbA1c on admission offers a way to estimate the pre-morbid metabolic state of patients with diabetes, and target those who may be more likely to benefit from a personalised approach to blood glucose control. However, there are challenges associated with measuring HbA1c, including additional costs and potential delays to an intervention if laboratory results are implemented (1, 2). It should be noted that guidelines from the American Diabetes Association recommend that a HbA1c should be measured in all hospitalised people with diabetes if a result in the preceding three months is unavailable, but no advice is provided as to whether this result should inform in-patient treatment (3).

The recently published CONTROLING trial illustrates the challenges in trying to incorporate HbA1c into treatment algorithms within the ICU (1). In this trial, 16% of ICU patients were unable to be assessed for eligibility within 96 hours, due to the lack of accessibility of central HbA1c results. Not only did this impact on the internal validity of the trial with the potential for unintended selection bias, but it highlights the major challenges in implementing such a strategy to inform timely emergency care (1). However, recent advancements in point-of-care HbA1c testing do provide rapid and accurate results (4), and future studies using such devices to inform enrolment is warranted.

It should be recognised that there are limitations to the widespread use of HbA1c testing. The non-enzymatic glycation of haemoglobin is used to determine HbA1c, which represents the mean blood glucose concentration over the lifespan of a red blood cell (4). Therefore, certain clinical conditions such as anaemia, massive transfusion, haemoglobin variants, and carbamylated haemoglobin can impact the accuracy of HbA1c results (5).

Despite these limitations, utilising HbA1c levels to determine pre-morbid glycaemia in critically ill patients is more appropriate as fasting blood glucose will be impacted by stressors of critical illness (6). More personalised algorithms based on admission HbA1c, perhaps with an ordinal scale approach, may be appropriate given that substantial variation in HbA1c in people with diabetes. It is also appreciated that when HbA1c is <8.0% its dominant determinant is the magnitude of the rise in blood glucose following a meal, rather than pre-prandial or fasting blood glucose (7). However, utilising various algorithms and targets based on HbA1c levels presents statistical challenges to achieve sufficient power within a trial and allow the implementation of the findings if such an approach was found to be beneficial. Observational data suggests that various HbA1c ranges behave differently to acute blood glucose management, and associations between hypoglycaemia and time-weighted mean blood glucose and mortality (8).

Utilising HbA1c may be appropriate despite the added complexity and cost, as it has the potential to better identify and target those who are most likely to benefit from personalised blood glucose control i.e. potentially, higher target blood glucose levels in these with worse pre-existing glycaemic control. Careful consideration of participant selection criteria is crucial in future studies.

Novel approaches to blood glucose lowering

An intravenous insulin infusion is the predominant treatment utilised to manage hyperglycaemia in clinically ill patients, with the infusion rate titrated according to blood glucose measurement results (9). Close monitoring of blood glucose is required due to the risk of insulin-induced hypoglycaemia, change in endogenous or exogenous catecholamines, intravenous dextrose, corticosteroids or nutrition support increase the risk of hypoglycaemia. The process of frequent monitoring and titrating is laborious for ICU staff and while this diminishes the risk of hypoglycaemia, this risk remains.

The so called incretin effect refers to the much greater plasma insulin response to a isoglycaemic oral or enteral compared to an intravenous glucose load and reflects the secretion of two hormones from the gastrointestinal tract, glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) (10). A feature of the insulinotropic response to both GLP-1 and GIP is that it is glucose dependant requiring a blood glucose concentration > 4 mmol/L (11). Accordingly, administration of the incretin hormones is not associated with a risk of hypoglycaemia. The recognition that the

insulinotropic capacity of GIP was markedly attenuated in type 2 diabetes, led to a focus on the development of therapy based on GLP-1 both inhibitors of breakdown (oral DPP-4 inhibitors) and agonists of GLP-1 which are all administered by subcutaneous injection, although an oral GLP-1 agent (semaglutide) has recently become available. GLP-1 RAs are used widely and increasingly in the management of type 2 diabetes and obesity apart from the avoidance of hypoglycaemia their use in the longer term is associated with both cardiovascular and renal protection, as well as weight loss (12, 13).

Studies of incretins in the critical care environment have to date been small in size and exploratory in nature (14-18), but native GLP-1 when administered intravenously appear effective at glucose-lowering with negligible risk of hypoglycaemia (16). It has been demonstrated that intravenous infusions of GIP has no significant impact on glycaemia in critically ill patients with stress induced hyperglycaemia, along with no additive glucose lowering effect in combination with GLP-1(19). Currently commercially available GLP-1 administered subcutaneously would have limitation in the critically ill due to attenuated absorption, potentially altered metabolism and excretion in hepatic and renal dysfunction. Intravenous administration of GLP-1 may be more effective and is an appropriate delivery route in an intensive care unit. These features support the development of further studies exploring GLP-1 based therapies, potentially including native GLP-1 to manage hyperglycaemia in the critically ill population.

Blood glucose technology

Continuous blood glucose monitoring

The current approach to monitoring blood glucose levels during critical illness is with point-of-care glucometers or arterial blood gas analysers (2, 9, 20-22). Point-of-care glucometers tend to be frequently used despite evidence that these devices are less accurate in the critical care environment (23-26). Central laboratory measurement is the reference ‘gold standard’ but this approach is costly and does not provide timely results. Hence, this approach is rarely used in ICUs in Australia and New Zealand (9). Blood gas analysers offer a comparable accuracy to a central laboratory and most ICUs have ready access to these devices; however, this approach comes at a considerable cost in both consumables and time (21). This approach is also limited because it is intermittent and not all fluctuations are measured. It has been reported that between 4% and 15% of

hypoglycaemic events in ICU are undetected, with longer measurement intervals not surprisingly being associated with a greater frequency of undetected hypoglycaemia (27). Continuous blood glucose monitoring (CGM) devices have been developed aimed largely at the ambulatory type 1 diabetic population, recent devices are linked to high and low glucose alarms and finger picks blood glucose measurement is not necessarily required (28). Limited data exists around the use of these devices in the critical care setting, thus CGM devices are not routinely used in Australian or New Zealand ICUs (9, 21). CGM units can provide an almost continuous reading of subcutaneous blood glucose concentrations, creating the ability to continuously monitor for smaller fluctuations in blood glucose (21, 29). The prompt recognition of hypoglycaemia would be a major asset in commencing treatment and reducing harmful glycaemic variability. Although CGMs provide the ability to continuously monitor blood glucose, broad adoption in the critical care setting has not occurred (29). The measurements are obtained in varying ways, from glucose oxidase, mid-infrared spectroscopy or fluorescence. Commercially available measurements utilise interstitial sampling, but intravascular sampling has been used (28). The accuracy of devices may be compromised as subcutaneous sensors have limitation in the critically ill population due to physiological changes, administration of medications, and the frequency of calibration. Evidence on accuracy is lacking for clinical conditions such as hypotension, hypothermia and hypoxia, which are ubiquitous to critical illness (28). Future studies of CGM should explore accuracy and impact of various co-administered medications the critically ill, for example acetaminophen is known to impact results in the ambulant population on certain devices and this is yet to be explored in the critically ill setting (28). Cost considerations are an important factor as CGM devices and consumables are more expensive than point of care glucometers, however a reduction in nursing workload is likely to translate into a net reduction in cost. Cost analysis has hitherto only been reported in a small single centre study (30). Further assessment of CGM devices in the critical care population accordingly represents a priority.

Closed loop systems

Close loop systems consist of three interconnected components a blood glucose sensor, computerised treatment algorithm and insulin delivery pump (31). These devices have been developed mainly for ambulant with type 1 diabetes and are recommended in the Australian Evidence-Based clinical guidelines for diabetes (32). While these systems

have demonstrated to be effective in the ambulant type 1 patient population, their use in hospital use has been limited (33).

Recently a small open label trial of 138 non-critically ill patients with type 2 diabetes was conducted utilising a fully automated closed-loop system, on general wards at two hospitals in Europe demonstrating the potential of a fully automated close-loop system in a hospital setting (33). The study utilised a control algorithm on a tablet connected via USB to CGM receiver and subcutaneous insulin pump via Bluetooth. The primary endpoint was time in range (5.6 to 10 mmol/L), which was greater with the intervention (66% vs 42%). Glucose variability was also reduced with the intervention, although the risk of hypoglycaemia was not altered (33).

While this is an exploratory study, it does establish the potential of existing technology to enhance blood glucose control in a hospital setting. Furthermore, this approach may be of greater benefit in the critically ill population due to high incidence of stress hyperglycaemia.

Electronic insulin infusion protocols

Although simple nomogram protocols are the most common method to titrate insulin infusions, they vary greatly reflecting the lack of evidence supporting a specific protocol (9, 34). While guidelines provide some parameters for blood glucose target ranges and intervals between measurements, local protocols are often developed by clinicians and units based on personal preference (35). This approach can be cost-effective and easily adapted to local practice and preferences, allowing clinical staff to become familiar and confident in their use. However, they may lack information or become complicated with additional details, with inherent risk of calculation or execution errors. The increasing adoption of electronic medical records may also allow for a more integrated approach with greater capacity to improve and measure practice.

Recently, electronic management systems have been developed to guide insulin infusions and are gaining popularity in the hospital setting (31). These systems provide clinical staff with information to support decision making by performing calculations and providing insulin dosing on a digital platform that can be integrated with the electronic health record system (31). Four commercially available systems utilise various algorithms to achieve blood glucose within the target range (36-39). Although studies comparing these systems to basic nomogram protocols show promise in achieving and maintaining specific blood

glucose rage, they have been exploratory in size and methodology, particularly in the ICU setting (36-39). While many have reported a reduction in hypoglycaemic events, decreased glycaemic variability, and increased time in range, there have been substantial methodological limitation and clinically important outcomes have been less of a focus. For example, only one study was a randomized controlled trial, with insufficient power to be clinically informative (38).

Accordingly, while these technologies are intuitively appealing, and may be safer and easier for clinical staff to achieve and maintain blood glucose, they require further investigation in more rigorous trials to determine if they provide clinical benefit for the cost outlay (38).

4.3 CONCLUSIONS

4.3.1 Introduction

In the last twenty years, several trials have evaluated glycaemic control in critically ill patients which yielded results that have impacted on clinical practice. However, despite these strides, there remain a number of important questions that require further exploration particularly in relation to the management of critically ill patients with type 2 diabetes. With the advent of cutting-edge technologies and therapeutics, such as continuous glucose monitoring (CGM), point of care testing, electronic management and GLP-1 based therapy, it is imperative that the potential benefits of such approaches are rigorously evaluated. It would be surprising if the exploration of these advances did not lead to optimizing glycaemic control in critically ill patients at lower risk, leading to improved clinical outcomes.

4.3.2 Contribution of the work described to future explorations of personalised glucose targets in critically ill patients with pre-existing type 2 diabetes.

While the work published in this thesis provides information on current practice and, more importantly, on the impact of a more personalised approach, it equally possesses a number of questions that warrant future investigation. Future trials of glycaemic control in critically ill patients with type 2 diabetes are required for clinicians to be confident in the commencement point for insulin administration. The work presented in this thesis shows that despite relatively limited funding, it is feasible to conduct multicentre trial to evaluate blood glucose in the critically ill. More expansive funding would provide the opportunity to use emerging technologies to achieve closer compliance with target ranges.

4.4 FUTURE DIRECTIONS

Future studies should explore the premise that type 2 diabetes is a spectrum, with the potential that different targets may be required depending on antecedent glycaemic control prior to the acute illness or injury. This could be achieved though the utilisation of point of care HbA1c testing. Blinding of insulin administration has been demonstrated to be feasible (1). This approach adds rigour to future trials of glucose management and should be considered in any future study design. In ambulatory individuals technological advancements, such as CGM and closed-loop systems linked to alarm, clearly lead to time within target ranges, including a lower risk of hypoglycaemia which could provide a clinical benefit but require further evaluation. While short acting insulin is cost effective and is familiar to clinicians, newer drugs such as native GLP-1 and GLP-1 agonist have major attributes that warrant further investigation in the critically ill population.

Significant areas of enquiry still exist in the domain of blood glucose control in the critically ill and certainly for those patients with pre-existing type 2 diabetes. The incremental growth in knowledge will hopefully inform which interventions or approaches have the greatest capacity to benefit patients.

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Appendices

Appendix A

Presentations at national or international meetings

2022

ANZICS/ACCCN Annual Scientific Meeting

The effect of a liberal approach to glucose control on hypoglycaemia in critically ill patients with type 2 diabetes LUCID Randomized Clinical Trial.

2021

ANZICS CTG 23nd Annual Meeting on Clinical Trials in Intensive Care

A Phase II Study of Liberal Glucose Control in Critically Ill Patients With Pre-existing Type 2 Diabetes (LUCID)

Virtual meeting, Australia

2020

ANZICS CTG 22nd Annual Meeting on Clinical Trials in Intensive Care

A Phase II Study of Liberal Glucose Control in Critically Ill Patients With Pre-existing Type 2 Diabetes (LUCID)

2019

World Congress of Intensive Care: Invited speaker

Conservative vs. liberal: How politics can inform glucose management

2019

ANZICS CTG 21st Annual Meeting on Clinical Trials in Intensive Care

A Phase II Study of Liberal Glucose Control in Critically Ill Patients With Pre-existing Type 2 Diabetes (LUCID)

2018

ANZICS Annual Scientific Meeting: Invited speaker

A Phase II Study of Liberal Glucose Control in Critically Ill Patients With Pre-existing Type 2 Diabetes (LUCID)

Appendix B

Other publications completed during candidature

2023

National COVID-19 clinical evidence taskforce (October 2020 onwards):

Methods chair for up to five clinical panels. The Taskforce's 15 expert panels developed 23 clinical flowcharts and updated the national COVID-19 clinical guidelines over 100 times with more than 200 recommendations. Clinical scope expanded over time to include guidance for the care of children, adolescents, adults, pregnant or breastfeeding women, and older people.

Methods chair for Monkeypox (MPX) treatment guidelines.

The Guidelines were updated four times with 9 recommendations over a period of 9 months.

Bridget E Barber, Heath White, **Alexis P Poole**, Steve A McGloughlin, Tari Turner, and the COVID-19 Drug Treatment Panel of the National Clinical Evidence Taskforce, **Australian National Clinical Evidence Taskforce COVID-19 Drug Treatment Guidelines: challenges of producing a living guideline,** Medical Journal Australia Accepted for publication 18 May 2023

J Hewitt, S McDonald, **A Poole**, Heath White, Simon Turner, Tari Turner, **Weekly updating of guideline recommendations was feasible: the Australian National COVID-19 Clinical Evidence Taskforce**, Journal of Clinical Epidemiology, February 2023

S Cheyne, D F Navarro, A K. Buttery, S Chakraborty, O Crane, Kelvin Hill, E McFarlane, R L Morgan, R A Mustafa, **A Poole**, D Tunnicliffe, J P Vogel, H White, S Whittle, T Turner, on behalf of the ALEC Methods and Processes Working Group and Collaborators, **Methods for living guidelines: early guidance based on practical**

experience. Paper 3: selecting and prioritizing questions for living guidelines, Journal of Clinical Epidemiology, January 2023

2022

D F Navarro, S Cheyne, T Turner, G Johnson, S McDonald, K Hill, J Vogel, S Chakraborty, H White, D J Tunnicliffe, S Whittle, L Cusack, A Buttery, **A Poole**, A Synnot, On behalf of **ALEC Living Methods Group, The Living Guidelines Handbook Guidance for the production and publication of living clinical practice guidelines**, Version 1.0. October 2022

K Sundararajan, P Bi, A Milazzo, **A Poole**, B Reddi, M A Mahmood, **Preparedness and response to COVID-19 in a quaternary intensive care unit in Australia: perspectives and insights from frontline critical care clinicians.** British Medical Journal Open. February 2022

2021

L Milross, T O'Donnell, T Bucknall, D V Pilcher, **A Poole**, B A J Reddi, J F Ihle, **Perceptions held by healthcare professionals concerning organ donation after circulatory death in an Australian intensive care unit without a local thoracic transplant service: A descriptive exploratory study**, Australian Critical Care, July 2021

L Weinel, M Summers, **A Poole**, L Chapple, **Are point-of-care urine albumin/–creatinine ratio measurements accurate in the critically ill?** *Australian Critical Care,* Volume 34 November 2021

L Chapple, M Summers, L Weinel, Y Ali Abdelhamid, P Kar, S Hatzinikolas, D Calnan, M Bills, K Lange, **A Poole**, S O'Connor, M Horowitz, K Jones, A Deane, M Chapman, **Effects of Standard vs Energy-Dense Formulae on Gastric Retention, Energy**

Delivery, and Glycemia in Critically Ill Patients. *Journal of Parenteral and Enteral Nutrition.* Volume 45 May 2021

2019

L Weinel, M Summers, M Finnis, **A Poole**, P Kar, M Chapman, A Deane, Y Abdelhamid, **Are point-of-care measurements of glycated haemoglobin accurate in the critically ill?.** *Australian Critical Care* Volume 32 November 2019

Appendix C

Grants awarded during candidature

2019

AM Deane, R Bellomo, C French, A Tobin, J Anstey, A Ghosh, **A Poole**, M Finnis, M Horowitz, Melbourne Academic Centre for Health RART Translational Research Project 2019, Liberal glucose Control in critically ill patient with pre-existing type 2 Diabetes (LUCID).
Value: $75,000

A Poole, RAH Research Committee Dawes Scholarship – Top Up, *Liberal glUcose Control in critically Ill patient with pre-existing type 2 Diabetes (LUCID): a phase II multicentre randomised controlled trial.*
Value: $12,500 ($5,000 per annum)

2018

AM Deane, R Bellomo, C French, A Tobin, J Anstey, A Ghosh, **A Poole**, M Finnis, M Horowitz, Melbourne Academic Centre for Health RART Translational Research Project 2019, *Liberal glucose Control in critically ill patient with pre-existing type 2 Diabetes (LUCID).*
Value: $180,000

A Poole, Faculty of Health Sciences Divisional Scholarship, University of Adelaide
Value: $81,246 ($27,082 per annum)

Appendix D

Awards during candidature

Monash University: **2021 Vice-Chancellor's Award for Research Enterprise**; National COVID-19 Clinical Evidence Taskforce: J Elliott, B Tendal, T Turner, R Tate, B Morris-Donovan, E Hudson, S McDonald, H White, S Cheyne, Dr D Fraile Navarro, J Vogel, S Chakraborty, D Primmer, S Timms, **A Poole**, B Kunstler, S Gurry, S Hurley, J Hewitt, M Cumpston, J Sidhu, T Millard, M Murano, L Tieu, U Symonds and J Henty